Development of Gold-Catalysed Glycosylation Reactions and TfOH-Promoted α-Functionalization of Unactivated Ketones

DOCTOR OF PHILOSOPHY

by

Koppolu Srinivasa Rao

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UNIVERSITY OF HYDERABAD
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Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Dr. Rengarajan Balamurugan**.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

University of Hyderabad
May, 2014

Koppolu Srinivasa Rao
07CHPH01

School of Chemistry
University of Hyderabad
Central University P.O.
Hyderabad 500 046
India

Certificate

Certified that the work embodied in this thesis entitled **"Development of Gold-Catalysed Glycosylation Reactions and TfOH-Promoted α-Functionalization of Unactivated Ketones"** has been carried out by **Mr. KOPPOLU SRINIVASA RAO** under my supervision and the same has not been submitted elsewhere for a degree.

Dr. R. BALAMURUGAN
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

Dedicated to My Mother

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Koppolu Srinivasa Rao

Table of Contents

PART-B

List of acronyms used

[α]	Specific rotation [expressed without units; the actual units are deg $dm^{-1}cm^3$ g^{-1}]
Aq.	Aqueous
Ac	Acetyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
BINSA	1,1'-Binaphthyl-2,2'-disulfonic acid
Bn	Benzyl
BSTFA	*N*,*O*-Bis(trimethylsilyl)trifluoroacetamide
Bz	Benzoyl
br s	Broad singlet (spectral)
BTEACl	Benzyl tetraethyl ammonium chloride
Bu	Butyl
t-Bu	*tert*-Butyl
CAN	Ceric ammonium nitrate
^oC	Degree Celsius
cat.	Catalyst
conc.	Concentrated
cm^{-1}	Wavenumber(s)
CSA	Camphorsulfonicacid
δ	Chemical shift in parts per million
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-4,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
dil.	Diluted
DMDO	Dimethyldioxirane

DMF	N,N-Dimethylformamide
DNBA	2,4-Dinitrobenzoic acid
dr	Diastereomeric ratio
DTBBP	Di(*tert*-butyl)-2-biphenylphosphine
ee	Enantiomeric excess
ESI	Electron spin ionisation
Et	Ethyl
EtOH	Ethyl alcohol
equiv	Equivalent
g	Gram(s)
h	Hour(s)
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
HSAB	Hard soft acid base
Hz	Hertz
IDCP	Iodonium dicollidinium perchlorate
i-Pr	Isopropyl
IR	Infrared
J	Coupling constant (in NMR Spectroscopy)
LA	Lewis acid
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyl disilazide
LCMS	Liquid chromatography-mass spectrometry
LUMO	Lowest unoccupied molecular orbital
m	Multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
min	Minute(s)

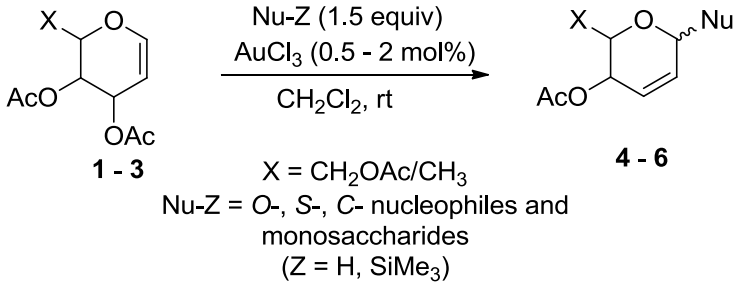
mmol	Millimoles
mp	Melting point
MS	Molecular sieves
MVK	Methyl vinyl ketone
NGP	Neighboring group participation
NMR	Nuclear magnetic resonance
Nu	Nucleophile
ORTEP	Oak ridge thermal ellipsoid plot
OTf	Trifluoromethanesulfonate
PMA	Phosphomolybdic acid
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
q	Quartet (in spectroscopy)
rt	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TFA	Trifluoroacetic acid
TfOH	Triflic acid
UV	Ultraviolet

SYNOPSIS

This thesis entitled "**Development of Gold-Catalysed Glycosylation Reactions and TfOH-Promoted α-Functionalization of Unactivated Ketones**" is divided into two parts (A and B). Part-A discusses about gold-catalysed glycosylation reactions and comprises of chapters 1 and 2. In Part-B, methodologies for α-alkylation of unactivated ketones using *in situ* formed acetals are discussed in chapters 3 and 4. Each chapter is generally subdivided into six sections namely Introduction, Results and discussion, Conclusions, Experimental section, References along with Representative spectra. The theme of each chapter has been highlighted here briefly.

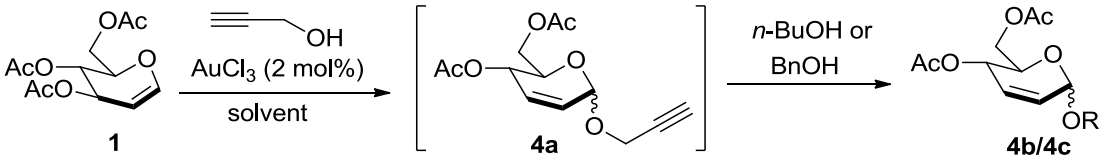
Part-A

Chapter 1: Gold-Catalysed Synthesis of 2,3-Unsaturated Glycosides



Scheme 1. $AuCl_3$-catalysed Ferrier reaction

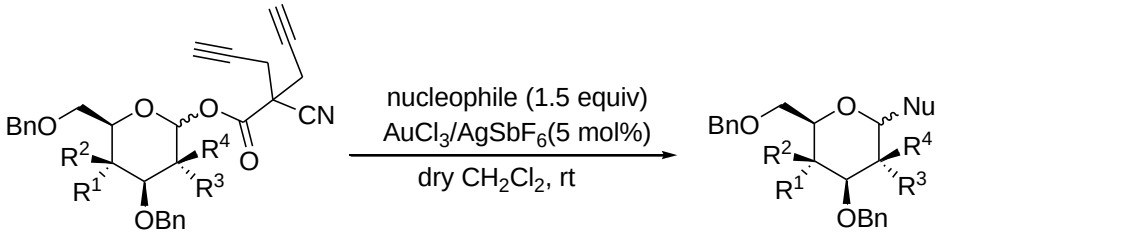
Gold(III) chloride in catalytic amount activates 3,4,6-tri-*O*-acetyl-D-glucal **1**, 3,4,6-tri-*O*-acetyl-D-galactal **2**, and 3,4-di-*O*-acetyl-L-rhamnal **3** efficiently. The activated species was employed in the Ferrier reaction to furnish 2,3-unsaturated glycosides **4**-**6** in excellent yields and good α-selectivity. Several *O*-, *S*-, *C*-based nucleophiles and sugar monosaccharide acceptors have been employed in the Ferrier reaction.



Scheme 2. $AuCl_3$-catalysed one pot Ferrier reaction and subsequent transglycosylation

Gold-catalysed one pot Ferrier reaction followed by transglycosylation reaction was attempted. The idea for doing this is to make first the α-anomer of propargyl Ferrier product under gold catalysis and check whether another nucleophile could be added to it from β-face in the presence of $AuCl_3$. This way, the α-selectivity was found to reduce and complete reversal of selectivity could not be achieved.

Chapter 2: Gold-Catalysed Glycosylation Reaction: Development of an Easily Accessible Glycosyl Donor



7, $R^1 = R^3 = OBn$; $R^2 = R^4 = H$; gluco-
8, $R^1 = R^4 = OBn$; $R^2 = R^3 = H$; manno-
9, $R^2 = R^3 = OBn$; $R^1 = R^4 = H$; galacto-

10, $R^1 = R^3 = OBn$; $R^2 = R^4 = H$; gluco-
11, $R^1 = R^4 = OBn$; $R^2 = R^3 = H$; manno-
12, $R^2 = R^3 = OBn$; $R^1 = R^4 = H$; galacto-

Scheme 3. Gold-catalysed glycosylation reaction

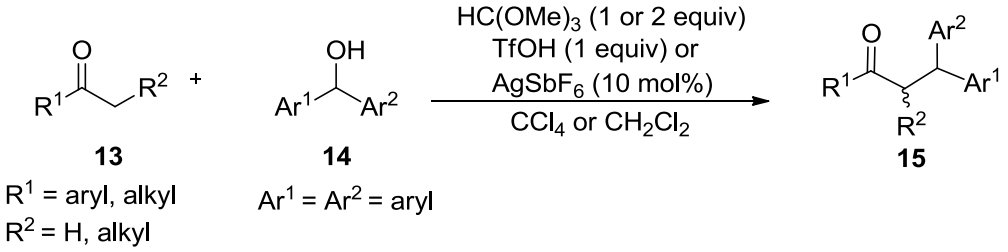
Gold-catalysed glycosylation strategy has been developed using an easily accessible activator derived from commercially available ethyl cyanoacetate. Several nucleophiles such as *O*-, *S*-, and *C*-based nucleophiles, azides and hydrides have been employed in the glycosylation reaction which happens at room temperature. While glucosides and galactosides formed as a mixture of anomers, mannosides formed exclusively as α-anomers. Disaccharide formation was attempted but the reaction was not fruitful.

PART-B

Chapter 3: Triflic Acid-Promoted and Lewis Acid-Catalysed α-Alkylation of Unactivated Ketones Using *In situ* Formed Acetals

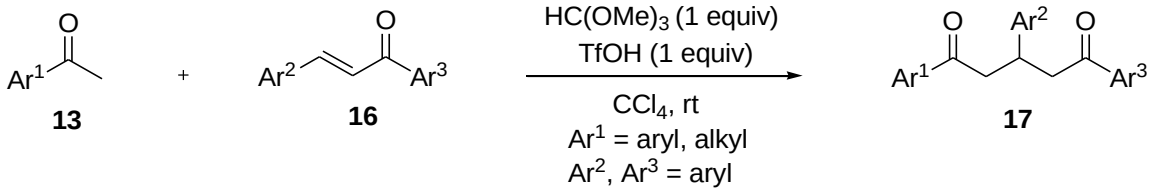
A simple, one pot enol ether formation and α-alkylation of unactivated aryl and alkyl ketones with benzhydrols has been developed using *in situ* formed acetals under triflic acid-promoted and $AgSbF_6$-catalysed conditions. The reactions occur at room temperature with near stoichiometric amounts of ketones and alcohols. A wide variety of ketones were employed in the reaction such as chloro, bromo, iodo, methyl and methoxy substituted acetophenones, cyclohexanones and 4-phenylbut-3-en-2-ones to get the alkylated products in

good yields. Similarly, a range of substituted benzhydrols with different electrophilicities have been employed as electrophiles.



Scheme 4. Triflic acid-promoted or Lewis acid-catalysed α-alkylation of simple ketones

Chapter 4: Triflic Acid-Promoted Synthesis of 1,5-Diketones from Unactivated Ketones



Scheme 5. Triflic acid-promoted Michael reaction

In search of more applications of the enol ether formed *via in situ* formed acetal, a facile Michael reaction of unactivated ketones with chalcones has been developed. These reactions result in unsymmetrical 1,5-diketones at room temperature. The stoichiometry of the reactants is crucial for the efficiency of this reaction and 5 fold excess of ketone with respect to chalcone is required for better outcome of the reaction. A wide variety of ketones could be employed in the Michael reaction such as aryl methyl ketones and cyclohexanones as Michael donors. These 1,5-diketones are useful compounds in organic synthesis.

Note: Scheme numbers and compound numbers given in this synopsis are different from those given in chapters.

Part-A

Gold-Catalysed Glycosylation Reactions

Chapter 1

Gold-Catalysed Synthesis of 2,3-Unsaturated Glycosides

1.1 Introduction

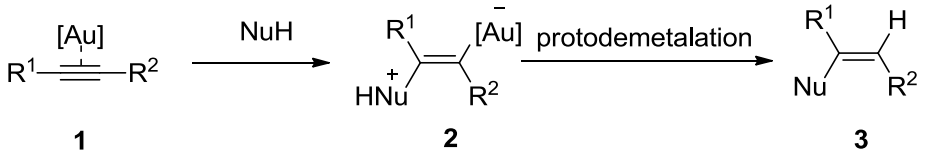
In many catalysis reactions, Lewis acid-base interactions play vital role in promoting the reaction. Several Lewis acids have been known for the activation of carbonyl groups such as halides of group 3, 4 and early transition metals like titanium,. etc. Here, the Lewis acidic metal coordinates to the hard Lewis basic site (oxygen) through a weak σ-bond. These type of Lewis acids come under the category of σ-acids. Few Lewis acids are known for their exceptional ability to coordinate to π-systems of alkynes, alkenes and allenes to activate them for nucleophilic attack. Au(I), Au(III), Pt(IV), etc. compounds come under π-acidic Lewis acids.[1]

1.1.1 Carbophilicity of gold compounds

Until last decade, gold compounds were considered as catalytically inert because of inertness of metallic gold and its precious nature. Gold is precious but metals like rhodium, palladium and platinum are even more precious than gold but their catalytic behavior is very well explored. During the last decade, gold compounds have evolved as powerful homogeneous catalysts for the activation of alkynes, allenes and alkenes by pushing other heavy metal catalysts like Hg^{+2} backwards.[1]

1.1.1.1 Gold-catalysed activation of alkynes

Gold catalysts being soft Lewis acids coordinate to the triple bond of alkyne **1** very effectively and the activated species can be attacked by a variety of nucleophiles. The addition takes place in *anti* fashion to give vinyl gold species **2**. This vinyl gold species undergo protodemetalation to give the addition product **3** (Scheme 1).

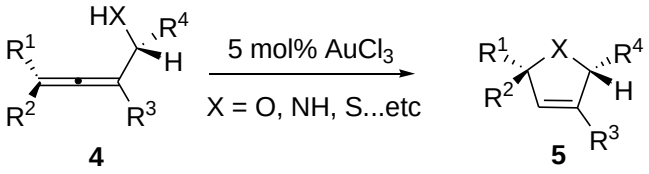


Scheme 1. Activation of alkyne by gold

Several nucleophiles have been employed till date such as alcohols,[2] amines,[3] carboxylic acids,[4] esters,[5] thiols,[6] phenols,[7] arenes,[8] etc.

1.1.1.2 Gold-catalysed activation of allenes

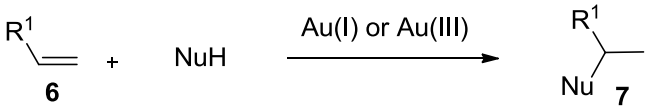
Allenes can be activated by gold(I) and gold(III) complexes to form alkene containing molecular architectures. Allene activation has not been studied as extensively as alkyne activation by gold. Most of the studied allene activation involve intramolecular cyclization of alcohols,[9] thiols,[10] esters[11] and amines[12] to give 5-*endo-dig* products preferentially.



Scheme 2. Activation of allene by gold

1.1.1.3 Gold-catalysed activation of alkenes

Only few reports are there in literature for the activation of alkene by gold.[13] However enyne activation using gold is well explored. It results in the addition product generally.

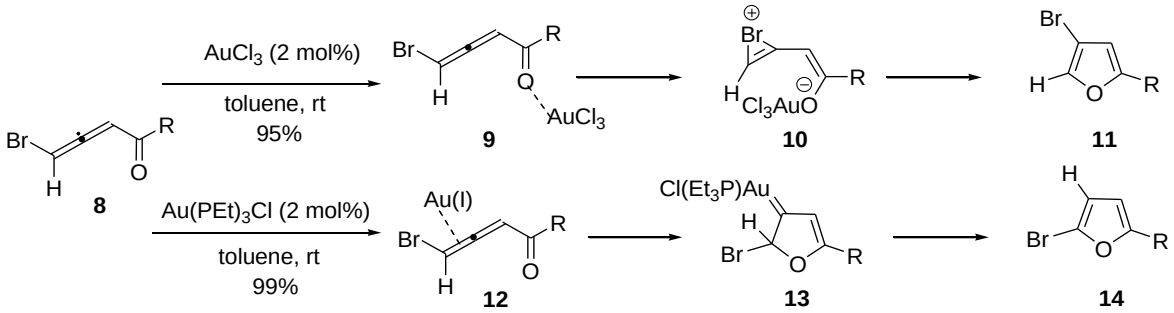


Scheme 3. Activation of alkene by gold

1.1.2 Oxophilicity of gold compounds

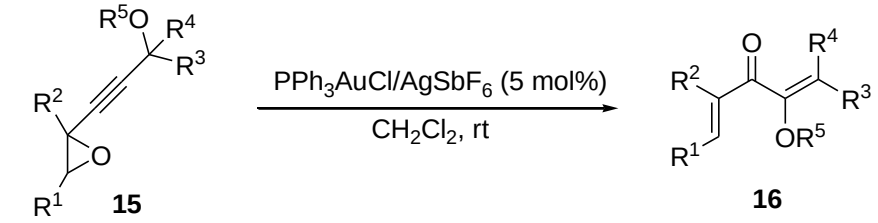
Gold in metallic form has poor oxophilicity as it does not get oxidised to oxides readily. Moreover, the oxides of gold Au_2O_3, Au_2O are less stable.[11] However, gold complexes show considerable oxophilicity in addition to alkynophilicity. Yamamoto predicted the oxo- and carbophilicities of metal chlorides, based on the computed heats of formation of complexes of different metal chlorides with carbonyl compounds, alkynes and alkenes.[14] This computational study shows that gold has oxo as well as carbophilicities in both +1 and +3 oxidation states. Further it was postulated that gold in lower oxidation state preferably coordinates to π-system and in higher oxidation state coordinates effectively with heteroatom.

Gevorgyan and co-workers reported the regiodivergent cyclization of bromo allenyl ketones **8** to 3-bromo (**11**) and 2-bromo (**14**) furans with gold(III) and gold(I) catalysts respectively (Scheme 4).[15a] Here, more oxophilic gold(III) coordinates to the ketone **8** which favors 3-bromofuran derivatives **11** by 1,2-bromide shift followed by cyclization. Carbophilic Au(I) coordinates to the distal double bond of allene and nucleophilic attack at carbonyl oxygen leads to gold carbenoid which on 1,2-hydride shift gives 2-bromofuran derivative **14**. It was believed that 1,2-hydride shift in Au(I)-catalysed cyclization is facilitated by the ligands attached to gold. In this case, two different oxidation states of metal gave two different regioisomers because of difference in their relative acidity. The same group theoretically investigated the mechanistic pathway and postulated that gold first coordinates to allene in both the cases. Further hydrogen migration leads to 2-bromofuran and bromine migration leads to 3-bromofuran product formation.[15b]



Scheme 4. Gold-catalysed regiodivergent synthesis of bromofurans **11** and **14**

Pale and co-workers reported a novel cyclization of alkynyl oxiranes with Au(I) salts to make substituted furans by utilizing both alkyno- and oxophilicities of the gold catalysts.[16a]

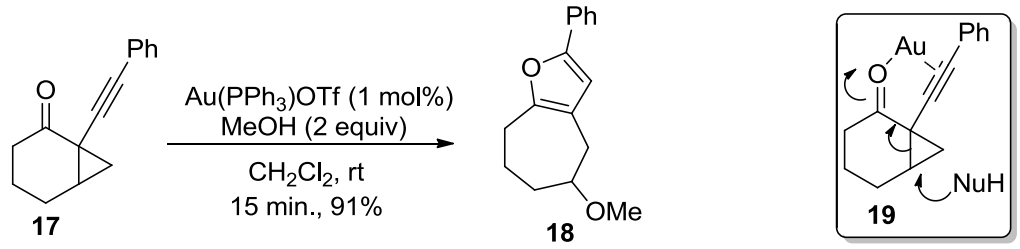


R^1, R^2 = alkyl
R^3, R^4 = alkyl, aryl, H
R^5 = Ac, Piv, Bz

Scheme 5. Gold-catalysed tandem activation of epoxide and alkyne

In their mechanistic discussion, it was proposed that gold(I) coordinates to both epoxide oxygen and alkyne (as suggested by Yamamoto σ-π chelation). The same group reported the gold(I)-catalysed rearrangement of (3-acyloxyprop-1-ynyl)oxiranes **15** to acyloxylated divinyl ketones **16** (Scheme 5).[16b] Here, the alkyno- and oxophilicities were successfully utilised in tandem to effect the reaction. 1,2-Migration of carboxylate followed by rearrangement leads to the divinyl ketone product **16**.

Schmalz and co-workers have reported gold(I)-catalysed highly efficient cascade ring expansion of acyclic alkynyl ketones **17** in presence of nucleophiles to form nucleophile incorporated ring fused furan **18** (Scheme 6).[16c] In their proposed mechanistic pathway, gold complex chelates to both carbonyl and alkyne functionalities and further nucleophile-assisted cleavage of cyclopropane leads to cycloheptene derivative fused with furan **18**. A variety of Lewis acids were tested for this cyclization and Cu and Ag complexes also gave moderate to good yields of the product.

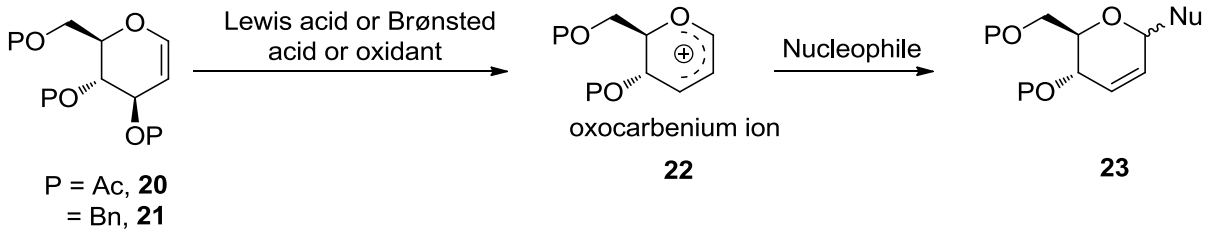


Scheme 6. Gold-catalysed cycloheptano-fused furan **18** formation from alkynyl ketone **17**

Few other reports were also found utilising gold complexes as oxo- and carbophilic catalysts. These include the regio- and diastereoselective intermolecular addition of water and alcohols to epoxyalkynes,[17] 2-alkenylphenyl carbonyl compounds to indene derivatives.[18] Our group reported the gold-catalysed activation of epoxides in the synthesis of bicyclic ketals by utilizing both oxo- and carbophilicities of gold complexes.[19]

1.1.3 Ferrier rearrangement

Ferrier rearrangement is an acid-catalysed rearrangement of glycals in the presence of nucleophiles to form 2,3-unsaturated glycosides through an oxocarbenium ion intermediate (Scheme 7).[20]



Scheme 7. Schematic representation of Ferrier reaction

The first step involves delocalized cyclic allyloxocarbenium ion formation facilitated by the catalyst and the resulting oxocarbenium ion reacts with nucleophiles to form 2,3-unsaturated glycosides. Several Lewis acids, Brønsted acids and oxidants are known to catalyse this transformation.

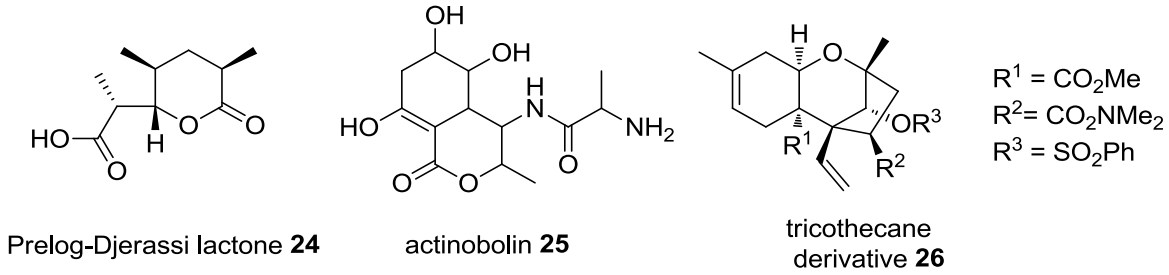


Figure 1

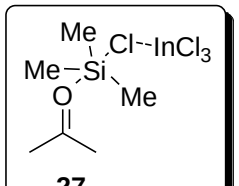
The product of Ferrier rection *i.e.*, 2,3-unsaturated glycosides are useful intermediates in carbohydrate chemistry to synthesize compounds with wide range of biological activities.[21] This class of compounds gained much attention of synthetic chemists because these compounds can further be functionalized by epoxidation/dihydroxylation/aminohydroxylation to make interesting sugar motifs. 2,3-Dideoxy glycosides which are widely known for their biological applications can be made by hydrogenating the 2,3-unsaturated glycosides. Several important chiral intermediates and natural products such as Prelog-Djerassi lactone **24**, actinobolin **25** and tricothecane core **26** (Figure 1) were synthesized *via* Ferrier reaarangement.[22]

Although there are other indirect methods[21c, 23] to make 2,3-unsaturated sugars, Ferrier reaction is simple, straight forward and high yielding reaction.

1.1.3.1 Lewis acids as catalysts in Ferrier rearrangement

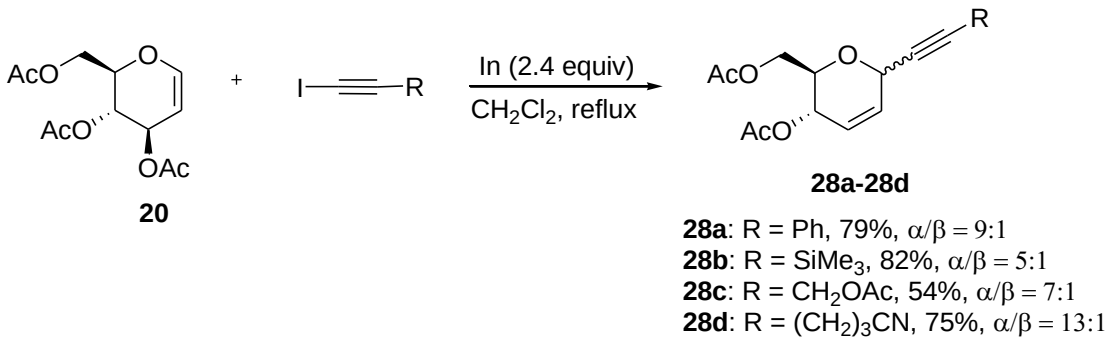
Lewis acids are known for their exceptional activation of carbonyl groups and other functional groups having *O*- and *N*- basic sites. A wide array of Lewis acids including transition metal salts, main group complexes and lanthanide complexes have been known to catalyse Ferrier reaction. Most of the catalysts give 2,3-unsaturated glycosides in excellent yields and α-selectivity due to anomeric effect.

Transition metals act as very good Lewis acidic catalysts because of their capability to exhibit variable oxidation states by electron transactions. Transition metal chlorides and triflates have been reported in literature to catalyse the Ferrier reaction. Balasubramanian and co-workers reported the indium(III) chloride-catalysed Ferrier reaction with alcohols, phenols and sugar fragments to form corresponding unsaturated glycosides.[24a] Later, using TMSCl along with $InCl_3$ catalyst system, synthesis of *C*-glycosides was achieved by Ferrier reaction.[25a] Baba and co-workers explained the effect of indium(III) chloride on the Lewis acidity of trimethylsilyl chlorides.[25b] The increase of Lewis acidity of trimethylsilyl chlorides is due to the possible coordination of chloro of silyl chloride with the indium metal of indium(III) chloride which makes the silicon center more acidic (as shown in Figure 2).



27

Figure 2



20

28a-28d

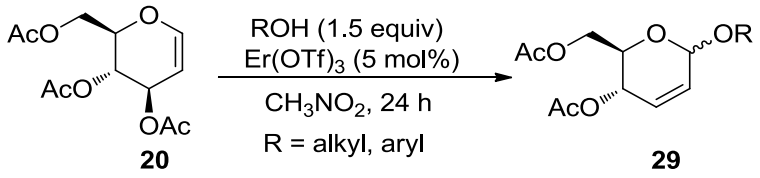
28a: R = Ph, 79%, α/β = 9:1
28b: R = $SiMe_3$, 82%, α/β = 5:1
28c: R = CH_2OAc, 54%, α/β = 7:1
28d: R = $(CH_2)_3CN$, 75%, α/β = 13:1

Scheme 8. Indium-mediated synthesis of 1-alkynyl 2,3-unsaturated glycosides **28a-28d**

Chiral 2-*C*-methylene glycosides have been synthesized from 2-*C*-acetoxymethyl glycals and phenols by indium(III)-catalysed Ferrier reaction. By using this methodology, carbohydrate-derived pyrano[2,3-b]benzopyrans were prepared in tandem from Ferrier reaction followed by intramolecular cyclization.[25c] Ferrier type alkynylation reaction was

reported with indium metal as the stoichiometric reagent to form 1-alkynyl 2,3-unsaturated glycosides **28a-d** under Barbier type conditions (Scheme 8).[26] Other Lewis acids like $NbCl_5$,[27] $CeCl_3 \cdot 7H_2O$,[28] $Fe(OTf)_3$,[29] $FeCl_3$[30] have also been reported in the literature to facilitate Ferrier reaction.

Lanthanide triflates continue to play major role in catalysis reactions because of their considerable oxophilicity and the labile nature of their bonds with heteroatoms especially with oxygen. Due to this exceptional behavior, these catalysts are required in sub-stoichiometric amounts to get good reaction outcome. Procopio and co-workers reported the erbium(III) triflate-catalysed Ferrier rearrangement and the scope of the reaction has been explored by employing *O*-, *S*- and sugar nucleophiles (Scheme 9).[31] In all the cases, α-selectivity was observed. Other lanthanide triflates such as $Dy(OTf)_3$,[32] $Yb(OTf)_3$[33] are also known to catalyse Ferrier reaction.



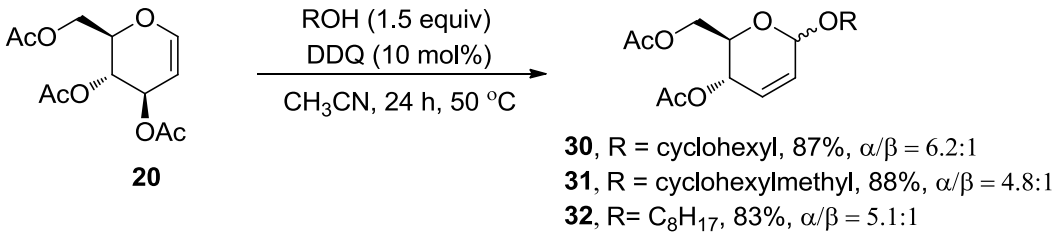
Scheme 9. Erbium(III)-catalysed synthesis of 2,3-unsaturated glucosides

Only a few salts of main group elements are known to act as catalysts to effect organic transformations, because of their inability to exhibit multiple oxidation states. Kamble and co-workers have reported the magnesium perchlorate-catalysed Ferrier rearrangement of glycals to furnish 2,3-unsaturated glycosides.[34] Other main group compounds such as $BF_3 \cdot Et_2O$,[35] $LiBF_4$,[36] $B(C_6F_5)_3$[37] and molecular iodine[38] were used to furnish 2,3-unsaturated glycosides from glycals.

1.1.3.2 Ferrier reaction catalysed by oxidants

Fraser-Ried and co-workers reported a non-acidic alternative to promote Ferrier reaction by treating glycal with iodonium dicollidinium perchlorate (IDCP) to form 2,3-unsaturated glycosides.[39] In due course DDQ evolved as a mild oxidative catalyst to carry out Ferrier reaction. Alcohol nucleophiles have only been used in the reaction (Scheme 10). First, DDQ oxidises the glycal to the glycal radical cation. This radical cation on elimination of

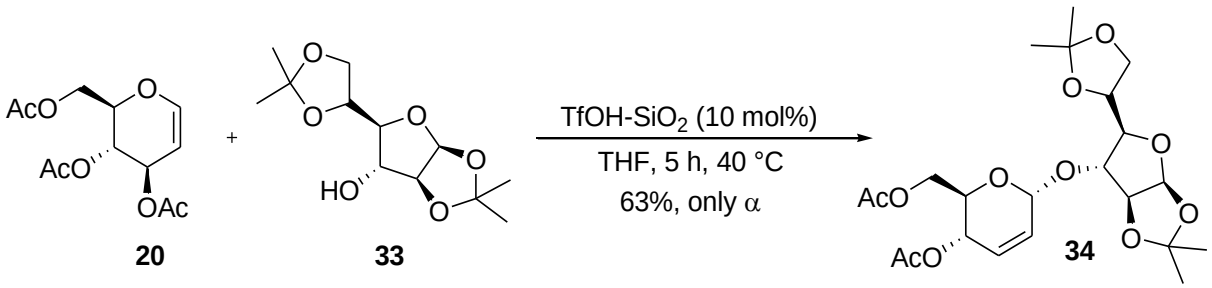
acetoxy radical by assistance from the sugar ring oxygen leads to allyl oxocarbenium ion. This on further attack by the nucleophile give 2,3-unsaturated glycoside.[40] Yadav and co-workers have reported the ceric ammonium nitrate (CAN)-catalysed synthesis of 2,3-unsaturated glycosides from acetyl and benzoyl glucals.[41a] The reaction needs reflux condition to get the product in good yield and in most of the cases α-selectivity was observed. Vankar and co-workers reported the CAN employed synthesis of 2-deoxy sugars from glycals with the formation of trace amounts of the Ferrier product.[41b]



Scheme 10. DDQ-catalysed synthesis of 2,3-unsaturated glucosides

1.1.3.3 Brønsted acid-SiO_2 impregnated catalysts

Usage of immobilized catalysts over pure catalysts is better because of their easy removal and recycling after completion of the reaction. Brønsted acids like phosphomolybdic acid,[42] triflic acid,[43] sodium hydrogen sulfate[44] and perchloric acid[45] were adsorbed on silica gel and utilized in the Ferrier reaction.



Scheme 11. TfOH-SiO_2-catalysed synthesis of 2,3-unsaturated glucoside **34**

1.1.3.4 Palladium-catalysed *O*-glycosylation

Kim *et al.* reported the palladium-catalysed *O*-glycosylation reaction with a switch in α to β selectivity by changing the ligand in the reaction.[46] The stereochemical outcome of the reaction mainly depends on the orientation of the ligand coordinated allylic palladium intermediate as portrayed beside. 3-Acetyl-4,5-di-*O*-benzyl-D-glucal **37** reacts with benzyl

alcohol in the presence of diethyl zinc using Pd(II) as catalyst to furnish glycoside **38** (Scheme 12). In presence of DTBBP ligand, β-selectivity was observed through palladium complex **35**, and with $P(OMe)_3$ ligand, α-selectivity was achieved *via* palladium complex **36**.

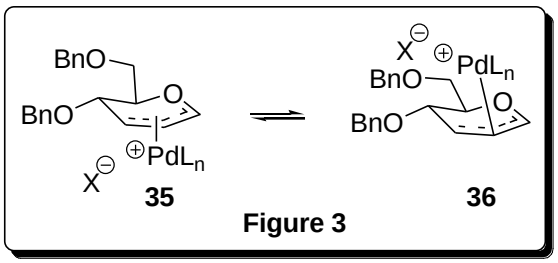
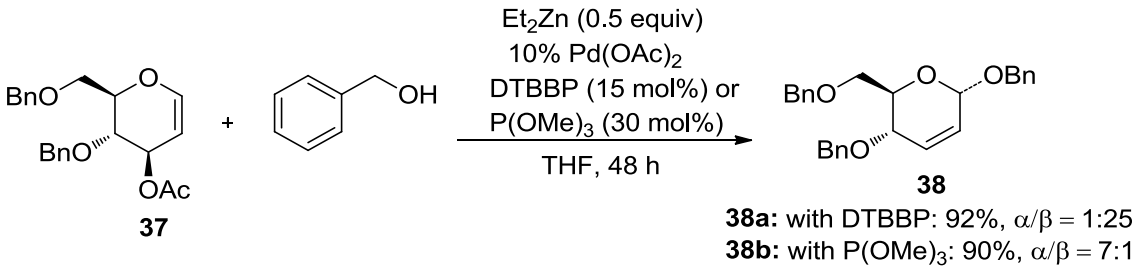


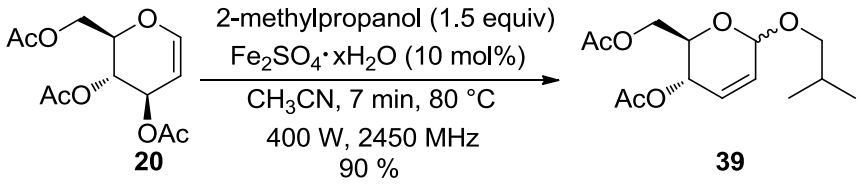
Figure 3



Scheme 12. $Pd(OAc)_2$-catalysed stereoselective synthesis of 2,3-unsaturated glucoside

1.1.3.5 Microwave induced Ferrier reaction

Microwave heating is very effective in promoting several reactions than the conventional heating if the reactants are enough polar to absorb microwave radiation. Ferrier reaction also have been reported under microwave conditions with few catalysts like $Fe_2SO_4 \cdot xH_2O$,[47a, 47b] silica gel[47c] and even in the absence of catalyst under solvent free conditions.[47c]



Scheme 13. $Fe_2SO_4 \cdot xH_2O$-catalysed microwave-assisted synthesis of 2,3-unsaturated glucoside

1.2 Results and discussion

Although there are several catalysts available for promoting Ferrier reaction, most of them are restricted to oxygen-based nucleophiles. Since the oxophilicity of gold is not well explored, Ferrier reaction is an opt reaction to check. Moreover, due to poor stability of gold oxides, the catalytic property of gold utilizing its oxophilicity is expected to be superior than that of other Lewis acid catalysts. For the Ferrier reaction three substrates **20**, **40**, **41** were

used (Figure 4). Starting materials for the Ferrier reaction 3,4,6-tri-*O*-acetyl-D-glucal **20**, 3,4,6-tri-*O*-acetyl-D-galactal **40** and 3,4-di-*O*-acetyl-L-rhamnal **41** were synthesized using reported procedures starting from dextrose, D-galactose and L-rhamnose respectively.

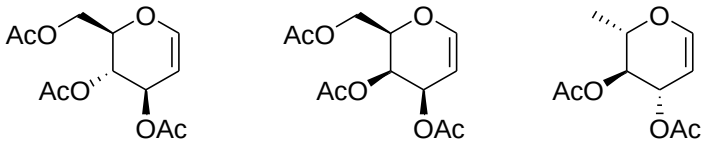
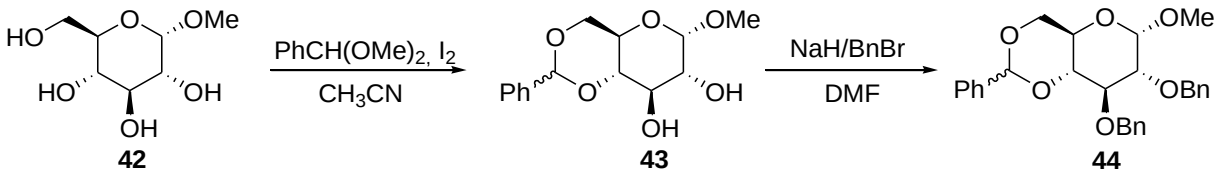
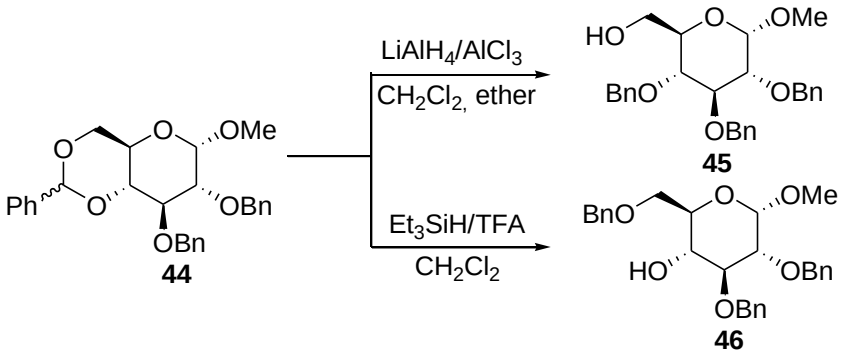


Figure 4

Monosaccharide acceptors were synthesized starting from commercially available methyl glycoside **42**. By following the literature procedure, benzylidine group was introduced between 4 and 6 positions followed by benzylation at 2 and 3 position to get **44**. Compound **44** on regioselective cleavage gave 1-methoxy-2,3,4-tri-*O*-benzyl-D-glucose **45** and 1-methoxy-2,3,6-tri-*O*-benzyl-D-glucose **46** by employing known procedures.



Scheme 14. Synthesis of methyl 4,6-di-*O*-benzylidene-2,3-di-*O*-benzyl-D-glucopyranoside **44**



Scheme 15. Synthesis of monosaccharide acceptors **45** and **46**

1.2.1 Gold-catalysed Ferrier reaction

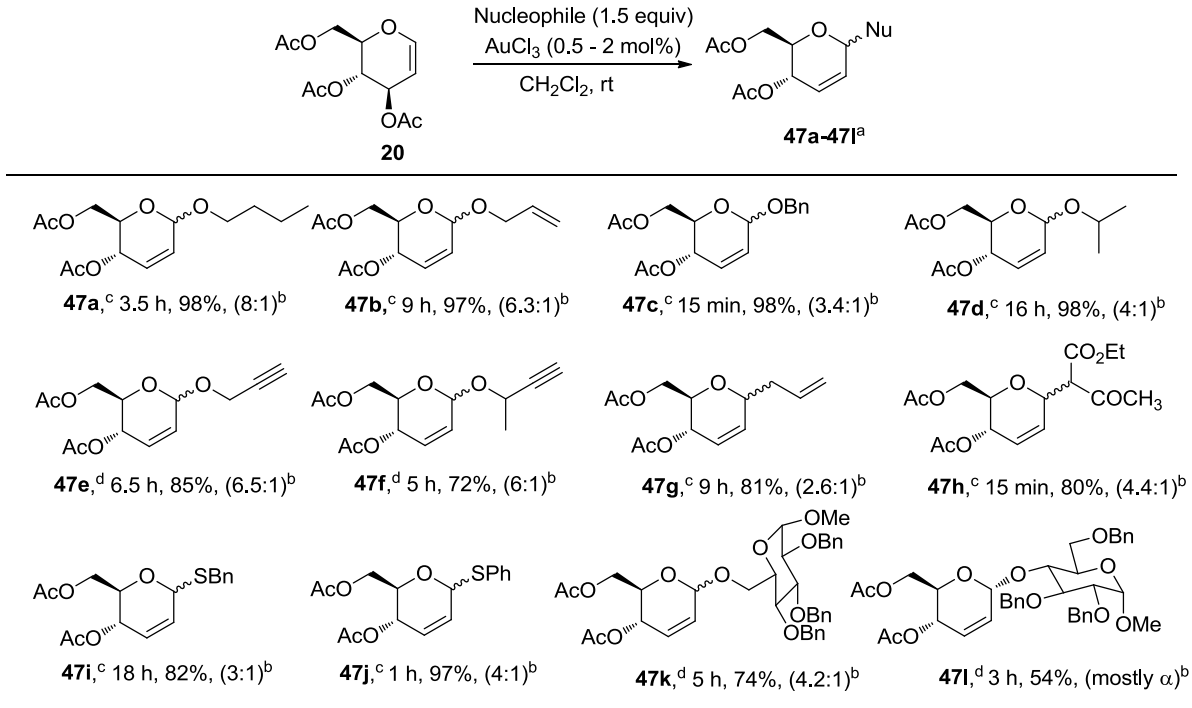
Gold-catalysed Ferrier reaction was studied by reacting 3,4,6-tri-*O*-acetyl-D-glucal **20** with different nucleophiles and the reaction scope was extended by reacting with sugar

acceptors (Scheme 16). The reaction occurred with catalytic amount of $AuCl_3$ (0.5-2 mol%) at room temperature. Several *O*-nucelophiles were employed in the reaction like primary alcohols such as *n*-butyl, benzyl and allyl alcohol and secondary alcohols like isopropyl alcohol (Scheme 16, **47a-47d**). Substrates with a carbon-carbon triple bond like propargyl alcohol and 3-butyn-2-ol needed 2 mol% of the catalyst for complete conversion (Scheme 16, **47e** and **47f**). The reason might be the coordination of gold to the triple bond makes it unavailable for glycal activation. Interestingly, allyltrimethyl silane and even active methylene compound such as ethyl acetoacetate smoothly reacted to give a mixture of anomeric *C*-glucosides with slightly less α-selectivity (Scheme 16, **47g** and **47h**). *S*-nucleophiles like benzyl mercaptan and thiophenol worked well to give corresponding *S*-glucosides as a mixture of anomers (Scheme 16, **47i** and **47j**). 1-Methoxy-2,3,4-tri-*O*-benzylglucopyranose **45** and 1-Methoxy-2,3,6-tri-*O*-benzylglucopyranose **46** were employed as glycosyl donors in Ferrier reaction. We were delighted to observe that 4-hydroxy and 6-hydroxy sugars also reacted and resulted in respective disaccharides with good yields. 6-Hydroxy free sugar **45** resulted in 4.2:1 anomeric ratio of disaccharide **47k** and 4-hydroxy sugar **46** resulted in disaccharide **47l** as α-anomer exclusively. Most of the products were formed predominantly as α-anomer. The α/β ratios were determined from the integrations of the C-1 protons in ^{1}H NMR spectrum of the mixture.

Then, we attempted Ferrier reaction on 3,4,6-tri-*O*-acetyl-D-galactal **40** under the same reaction conditions used for glucal **20**. When compared with the reactions of glucal, reactions of galactal were sluggish with nucleophiles and less efficient in terms of catalyst loading, reaction time and yields (Scheme 17). Most of the reactions were performed with 2 mol% of $AuCl_3$ and a wide variety of nucleophiles were employed in the reaction to get corresponding galactosides **48a-48h**. Initially, oxygen nucleophiles like *n*-butanol, allyl alcohol, benzyl alcohol were reacted with 3,4,6-tri-*O*-acetyl-D-galactal **40** under optimized conditions to get galactosides **48a-48c** in moderate yields and good α-selectivity. Like in the case of Ferrier reaction with 3,4,6-tri-*O*-acetyl-D-glucal **20**, propargyl alcohol reacted sluggishly with **40** as well and resulted in the product **48d** in low yield (31%) due to coordination of gold with the triple bond. The difference in reactivity of 3,4,6-tri-*O*-acetyl-D-glucal **20** and 3,4,6-tri-*O*-acetyl-D-galactal **40** in $AuCl_3$-catalysed Ferrier reaction was evaluated by doing a control experiment. A mixture of equimolar quantities of 3,4,6-tri-*O*-

acetyl-D-glucal **20** and 3,4,6-tri-*O*-acetyl-D-galactal **40** were treated with 1 equiv of *n*-butanol in dry CH_2Cl_2 containing 1 mol% of $AuCl_3$ for 3 hours. Analyzing the ^1H NMR spectra of the product mixture revealed that the corresponding Ferrier products of glucal **47a** and galactal **48a** were in the ratio of 3:2 respectively (Scheme 18). This result suggests that glucal is more reactive than galactal. Monosaccharide nucleophiles also reacted smoothly with galactal to give disaccharides (**48g** and **48h**) in moderate yields and with α-selectivity. As compared with selectivities in 3,4,6-tri-*O*-acetyl-D-glucal **25** case, galactal substrate furnished almost all the products **48a**-**48h** in better α-selectivity.

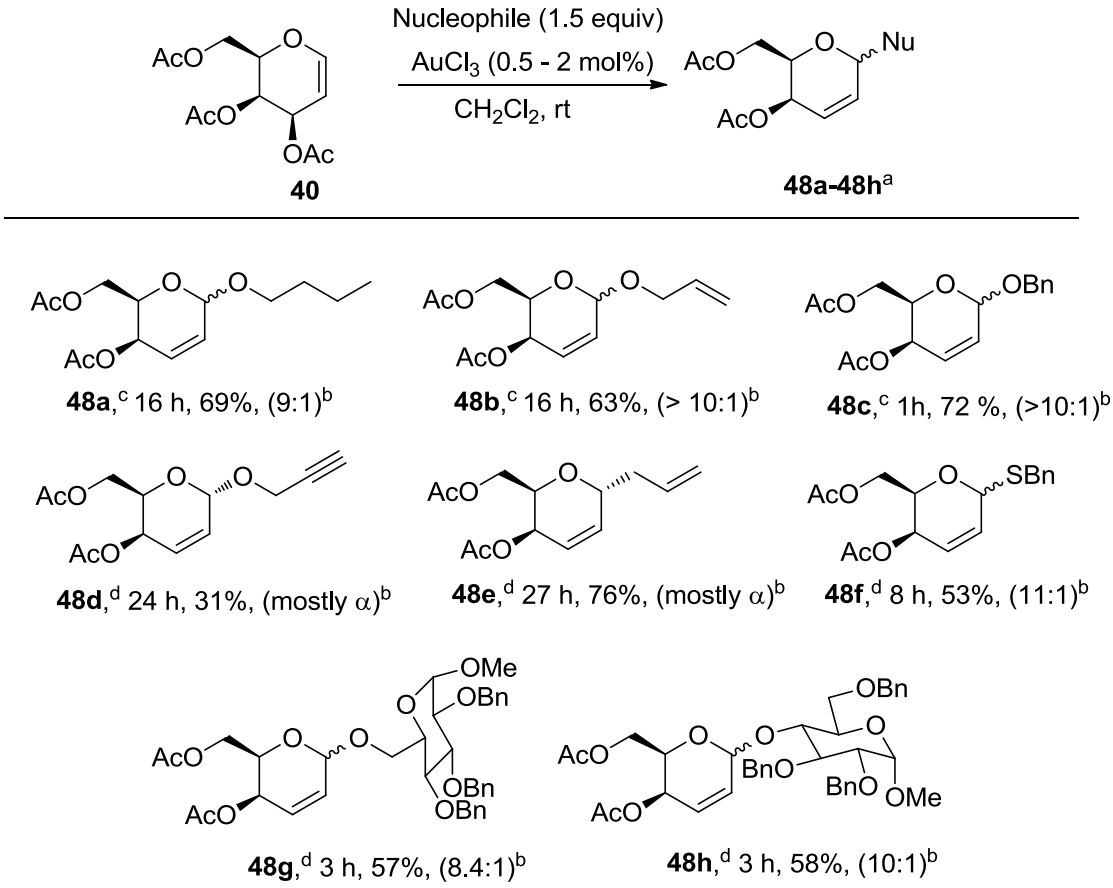
Scheme 16. Results of gold-catalysed synthesis of 2,3-unsaturated glycosides **47a-47l**



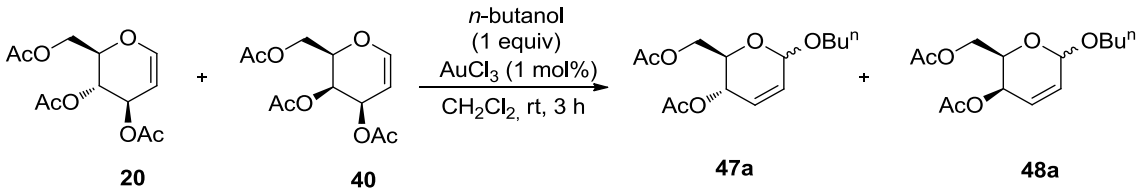
[a]Isolated yields. [b]Values in the parentheses represent α/β ratio determined by the integration of the corresponding anomeric protons in the ^1H NMR spectrum. [c]0.5 mol% of the catalyst was used. [d]2 mol% of the catalyst was used.

Ferrier reaction on 3,4-di-*O*-acetyl-L-rhamnal **41** was performed with *O*-nucleophiles like *n*-butanol, benzyl alcohol and propargyl alcohol, which resulted in 2,3-unsaturated rhamnosides **49a**-**49c** in good yields with α-selectivity. *S*- and *C*-nucleophiles were also employed in the reaction to get corresponding 4-acetyl-2,3-unsaturated rhamnosides **49d** & **49e** with better α-selectivity (Scheme 19).

Scheme 17. Gold-catalysed synthesis of 2,3-unsaturated galactosides **48a-48h**



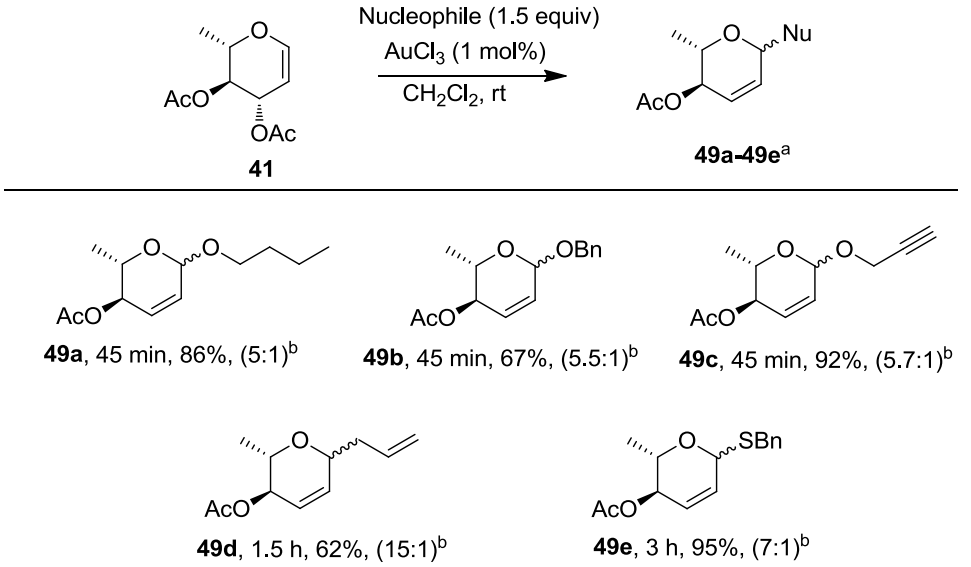
[a]Isolated yields. [b]Values in the parantheses represent α/β ratio determined by the integration of the corresponding anomeric protons in the ^{1}H NMR spectrum. [c]0.5 mol% of the catalyst was used. [d]2 mol% of the catalyst was used.



Scheme 18. Competitive glycosylation of 3,4,6-tri-*O*-acetyl-D-glucal **20** and 3,4,6-tri-*O*-acetyl-D-galactal **40**

The above results show the efficiency of $AuCl_3$ in Ferrier reaction with diverse variety of *O*-, *S*- and *C*- nucleophiles to furnish the 2,3-unsaturated glycosides. Very low catalytic loading is sufficient to get good yields of the products and the reaction gave products with α-selectivity.

Scheme 19. Results of gold-catalysed synthesis of 2,3-unsaturated rhamnosides **49a-49e**



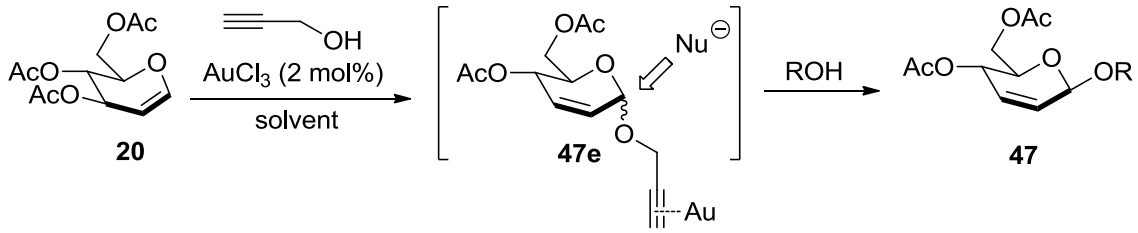
[a]Isolated yields. [b]Values in the parentheses represent α/β ratio determined by the integration of the corresponding anomeric protons in the ^{1}H NMR spectrum.

1.2.2 Gold-catalysed transglycosylation

Having achieved facile α-selective Ferrier reaction under gold catalysis, we wished to utilize the alkynophilicity of gold catalyst to attempt making β-glycosides. Making β-glycosides by Ferrier reaction is a challenging task due to anomeric effect exerted by the ring oxygen. There is only one report in the literature to make β-selective Ferrier reaction.[46] Our interest has been in the synthesis of β-glycosides from our Ferrier reaction.

Hotha and co-workers reported the gold(III)-catalysed glycosylation reaction by utilizing the leaving group ability of propargyloxy group upon activation by gold.[48] With their methodology, most of the products were obtained as a mixture of anomers with moderate β-selectivity. We hypothesized to make β-glycosides by first doing Ferrier reaction on 3,4,6-tri-*O*-acetyl-D-glucal **20** with propargyl alcohol to get α-anomer of propargyl 2,3-unsaturated glucoside **47e** and react it with other nucleophiles. It was anticipated that the α-propargyl glycoside under the activation by gold(III) conditions might give β-glycosides by a S_N2 displacement. With this idea we carried out the reaction in the following way.

$AuCl_3$-catalysed one-pot propargylation and subsequent glycosylation



Scheme 20. Gold-catalysed one pot Ferrier reaction and transglycosylation reaction

A mixture of 3,4,6-tri-*O*-acetyl-D-glucal **20** and propargyl alcohol (1.5 equiv) was treated with gold(III) chloride (2 mol%) at room temperature in different solvents. Except in DMF, Ferrier reaction worked in CH_2Cl_2, dioxane, THF, CH_3CN solvents. The results are shown on Table 1. The α/β ratio of propargyl glycoside **47e** formed in these reactions is in the range of 6:1. After completion of Ferrier reaction which took around 6 h, *n*-butanol (1.5 equiv) was added and the reaction was continued. In dichloromethane no glycosylation was noticed even after reflux. However the reaction occurred in CH_3CN under reflux condition to give butyloxy Ferrier product. The α/β ratio was found to be reduced to 5:1 (entry 2, table 1) which was 8:1 in the direct Ferrier reaction (Scheme 16).

Although the change in selectivity is marginal it encouraged us to attempt the reactions using $AgSbF_6$ and AgOTf as additives which will generate cationic Au species to activate the triple bond better. The reaction proceeded at room temperature, but the formation of β-isomer did not improve. Similar results were observed when benzyl alcohol was used as nucleophile (entries 11 and 12). From these results it is clear that there is no sign of S_N2 attack. Further it indicates that the activation of the propargyloxy group by $AuCl_3$ generates the oxocarbenium ion. The anomeric effect of the ring oxygen and the conformation of the ring favors the α-attack. Coordination of acetonitrile to the oxocarbenium ion from α- face to favor the β-attack of the nucleophile is also negligible. This result is in agreement with the results of reported Ferrier reactions catalysed by Lewis acids in acetonitrile solvent. Hence we wished to reduce the participation of ring oxygen to anomeric effect.

Table 1. Results of $AuCl_3$-catalysed one pot propargylation and subsequent glycosylation

Entry	ROH	Solvent and condition	**47**	Yield[a] (%)	α:β[b]
1	*n*-BuOH	CH_2Cl_2/reflux, 27 h	**47e**	80	6.4:1
2	*n*-BuOH	CH_3CN/reflux, 24 h	**47a**	50	5:1
3	*n*-BuOH	CH_3CN/rt, 22 h[c]	**47a**	68	7.6:1
4	*n*-BuOH	CH_3CN/rt, 22 h[d]	**47a**	66	7.4:1
5	*n*-BuOH	Dioxane/rt, 27 h	**47a**	61	5.5:1
6	*n*-BuOH	THF/rt, 21 h	**47a**	53	7:1
7	-	DMF/rt, 24 h	-	NR	-
8	*n*-BuOH	CH_3CN/rt, 24 h[e]	**47a**	41	6.2:1
9	-	CH_3CN/rt, 24 h[c,f]	-	NR	-
10	*n*-BuOH	*n*-BuOH/rt, 24 h[g]	**47a**	60	3:1
11	BnOH	CH_3CN/rt, 25 h[c]	**47c**	64	3.1:1
12	BnOH	CH_3CN/rt, 28 h[d]	**47c**	73	3.1:1

[a]Isolated yields. [b]Ratio was based on the integration of the corresponding anomeric protons in the ^{1}H NMR spectrum. [c]6 mol% of $AgSbF_6$ was used in addition. [d]6 mol% of AgOTf was used in addition. [e]2 equiv of $LiClO_4$ was used in addition. [f]20 mol% of PPh_3 was used in addition. [g]propargyl glycoside was taken directly for transglycosylation.

Since lithium is oxophilic, we believed that addition of 2 equivalents of $LiClO_4$ with respect to the amount of 3,4,6-tri-*O*-acetyl-D-glucal **20** would block the ring oxygen to participate in resonance. However it did not help in preventing the ring oxygen participation and α:β ratio of 6.2:1 was observed (entry 8). This may be due to the presence of many oxygen sites in the substrate for lithium ion coordination. It has to be mentioned that some amount (< 20%) of propargylated Ferrier product **47a** was also isolated from all the reactions except the reactions involving co-catalysts AgOTf/$AgSbF_6$. We then thought of sterically blocking the α-face of the gold-coordinated oxocarbenium species by coordinating gold with bulky ligands such as PPh_3. Lee *et al.* applied this strategy in the preparation of β-Ferrier

product using palladium catalyst (DTBPP).[46] However, in the presence of PPh_3 even the Ferrier reaction on 3,4,6-tri-*O*-acetyl-D-glucal **20** did not occur (entry 9). Then, we attempted the transglycosylation with *n*-butanol by taking it as solvent. Interestingly, α-selectivity decreased to 3:1.

With glycosyl acceptors 1-methoxy-2,3,4-tri-*O*-benzylglucopyranose **45** and 1-methoxy-2,3,6-tri-*O*-benzylglucopyranose **46**, the transglycosylation reaction with 3,4,6-tri-*O*-acetyl-D-glucal **20** did not occur. The transglycosylation reaction with 3,4,6-tri-*O*-acetyl-D-galactal **40** were not attempted as the Ferrier reaction with propargyl alcohol itself resulted in poor yield (Scheme 17).

1.2.3 Gold-catalysed enyne cyclizations

Gold catalysts are efficient for the cycloisomerisation reactions of enynes.[49] The Ferrier product of propargyl alcohol and 3,4,6-tri-*O*-acetyl-D-glucal **20** is an enyne system. In this regard we expected the corresponding cycloisomerisation product, a fused bicyclic system. However we got the Ferrier product only and did not observe any cycloisomerisation of the Ferrier product. Our attempt to cycloisomerise the above Ferrier product using $Ph_3PAuCl/AgSbF_6$ gave a complex mixture of products.

1.3 Conclusions

Gold-catalysed Ferrier reaction on 3,4,6-tri-*O*-acetyl-D-glucal **20**, 3,4,6-tri-*O*-acetyl-D-galactal **40** and 3,4-di-*O*-acetyl-L-rhamnal **41** was evaluated. The reaction just needs truly catalytic amount (0.5-2 mol%) of $AuCl_3$ to activate the substrates. A wide variety of nucleophiles such as *O*-, *S*- and *C*-nucleophiles have been employed and even monosaccharide building blocks like 1-methoxy-2,3,4-tri-*O*-benzylglucopyranose **45** and 1-methoxy-2,3,6-tri-*O*-benzylglucopyranose **46** were smoothly reacted to furnish corresponding disaccharides in moderate yields and with α-selectivity. Leaving group ability of propargyloxy group has been utilized to evaluate the synthesis of 2,3-unsaturated β-glycosides. With the anticipation of attack on preformed α-propargyl glycoside **47e** (α:β = 6.5:1) obtained in gold-catalysed Ferrier reaction, it was treated with other nucleophiles like *n*-butanol and benzyl alcohol to make β-glycosides. Additives such as $LiClO_4$, PPh_3 have

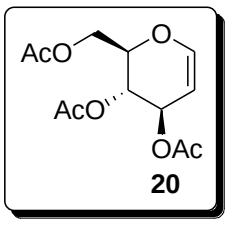
been used in the reaction to curtail the anomeric ring oxygen participation and to block the α-face of the oxocarbenium ion formed respectively. However, β-Ferrier products could not be obtained. But, the α-selectivity reduced moderately.

1.4 Experimental Section

General Information

All reagents were obtained commercially and used without further purification unless otherwise mentioned. Dichloromethane was freshly distilled over anhydrous CaH_2. Acetonitrile was distilled over CaH_2 and stored under argon atmosphere. Thin-layer chromatography was performed by using Merck silica gel F-254 coated aluminum plates and the visualization of spots were done using UV illumination and charring the TLC plates sprayed with Seebach solution or 5% H_2SO_4 solution in methanol. Column chromatography was performed over silica gel procured from Merck, using hexanes and ethyl acetate mixture as eluent. Solvents were removed under reduced pressure using rotovap. Dextrose, galactose were purchased from Merck and L-rhamnose was purchased from SISCO chemical company, India. $AuCl_3$ used in the reaction was purchased from Sigma-Aldrich. IR spectra were recorded using JASCO FT-IR spectrophotometer model 5300. The ^1H NMR spectra were recorded in a Bruker Avance 400 MHz NMR machine using solutions in $CDCl_3$ containing TMS as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ solvent with reference to central line of $CDCl_3$ peak. Elemental (C, H, N) analysis were done using Thermo Finnigan Flash EA 1112 analyzer. Optical rotations were measured using an AUTOPOL-II automatic polarimeter (readabllity ± 0.01°).

Preparation of 3,4,6-tri-*O*-acetyl-D-glucal 20 from Dextrose[50]



20

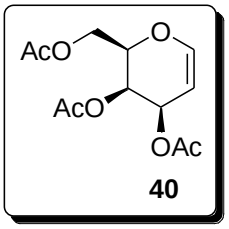
To a rb flask containing D-glucose (5.0 g, 27.8 mmol) in acetic anhydride (17.0 mL, 166 mmol) was added 31% HBr/AcOH (7.5 mL) at room temperature. The reaction mixture was stirred for 4 h during which time the suspended solid dissolved completely. This solution was then treated with an additional 22 mL of 31% HBr/AcOH and the reaction mixture was stirred overnight. Anhydrous NaOAc (9.2 g, 111 mmol) was added to neutralize the excess HBr in AcOH, and this mixture was added to a suspension of pulverized

$CuSO_4.5H_2O$ (1.5 g, 6 mmol) and Zn (29 g, 442 mmol) in a solution of water (20 mL) and AcOH (30 mL) containing NaOAc (5 g, 61 mmol). The resulting reaction mixture was stirred vigorously for 5 h. The solid was then removed by filtration and washed first with dichloromethane (50 mL) and then with ice-cold water (50 mL). The filtrate was extracted and the organic layer was washed with cold water (3 x 50 mL). The combined organic layers of the filtrate were washed with 50 mL of saturated aqueous $NaHCO_3$ (3 times) then with brine (50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purified by column chromatography to provide 3,4,6-tri-*O*-acetyl-D-glucal (3.0 g) **20** as a gummy liquid.

20: Yield: 40%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.47 (d, *J* = 6.1 Hz, 1H), 5.34 (t, *J* = 4.9 Hz, 1H), 5.23 (m, 1H), 4.85 (dd, *J* = 6.1, 3.3 Hz, 1H), 4.4 (dd, *J* = 12.0, 5.7 Hz, 1H), 4.28-4.24 (m, 1H), 4.22-4.18 (m, 1H), 2.10 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H).

Preparation of 3,4,6-tri-*O*-acetyl-D-galactal 40 from D-galactose[51]

3,4,6-tri-*O*-acetyl-D-galactal **40** was prepared from galactose (5 g, 27.8 mmol) following the protocol mentioned for the preparation of 3,4,6-tri-*O*-acetyl-D-glucal **20**.

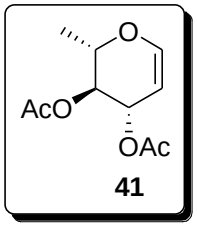


40

Gummy liquid, 5.2 g, Yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (d, *J* = 6.0 Hz, 1H), 5.57-5.54 (m, 1H), 5.44-5.42 (m, 1H), 4.74-4.72 (m, 1H), 4.34-4.20 (m, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H).

Preparation of 3,4-di-*O*-acetyl-L-rhamnal 41 from L-rhamnose:[52]

3,4-di-*O*-acetyl-L-rhamnal **41** was prepared from rhamnose (3.3 g, 20 mmol) using the procedure mentioned for 3,4,6-tri-*O*-acetyl-D-glucal **20**.

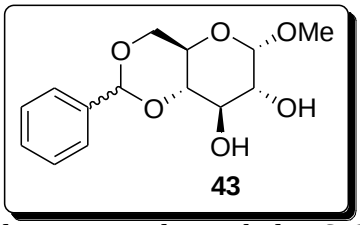


41

Gummy liquid, 3.1 g, Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (d, *J* = 5.5 Hz, 1H), 5.34 (m, 1H), 5.03 (m, 1H), 4.82-4.77 (m, 1H), 4.16-4.07 (m, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 3H).

Preparation of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside 43[53a]

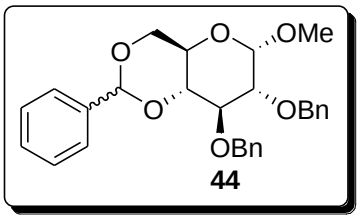
To a solution of methyl glucoside (1 g, 5.15 mmol) in dry CH_3CN (10 mL), benzaldehyde dimethylacetal (1.2 mL, 5.67 mmol) was added at room temperature. To this iodine (130 mg, 0.51 mmol) was added portions wise. The reaction mixture was stirred at rt. Progress of the reaction was monitored by TLC and after completion, the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with hypo solution to remove iodine and concentrated to get crude methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **43** (0.9 g, 62%) as white solid and it was directly used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.38-7.35 (m, 3H), 5.53 (s, 1H), 4.81 (d, *J* = 3.7 Hz, 1H), 4.29 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.93 (t, *J* = 9.5 Hz, 1H), 3.78 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.80-3.72 (m, 1H), 3.64 (td, *J* = 8.8, 3.6 Hz, 1H), 3.50 (m, 1H), 3.47 (s, 3H), 2.66 (br s, 1H), 2.24 (d, *J* = 2.2 Hz, 1H).



43

Preparation of methyl-4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside 44[53b]

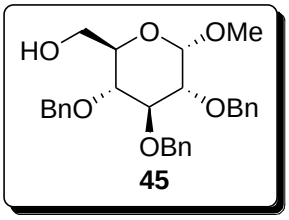
To a solution of methyl-4,6-*O*-benzylidene-α-D-glucopyranoside **43** (0.9 g, 3.19 mmol) in dry DMF (16 mL), NaH (60% dispersion in mineral oil) (0.345 g, 14.36 mmol) was added portion wise at 0 °C. After 25 min, benzyl bromide (1.9 g, 11.16 mmol) was introduced into the reaction. The reaction mixture was heated at 90 °C for 16 h. After completion of the reaction as judged by TLC, the reaction mixture was poured into water (50 mL) and it was washed with ethyl acetate (50 mL). The organic layer was washed with water (3 times) to remove DMF. The organic layer was concentrated and purified by column chromatography (ethyl acetate/hexanes = 1:5) to get methyl-4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside **44** (0.83 g, 56%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.41-7.26 (m, 13H), 5.55 (s, 1H), 4.91 (d, *J* = 11.3 Hz, 1H), 4.86 (d, *J* = 12.1 Hz, 1H), 4.84 (d, *J* = 11.1 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 3.7 Hz, 1H), 4.27 (dd, *J* = 10.1 Hz, 4.8 Hz, 1H), 4.05 (t, *J* = 9.4 Hz, 1H), 3.86-3.78 (m, 1H), 3.73-3.68 (m, 1H), 3.60 (t, *J* = 9.4 Hz, 1H), 3.58-3.54 (m, 1H), 3.40 (s, 3H).



44

Preparation of 1-methoxy-2,3,4-tri-*O*-benzyl-α-D-glucopyranose 45[53c]

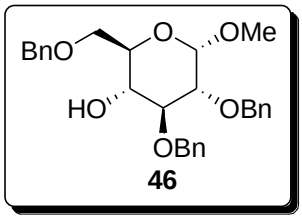
To a suspension of lithium aluminium hydride (40 mg, 1 equiv) in dichloromethane and diethyl ether (20 mL), compound **44** (0.5 g, 1.06 mmol) was added. The resulting suspension was stirred vigorously and an ethereal solution of aluminum trichloride (0.142 g, 1.06 mmol) was added (final ratio of dichloromethane and ether was 1:3 v/v). The reaction mixture was kept under reflux conditions under nitrogen atmosphere for 5 h. After completion of the reaction, It was quenched by adding cold water and the ether layer was separated. The aqueous phase was extracted several times with ether and once with chloroform. The combined organic layers were dried over K_2CO_3 and concentrated to afford required 1-methoxy-2,3,4-tri-*O*-benzylglucopyranose **45 (**0.36 g, 72%) as denser liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 15H), 4.99 (d, *J* = 11.1 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.82 (m, 2H), 4.65 (m, 2H), 4.56 (d, *J* = 3.5 Hz, 1H), 4.00 (t, *J* = 9.3 Hz, 1H), 3.79-3.74 (m, 1H), 3.71-3.62 (m, 2H), 3.53 (d, *J* = 9.7 Hz, 1H), 3.49 (dd, *J* = 5.9, 3.8 Hz, 1H), 3.36 (s, 3H).



45

Preparation of 1-methoxy-2,3,6-tri-*O*-benzyl-α-D-glucopyranose 46[54]

To a solution of compound **44** (0.83 g, 1.79 mmol) and triethylsilane (1.43 mL, 8.96 mmol) in dry dichloromethane (8 mL) at 0 °C, trifluoroacetic acid (0.67 mL, 8.96 mmol) was added dropwise. When addition was complete, the reaction was warmed to room temperature until starting material was consumed (4 h). The reaction mixture was diluted with ethyl acetate and washed with $NaHCO_3$ solution, brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by column chromatography to get 4-hydroxy sugar **46** (0.51 g, 62%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 15H), 5.00 (d, *J* = 11.3 Hz, 1H), 4.74 (t, *J* = 12.4 Hz. 1H), 4.67-4.60 (m, 2H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 3.78 (t, *J* = 9.3 Hz, 1H), 3.72-3.66 (m, 4H), 3.59 (t, *J* = 3.6 Hz, 1H), 3.53 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.38 (s, 3H), 2.33 (br s, 1H).



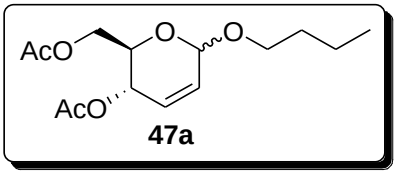
46

General procedure for the synthesis of 2,3-unsaturated glycosides

To a solution of 3,4,6-tri-*O*-acetyl-D-glucal **20**/3,4,6-tri-*O*-acetyl-D-galactal **40**/3,4-di-*O*-acetyl-L-rhamnal **41** (1 equiv) and acceptor (1.2 equiv) in anhydrous CH_2Cl_2 (3 mL/mmol), $AuCl_3$ (0.5 - 2 mol%) was added. The reaction was stirred at room temperature. After complete consumption of the starting glycal as judged by TLC, solvent was evaporated and the residue was loaded on a silica gel column. The product was purified using EtOAc/hexanes as eluent system.

Characterisation data for 2,3-unsaturated glucosides

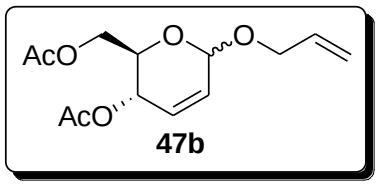
***n*-Butyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranoside 47a**[29]



47a

Oily liquid; Yield: 98%; α:β = 8:1; $[\alpha]_D^{25}$ = +87.748 (c, 1.0, $CHCl_3$); IR (neat, cm^{-1}): 2961, 2872, 1745, 1660, 1371, 1230, 1041; ^1H NMR (400 MHz, $CDCl_3$): δ 5.89-5.81 (m, 2H), 5.30 (dd, *J* = 9.6, 1.3 Hz, 1H), 5.02 (br s, 1H), 4.27-4.16 (m, 2H), 4.13-4.08 (m, 1H), 3.81-3.75 (m, 1H), 3.54-3.49 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.66-1.53 (m, 2H), 1.46-1.33 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.1, 128.8, 127.8, 94.2, 68.5, 66.7, 65.2, 62.9, 31.6, 20.8, 20.6, 19.2, 13.6; [Found: C, 58.65; H, 7.78. $C_{14}H_{22}O_6$ requires C, 58.73; H, 7.74%].

Allyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranoside 47b[28]

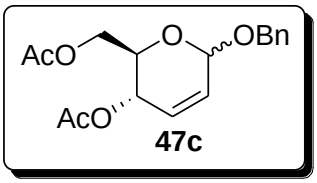


47b

Crystalline solid; mp: 40 °C - 42 °C; Yield: 97%; α:β = 6.3:1; $[\alpha]_D^{25}$ = +113.10 (c, 1.3, $CHCl_3$); IR (KBr, cm^{-1}): 3468, 2918, 1745, 1645, 1433, 1371, 1230, 1039; ^1H NMR (400 MHz, $CDCl_3$): δ 5.98-5.83 (m, 3H), 5.32-5.28 (m, 2H), 5.22 (m, 1H), 5.07 (br s, 1H), 4.28-4.19 (m, 5H), 2.09 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.0, 134.0, 129.1, 127.6, 117.3, 93.5, 69.1, 66.8, 65.1, 62.8, 20.8, 20.6; [Found: C, 57.85; H, 6.68. $C_{13}H_{18}O_6$ requires C, 57.77; H, 6.71%].

Benzyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranoside 47c[24]

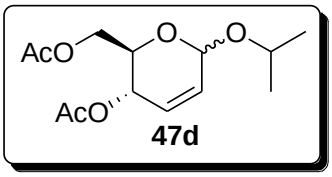
Viscous liquid; Yield: 98%; α:β = 3.4:1; $[\alpha]_D^{25}$ = +75.101 (c, 1.0, $CHCl_3$); IR (neat, cm^{-1}): 2924, 1745, 1657, 1493, 1450, 1373, 1232, 1041, 698; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 5.90-5.83 (m, 2H), 5.33 (d, *J* = 9.6 Hz, 1H), 5.12 (br s, 1H), 4.80 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.30-4.10 (m, 3H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.2, 137.5, 129.2, 128.4, 128.0, 127.8, 127.7, 93.6, 70.2, 67.0, 65.2, 62.9, 20.9, 20.7; [Found: C, 63.81; H, 6.26. $C_{17}H_{20}O_6$ requires C, 63.74; H, 6.29%].



47c

Isopropyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranoside 47d[29]

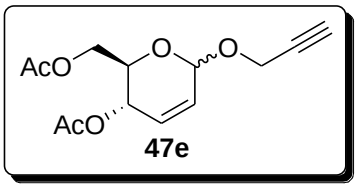
Oily liquid; Yield: 98%; α:β = 4:1; $[\alpha]_D^{25}$ = +121.52 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1})**:** 2972, 2930, 1745, 1371, 1236, 1035; ^1H NMR (400 MHz, $CDCl_3$): δ 5.87 (d, *J* = 10.4 Hz, 1H), 5.80 (dt, *J* = 10.4, 2.1 Hz, 1H), 5.29 (dd, *J* = 9.6, 1.3 Hz, 1H), 5.13 (br s, 1H), 4.26-4.12 (m, 3H), 4.03-3.94 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.3, 128.7, 128.4, 92.8, 70.7, 66.7, 65.4, 63.1, 23.4, 21.9, 20.9, 20.7; [Found: C, 57.28; H, 7.45. $C_{13}H_{20}O_6$ requires C, 57.34; H, 7.40%].



47d

2'-Propyn-1'-yl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranoside 47e[24]

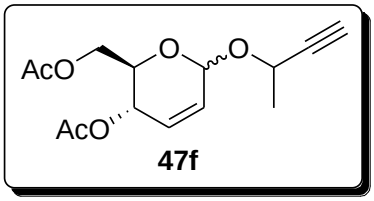
White solid; mp: 56 °C - 58 °C; Yield: 85%; α:β = 6.5:1; $[\alpha]_D^{25}$ = +105.51 (c, 1.0, $CHCl_3$); IR (KBr, cm^{-1}): 3275, 2935, 2112, 1747, 1662, 1454, 1373, 1236, 1041; ^1H NMR (400 MHz, $CDCl_3$): δ 5.92 (d, *J* = 10.2 Hz, 1H), 5.84 (ddd, *J* = 10.2, 2.7, 1.9 Hz, 1H), 5.34 (m, 1H), 5.24 (br s, 1H), 4.31 (d, *J* = 2.3 Hz, 2H), 4.27-4.22 (m, 1H), 4.20-4.17 (m, 1H), 4.11-4.07 (m, 1H), 2.47 (t, *J* = 2.3 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.2, 129.8, 127.2, 92.8, 79.1, 74.8, 67.2, 65.2, 62.8, 55.0, 20.9, 20.8; [Found: C, 58.25; H, 6.06. $C_{13}H_{16}O_6$ requires C, 58.20; H, 6.01%].



47e

1'-Methylprop-2'-yn-1'-yl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranoside 47f[55]

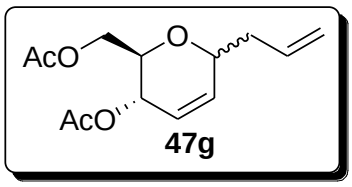
Viscous liquid; Yield: 72%; α:β = 6:1; $[\alpha]_D^{25}$ = +121.52 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1}): 3277, 2924, 2119, 1745, 1373, 1230, 1039, 912, 731; ^1H NMR (400 MHz, $CDCl_3$): δ 5.88-5.75 (m, 2H), 5.34 (br s, 1H), 5.28 (d, *J* = 12.0 Hz, 1H), 4.53 (dq, *J* = 6.6, 1.7 Hz, 1H), 4.23-4.13 (m, 2H), 4.06-4.00 (m, 1H), 2.42 (br s, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 1.44 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.2, 129.4, 127.7, 91.7, 82.9, 73.6, 67.2, 65.3, 63.0, 62.0, 22.0, 20.9, 20.7; [Found: C, 59.68, H, 6.46. $C_{14}H_{18}O_6$ requires C, 59.57, H, 6.43].



47f

C-Allyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranoside 47g[25a]

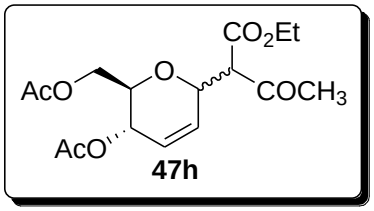
Colorless viscous liquid; Yield: 81%; α:β = 2.6:1; $[\alpha]_D^{25}$ = +71.808 (c, 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 2935, 1744, 1643, 1435, 1371, 1232, 1047, 914, 729; ^1H NMR (400 MHz, $CDCl_3$): δ 5.94 (ddd, *J* = 10.4, 2.4, 1.5 Hz, 1H), 5.88-5.78 (m, 2H), 5.16-5.10 (m, 3H), 4.28 (ddd, *J* = 7.8, 5.6, 2.3 Hz, 1H), 4.22 (dd, *J* = 11.8, 6.5 Hz, 1H), 4.15 (dd, *J* = 11.8, 3.4 Hz, 1H), 3.96 (td, *J* = 6.4, 3.4 Hz, 1H), 2.50-2.30 (m, 2H), 2.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.5, 134.0, 132.9, 123.7, 117.6, 71.4, 69.8, 65.0, 62.9, 37.9, 21.1, 20.8; [Found: C, 61.48, H, 7.11, $C_{13}H_{18}O_5$ requires C, 61.40, H, 7.14].



47g

2-*C*-(4,6-Di-*O*-acetyl-2,3-dideoxy-*erythro*-hex-2-eno-α/β-D-pyranosyl)ethyl-3-ketobutanoate 47h[45]

Pale yellow viscous liquid; Yield: 80%; α:β = 4.4:1; $[\alpha]_D^{25}$ = +31.854 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1}): 2986, 2932, 2137, 1751, 1714, 1601, 1437, 1371, 731; ^1H NMR (400 MHz, $CDCl_3$): δ 6.06 (m, 1H), 5.89-5.82 (m, 1H), 5.17-5.12 (m, 1H), 4.89 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.31-4.10 (m, 4H), 3.95-3.77 (m, 2H), 2.31 (s, 3H), 2.08 (s, 6H), 1.30 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 170.7,

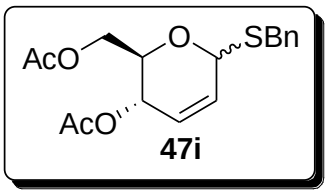


47h

170.1, 166.7, 130.0, 125.6, 70.3, 70.2, 64.4, 64.6, 62.6, 61.7, 20.9, 20.6, 13.9 (2C); [Found: C, 56.21; H, 6.45. $C_{16}H_{22}O_8$ requires C, 56.13; H, 6.48%].

Benzyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio-α/β-D-*erythro*-hex-2-enopyranoside 47i

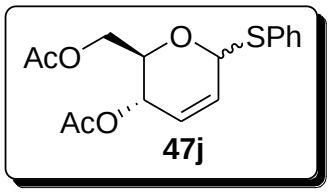
Viscous liquid; Yield: 82%; α:β = 3:1; $[\alpha]_D^{25}$ = +218.26 (c, 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3034, 2922, 1743, 1456, 1373, 1236, 1047, 702; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 5H), 5.86-5.76 (m, 2H), 5.40-5.35 (m, 1H), 5.30-5.24 (m, 1H), 4.36-4.31 (m, 1H), 4.30-4.20 (m, 1H), 4.12 (dd, *J* = 12.0, 2.1 Hz, 1H), 3.90 (d, *J* = 13.4 Hz, 1H), 3.78 (d, *J* = 13.4 Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.3, 137.9, 129.0, 128.7, 128.6, 128.5, 127.3, 127.2, 78.8, 67.0, 65.3, 63.0, 35.6, 21.0, 20.9; [Found: C, 60.64; 6.05. $C_{17}H_{20}O_5S$ requires C, 60.70; H, 5.99%].



47i

Phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio-α/β-D-*erythro*-hex-2-enopyranoside 47j[56]

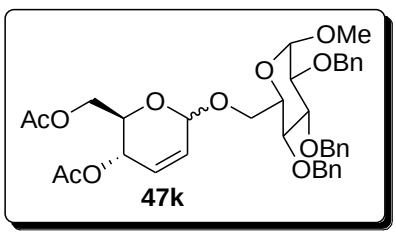
Colorless viscous liquid; Yield: 97%; α:β = 4:1; $[\alpha]_D^{25}$ = +160.27 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1}): 2945, 2359, 1745, 1645, 1581, 1371, 1236, 1055, 788; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.32-7.26 (m, 3H), 6.05 (ddd, *J* = 10.1, 2.8, 1.8 Hz, 1H), 5.86 (dt, *J* = 10.1, 1.8 Hz, 1H), 5.75 (br s, 1H), 5.37 (dd, *J* = 9.5, 1.8 Hz, 1H), 4.50-4.44 (m, 1H), 4.33-4.15 (m, 2H), 2.10 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.3, 132.6, 131.7, 128.9, 128.5, 127.6 (2C), 83.6, 67.3, 65.1, 63.0, 20.9, 20.7; [Found: C, 59.55; H, 5.66. $C_{16}H_{18}O_5S$ requires C, 59.61; H, 5.63%].



47j

Methyl 6-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*erythro*-hex-2-enopyranosyl)-2,3,4-tris-*O*-(phenylmethyl)-α-D-glucopyranoside 47k[57]

Viscous liquid; Yield: 74%; α:β = 4.2:1; $[\alpha]_D^{25}$ = +31.854 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1}): 3032, 2924, 1743, 1496, 1369, 1234, 1030, 910, 738; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 15H), 5.83 (m, 2H), 5.29 (d, *J* = 9.7 Hz, 1H), 5.10 (br s, 1H), 4.98 (d, *J* = 10.7 Hz, 1H), 4.92 (d, *J* = 11.1 Hz, 1H), 4.81-

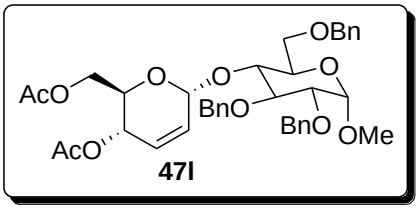


47k

4.77 (m, 2H), 4.67 (d, *J* = 12.2 Hz, 1H), 4.62-4.60 (m, 2H), 4.04-3.97 (m, 4H), 4.16 (dd, *J* = 12.2, 4.6 Hz, 1H), 3.76 (m, 1H), 3.71 (d, *J* = 11.2 Hz, 1H), 3.59-3.50 (m, 2H), 3.37 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.2, 138.7, 138.3, 138.1, 129.0, 128.5, 128.4, 128.1, 128.0, 127.7, 127.6, 127.4, 98.0, 94.8, 82.0, 79.9, 77.8, 75.7, 74.9, 73.3, 70.0. 67.0, 66.9, 62.7, 55.2, 21.0, 20.7; [Found: C, 67.51; H, 6.52 $C_{38}H_{44}O_{11}$ requires C, 67.44; H, 6.55%].

Methyl 6-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2,3,6-tris-*O*-(phenylmethyl)-α-D-glucopyranoside 47l[57]

Viscous liquid; Yield: 54% (mostly α); $[\alpha]_D^{25}$ = +41.863 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1}): 2928, 1745, 1454, 1371, 1238, 1047, 736, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 15H), 5.77 (d, *J* = 9.9 Hz, 1H), 5.50-5.45 (m, 2H), 5.20 (d, *J* = 9.6 Hz, 1H), 5.03 (d, *J* = 11.2 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 3.3 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.04 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.97-3.89 (m, 2H), 3.84 (t, *J* = 8.1 Hz, 1H), 3.78-3.75 (m, 2H), 3.65-3.58 (m, 2H), 3.52 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.41 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.0, 138.4, 138.2, 137.8, 128.8, 128.4, 128.3, 128.1, 127.9, 127.6, 127.5, 127.4, 127.3, 97.6, 95.5, 81.9, 80.1, 76.3, 75.5, 73.2, 73.0, 69.6, 69.4, 67.0, 64.8, 62.6, 55.1, 20.9, 20.7; [Found: C, 67.12; H, 6.32. $C_{38}H_{44}O_{11}$ requires C, 67.44; H, 6.55%].

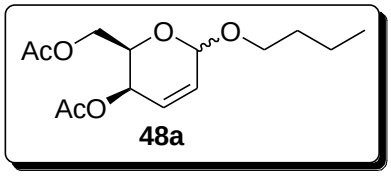


47l

Characterisation data for 2,3-unsaturated galactosides:

***n*-Butyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*threo*-hex-2-enopyranoside 48a**

Viscous liquid; Yield: 69%; α:β = 9:1; $[\alpha]_D^{25}$ = -144.65 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1}): 2959, 2876, 1745, 1371, 1230, 1105, 1045; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (dd, *J* = 10.0, 5.2 Hz, 1H), 6.03 (dd, *J* = 10.0, 2.8 Hz, 1H), 5.06 (d, *J* = 2.4 Hz, 1H), 5.02 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.37-4.34 (m, 1H), 4.27-4.18 (m, 2H), 3.82-3.76 (m, 1H), 3.54-3.48 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 1.64-1.54 (m, 2H), 1.44-1.33 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.3, 130.7, 124.9, 93.8, 68.2, 66.6,

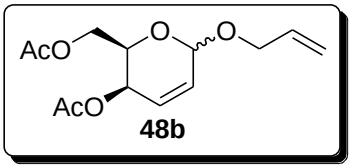


48a

62.9, 62.8, 31.6, 20.7, 20.7, 19.3, 13.7; [Found: C, 58.65; 7.78. $C_{14}H_{22}O_6$ requires C, 58.73; H, 7.74%].

Allyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*threo*-hex-2-enopyranoside 48b

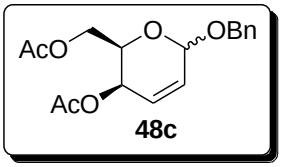
Yellow viscous liquid; Yield: 63%; α:β = >10:1; $[\alpha]_D^{25}$ = -69.879 (c, 1.0, $CHCl_3$); IR (neat, cm^{-1}): 2928, 1747, 1730, 1649, 1371, 1232, 1101, 1033; ^1H NMR (400 MHz, $CDCl_3$): δ 6.13 (dd, *J* = 10.0, 5.3 Hz, 1H), 6.04 (dd, *J* = 10.0, 2.9 Hz, 1H), 5.99-5.90 (m, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.21 (d, *J* = 10.1 Hz, 1H), 5.15-5.12 (m, 2H), 4.39-4.22 (m, 3H), 4.24-4.06 (m, 2H), 2.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.4, 134.0, 130.6, 125.3, 117.7, 93.1, 68.9, 66.8, 62.8 (2C), 20.8 (2C); [Found: C, 57.85; H, 6.65. $C_{13}H_{18}O_6$ requires C, 57.77; H, 6.71%].



48b

Benzyl 4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*threo*-hex-2-enopyranoside 48c[58]

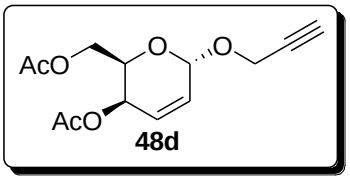
Yellow viscous oil; Yield: 72%; α:β = >10:1; $[\alpha]_D^{25}$ = -174.5 (c, 1.0, $CHCl_3$); IR (neat, cm^{-1}): 3032, 2928, 1743, 1454, 1371, 1228, 1101, 1022, 910, 740, 700; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 6.11 (dd, *J* = 5.3, 10.1 Hz, 1H), 6.03 (dd, *J* = 10.1, 2.9 Hz, 1H), 5.15 (d, *J* = 2.9 Hz, 1H), 5.02 (dd, *J* = 5.3, 2.9 Hz, 1H), 4.80 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.42-4.39 (m, 1H), 4.26-4.17 (m, 2H), 2.06 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.3, 137.4, 130.5, 128.4, 128.1, 127.9, 125.5, 92.9, 69.7, 66.9, 62.8 (2C), 21.0 (2C); [Found: C, 63.71; H, 6.31. $C_{13}H_{18}O_5$ requires C, 63.74; H, 6.29%].



48c

2'-Propyn-1'-yl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside 48d

Heavy liquid; Yield: 31% (mostly α); $[\alpha]_D^{25}$ = -107.9 (c, 0.5, $CHCl_3$); IR (neat, cm^{-1}): 2924, 2118, 1745, 1660, 1371, 1238, 1024; ^1H NMR (400 MHz, $CDCl_3$): δ 6.16 (dd, *J* = 10.0, 5.5 Hz, 1H), 6.04 (dd, *J* = 10.0, 2.9 Hz, 1H), 5.29 (d, *J* = 2.9 Hz, 1H), 5.03 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.35-4.31 (m, 3H), 4.23 (d, *J* = 6.2 Hz, 2H), 2.47

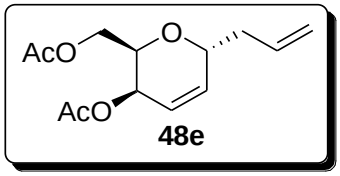


48d

(t, *J* = 2.3 Hz, 1H), 2.08 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.3, 130.1, 125.8, 92.1, 79.0, 74.9, 67.1, 62.6(2C), 54.6, 20.8(2C); [Found: C, 58.31; H, 6.06 $C_{13}H_{16}O_6$ requires C, 58.20; H, 6.01%].

Allyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside 48e[25a]

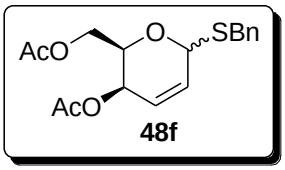
Colorless viscous liquid; Yield: 76% (mostly α); $[\alpha]_D^{25}$ = -280.8 (c, 1.0, $CHCl_3$); IR (neat, cm^{-1}): 2976, 2934, 1739, 1641, 1371, 1230, 1045, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (dd, *J* = 10.3, 2.7 Hz, 1H), 5.98 (dd, *J* = 10.3, 5.1 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.16-5.10 (m, 2H), 5.07 (dd, *J* = 4.7, 2.4 Hz, 1H), 4.38-4.33 (m, 1H), 4.21-4.12 (m, 3H), 2.48-2.26 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.4, 134.7, 133.8, 121.9, 117.6, 72.2, 67.9, 63.8, 62.9, 36.7, 20.8, 20.7; [Found: C, 61.35; H, 7.16. $C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%].



48e

Benzyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio-α/β-D-*threo*-hex-2-enopyranoside 48f

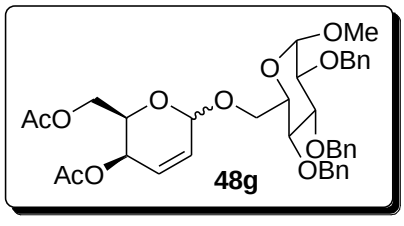
Viscous liquid; Yield: 53%; α:β = 11:1; $[\alpha]_D^{25}$ = -5.208 (c, 0.25, $CHCl_3$); IR (neat, cm^{-1}): 3063, 2924, 1743, 1494, 1454, 1371, 1230, 1070, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 5H), 6.05-5.96 (m, 2H), 5.45 (s, 1H), 5.10-5.08 (m, 1H), 4.59 (t, *J* = 6.4 Hz, 1H), 4.29-4.20 (m, 2H), 3.91 (d, *J* = 13.2 Hz, 1H), 3.74 (d, *J* = 13.2 Hz, 1H), 2.10 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.2, 137.7, 131.6, 129.4, 129.1, 128.6, 128.4, 127.1, 124.2, 78.0, 66.9, 63.4, 43.2, 34.7, 20.8, 20.8.; [Found: C, 60.75; H, 6.05. $C_{17}H_{20}O_5S$ requires C, 60.70; H, 5.99%].



48f

Methyl 6-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*threo*-hex-2-enopyranosyl)-2,3,4-tris-*O*-(phenylmethyl)-α-D-glucopyranoside 48g[57]

Viscous liquid; Yield: 57%; α:β = 8.4:1; $[\alpha]_D^{25}$ = -45.066 (c, 0.1, $CHCl_3$); IR (neat, cm^{-1}): 3030, 2926, 1745, 1454, 1369, 1230, 1028, 754, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 15H), 6.13-6.04 (m, 2H), 5.16 (br s, 1H), 5.02 (m, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.83-4.79 (m,

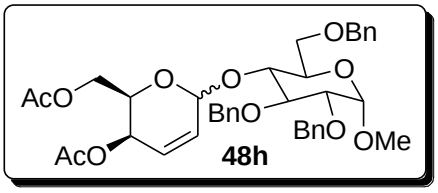


48g

2H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 3.3 Hz, 1H), 4.32-4.29 (m, 1H), 4.23-4.19 (m, 1H), 4.15-4.10 (m, 1H), 4.04-3.96 (m, 2H), 3.80-3.74 (m, 2H), 3.58-3.51 (m, 2H), 3.39 (s, 3H), 2.08 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.4, 138.7, 138.3, 138.1, 130.6, 128.5, 128.4, 128.4, 128.1, 128.0, 128.0, 127.8, 127.7, 127.5, 125.0, 98.0, 94.3, 82.1, 80.0, 77.9, 75.8, 75.0, 73.4, 70.0, 66.8, 66.8, 62.7, 62.6, 55.2, 20.9, 20.7; [Found: C, 67.51; H, 6.52 $C_{38}H_{44}O_{11}$ requires C, 67.44; H, 6.55%].

Methyl 4-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α/β-D-*threo*-hex-2-enopyranosyl)-2,3,6-tris-*O*-(phenylmethyl)-α-D-glucopyranoside 48h[57]

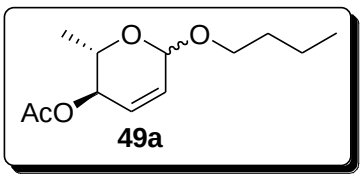
Viscous liquid; Yield: 58%; α:β = 10:1; $[\alpha]_D^{25}$ = +17.169 (c, 0.2, $CHCl_3$); IR (neat, cm^{-1}): 3458, 2924, 2860, 1741, 1454, 1365, 1195, 1057, 738, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 15H), 5.99 (dd, *J* = 9.9, 5.5 Hz, 1H), 5.69 (dd, *J* = 9.9, 2.6 Hz, 1H), 5.49 (d, *J* = 2.2 Hz, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.90 (d, *J* = 5.4 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.64-4.61 (m, 3H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.07 (m, 3H), 3.95 (t, *J* = 9.1 Hz, 1H), 3.85-3.77 (m, 2H), 3.70-3.62 (m, 2H), 3.53 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.40 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.4, 138.6, 138.3, 137.9, 130.6, 128.5, 128.3, 128.2, 128.2, 128.0, 127.6, 127.6, 127.5, 127.5, 124.5, 97.7, 95.2, 81.9, 80.2, 76.2, 75.6, 73.3, 73.0, 69.6, 69.6, 66.9, 62.6, 62.4, 55.2, 20.8, 20.8; [Found: C, 67.35; H, 6.58 $C_{38}H_{44}O_{11}$ requires C, 67.44; H, 6.55%].



Characterisation data for 2,3-unsaturated rhamnosides:

(2S,3R)-6-butoxy-2-methyl-3,6-dihydro-2H-pyran-3-yl acetate 49a

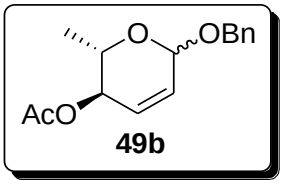
Oily liquid; R_f (1:3 EtOAc/Hexane) 0.60; Yield: 86%; α:β = 5:1; $[\alpha]_D^{25}$= -140.60 (c, 0.25, $CHCl_3$); IR (neat, cm^{-1}): 2957, 2935, 1743, 1373, 1236, 1039, 918; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.77 (m, 2H), 5.04 (d, *J* = 9.0 Hz, 1H), 4.95 (br s, 1H), 3.97 (dq, *J* = 9.2, 6.3 Hz, 1H), 3.80-3.73 (m, 1H), 3.52-3.46 (m, 1H), 2.07



(s, 3H), 1.62-1.55 (m, 2H), 1.44-1.35 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.94-0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 129.5, 128.0, 94.4, 71.0, 68.4, 64.8, 31.9, 21.1, 19.4, 18.0, 13.8; [Found: C, 63.09; H, 8.85 $C_{12}H_{20}O_4$ requires C, 63.14; H, 8.83%].

(2S,3R)-6-(benzyloxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl acetate 49b[59]

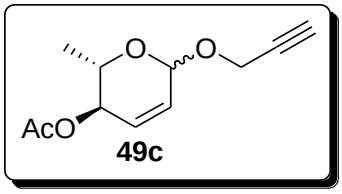
Oily liquid; Yield: 67%; α:β = 5.5:1; $[\alpha]_D^{25}$= -106.95 (c, 0.25, $CHCl_3$); IR (neat, cm^{-1}): 2980, 2934, 1745, 1454, 1373, 1236, 1037, 731; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 5.87-5.80 (m, 2H), 5.08-5.05 (m, 2H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.04-3.97 (m, 1H), 2.08 (s, 3H), 1.19 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 138.0, 129.8, 128.5, 128.0, 127.8, 93.7, 71.0, 70.2, 65.0, 21.1(2C), 17.9; [Found: C, 68.55; H, 6.95 $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92%].



49b

(2S,3R)-2-methyl-6-(prop-2-yn-1-yloxy)-3,6-dihydro-2H-pyran-3-yl acetate 49c

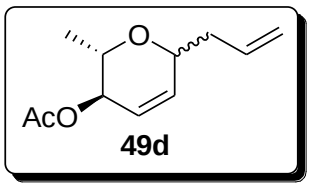
Colorless liquid; Yield: 92%; α:β = 5.7:1; $[\alpha]_D^{25}$ = -183.08 (c, 0.25, $CHCl_3$); IR (neat, cm^{-1}): 3285, 2982, 2934, 1743, 1404, 1375, 1238, 1105, 1037, 918; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89-5.87 (m, 1H), 5.82-5.79 (m, 1H), 5.17 (br s, 1H), 5.07 (dd, *J* = 9.2, 1.4 Hz, 1H), 4.30 (d, *J* = 2.4 Hz, 2H), 4.00-3.91 (m, 1H), 2.45 (t, *J* = 2.4 Hz, 1H), 2.08 (s, 3H), 1.23 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 130.2, 127.2, 92.7, 74.5, 70.7, 65.1, 54.9, 21.0, 17.8; [Found: C, 62.78; H, 6.74 $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.71%].



49c

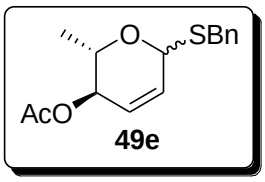
(2S,3R)-6-allyl-2-methyl-3,6-dihydro-2H-pyran-3-yl acetate 49d[25a]

Pale yellow oil; Yield: 62%; α:β = >15:1; $[\alpha]_D^{25}$ = -141.41 (c, 0.25, $CHCl_3$); IR (neat, cm^{-1}): 2980, 2935, 1739, 1641, 1373, 1238, 1101, 1024, 916, 727; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.95-5.92 (m, 1H), 5.90-5.82 (m, 1H), 5.80-5.76 (m, 1H), 5.15-5.09 (m, 2H), 4.90-4.87 (m, 1H), 4.23-4.18 (m, 1H), 3.93 (dq, *J* = 6.4, 4.8 Hz, 1H), 2.48-2.28 (m, 2H), 2.08 (s, 3H), 1.24 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 134.3, 133.4, 123.0, 117.4, 69.8, 69.5, 68.8, 38.4, 21.3, 16.9; [Found: C, 67.28; H, 8.19 $C_{11}H_{14}O_4$ requires C, 67.32; H, 8.22%].



49d

(2S,3R)-6-(benzylthio)-2-methyl-3,6-dihydro-2H-pyran-3-yl acetate 49e



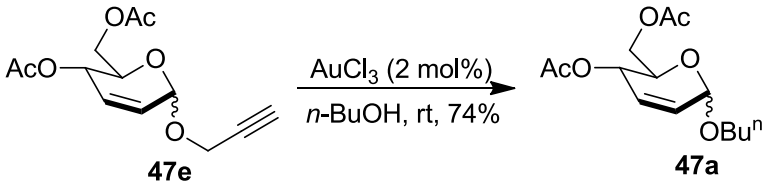
49e

White solid; mp: 52 - 54 °C; R_f (1:3 EtOAc/Hexane) 0.65; Yield: 95%; α:β = 7:1; $[\alpha]_D^{25}$ = -392.21 (c, 0.25, $CHCl_3$); IR (KBr, cm^{-1}): 3028, 2930, 1738, 1454, 1373, 1236, 1035, 781, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 5H), 5.83-5.79 (m, 1H), 5.75-5.72 (m, 1H), 5.34 (br s, 1H), 5.10 (dd, *J* = 9.0, 1.7 Hz, 1H), 4.18-4.11 (m, 1H), 3.90 (d, *J* = 13.3 Hz, 1H), 3.76 (d, *J* = 13.3 Hz, 1H), 2.08 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 138.4, 129.0, 128.8, 128.6, 127.7, 127.1, 78.8, 70.9, 65.1, 35.7, 21.2, 18.0; [Found: C, 64.78; H, 6.49 $C_{15}H_{18}O_3S$ requires C, 64.72; H, 6.52%].

General procedure for the $AuCl_3$-catalysed one-pot Ferrier and subsequent glycosylation reaction

To a solution of 3,4,6-tri-*O*-acetyl-D-glucal **20** (1 equiv) and propargyl alcohol (1.2 equiv) in dry solvent (5 mL/mmol) $AuCl_3$ (2 mol%) was added. The reaction mixture was stirred at room temperature. On complete consumption of **20** to form **47e** which generally takes around 6 h, nucleophile (1.2 equiv) was added. The reaction mixture was stirred under inert atmosphere. After stirring for specified time given in the Table 1, it was purified by silica gel column using ethyl acetate and hexane mixture as eluent.

With *n*-butanol as the solvent:



47e **47a**

Scheme 18. Gold-catalysed transglycosylation in *n*-butanol

To a solution of propargyl glycoside **47e** (100 mg, 0.38 mmol) in *n*-BuOH (2 mL), $AuCl_3$ (2 mol%) was added. The reaction mixture was stirred for 24 h at room temperature. *n*-butanol was evaporated and crude transglycoside was purified by silica gel column chromatography to get butyl glycoside **47a**. Yield: 74%, α:β = 3:1.

Procedure for competitive glycosylation of 3,4,6-tri-*O*-acetyl-D-glucal 20 and 3,4,6-tri-*O*-acetyl-D-galactal 40

A mixture of (50 mg, 0.18 mmol) 3,4,6-tri-*O*-acetyl-D-glucal **20** and (50 mg, 0.18 mmol) 3,4,6-tri-*O*-acetyl-D-galactal **40** in dry dichloromethane (2 mL) was stirred for 5 min. at room temperature. To this mixture *n*-butanol (14 mg, 0.18 mmol) and $AuCl_3$ (1 mol%) were added. The reaction was stirred for 3 h at room temperature. The solvent was evaporated and the residue was purified by column chromatography. A mixture of *n*-butyl glucoside **47a** and *n*-butyl galactoside **48a** was obtained. From ^{1}H NMR integration of these epimeric mixture, the ratio of glucoside to galactoside was found as 3:2.

1.5 References

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Chapter 1

1.6 Representative ^{1}H NMR and ^{13}C NMR spectra

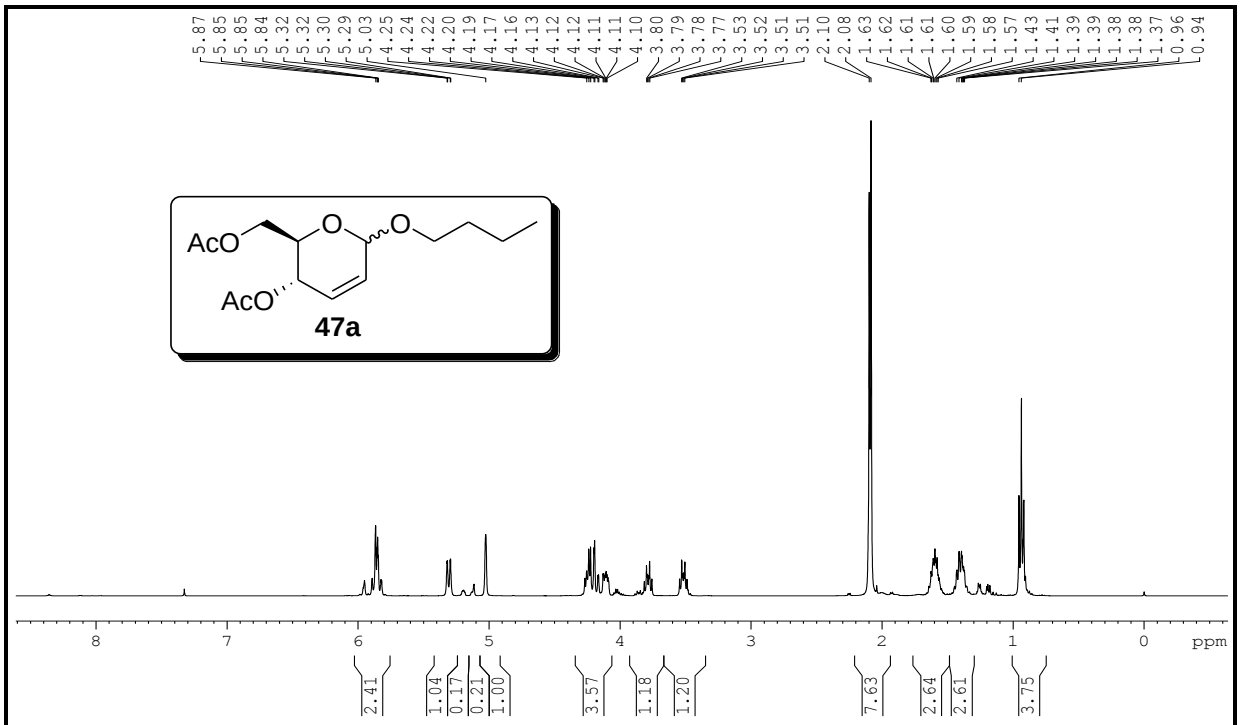


Figure 5. 400 MHz ^{1}H NMR spectrum of compound **47a**

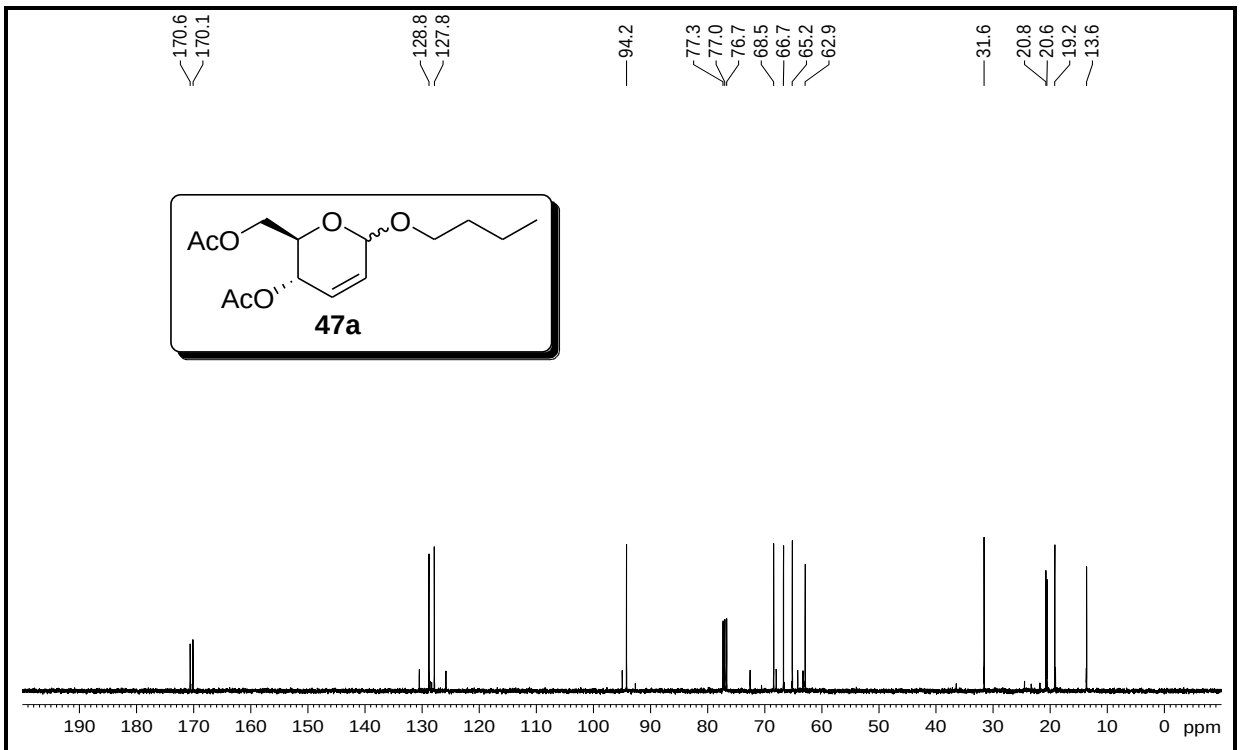


Figure 6. 100 MHz ^{13}C NMR Spectrum of **47a**

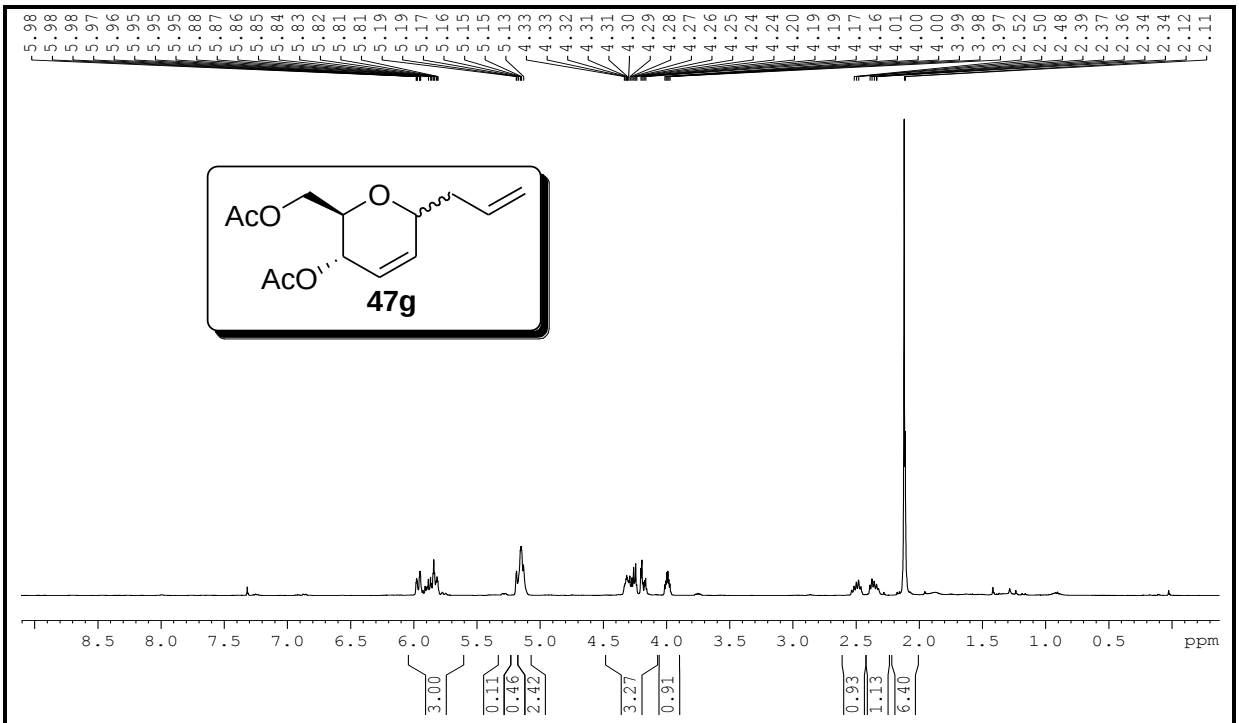


Figure 7. 400 MHz ^{1}H NMR spectrum of compound **47g**

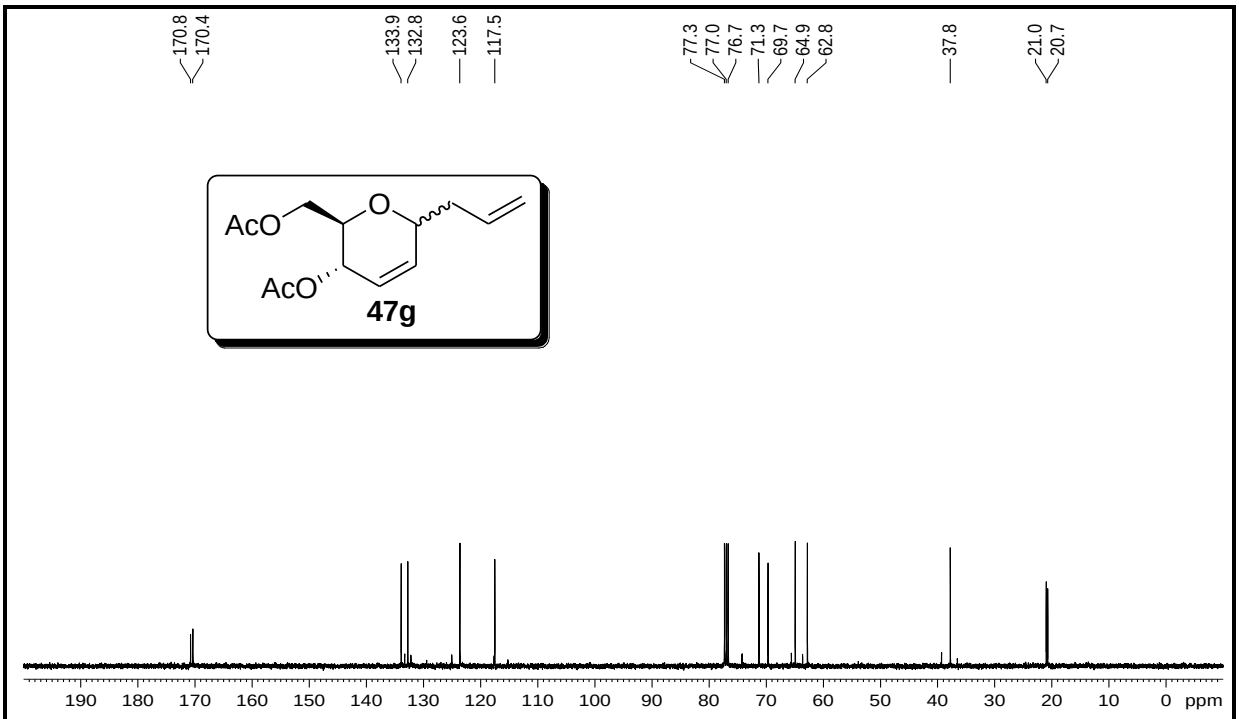


Figure 8. 100 MHz ^{13}C NMR Spectrum of **47g**

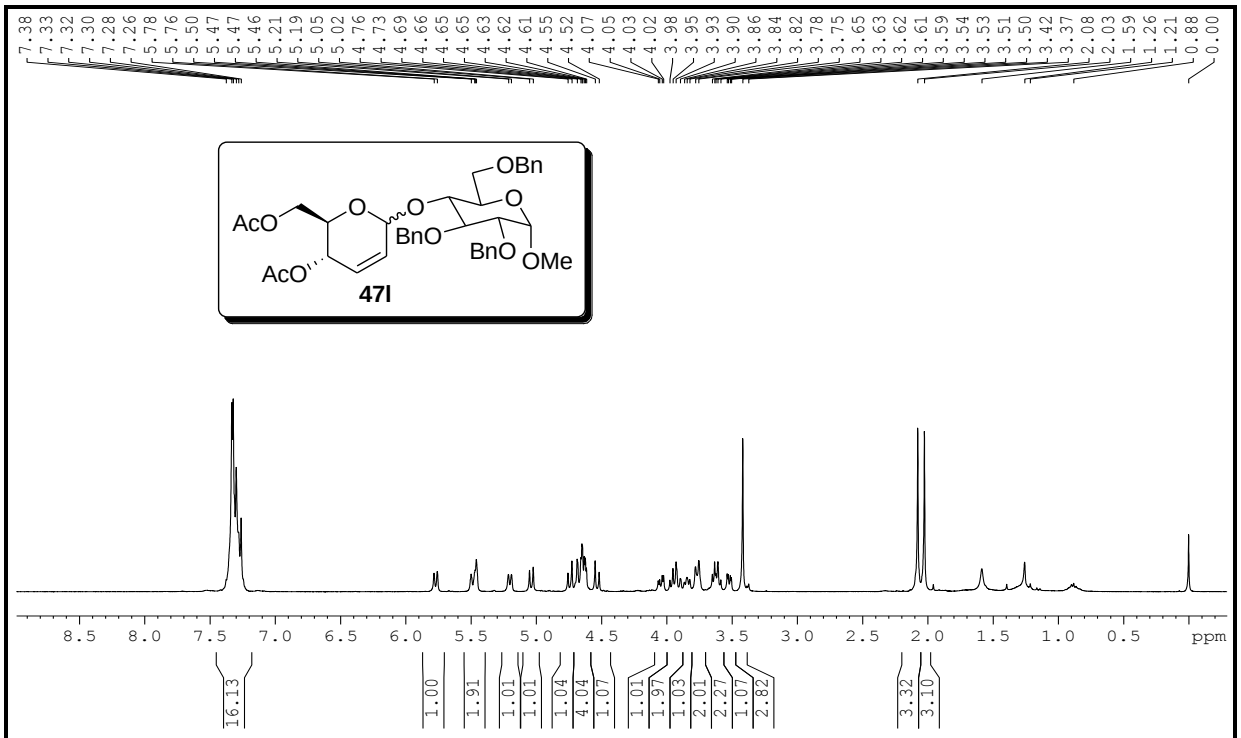


Figure 9. 400 MHz ^{1}H NMR spectrum of compound **47l**

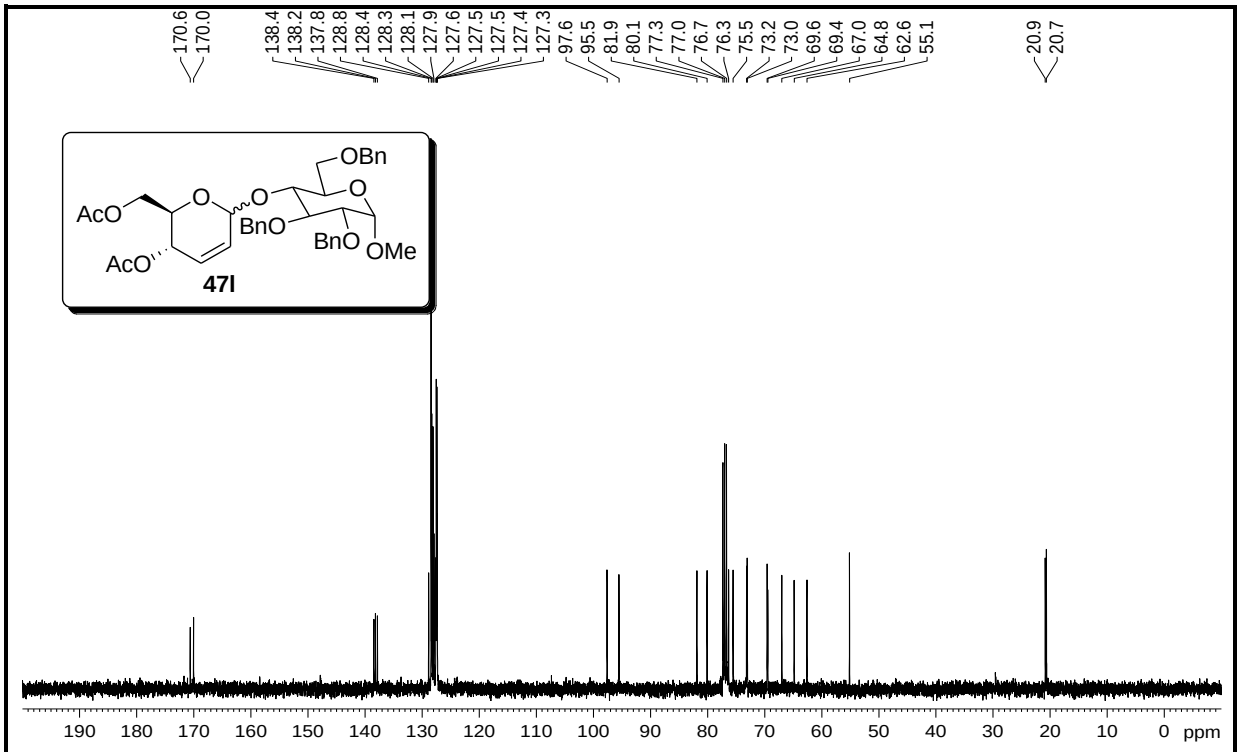


Figure 10. 100 MHz ^{13}C NMR Spectrum of **47l**

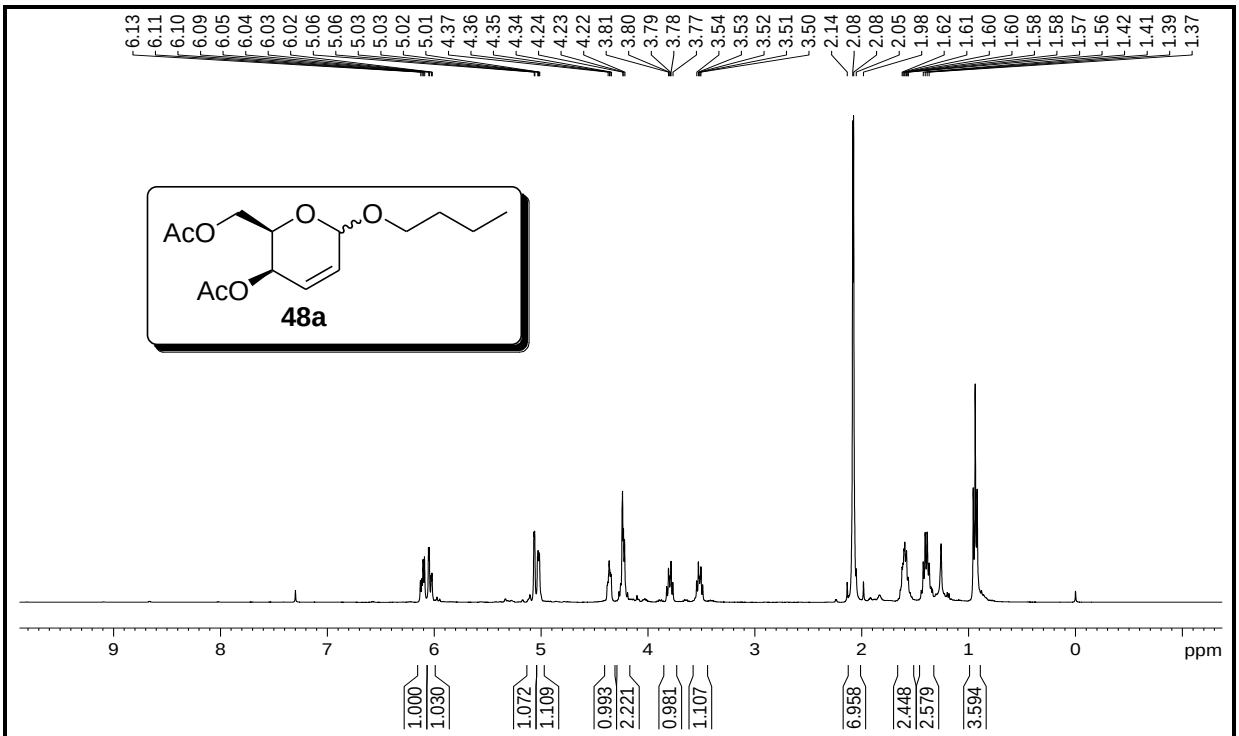


Figure 11. 400 MHz ^{1}H NMR spectrum of compound **48a**

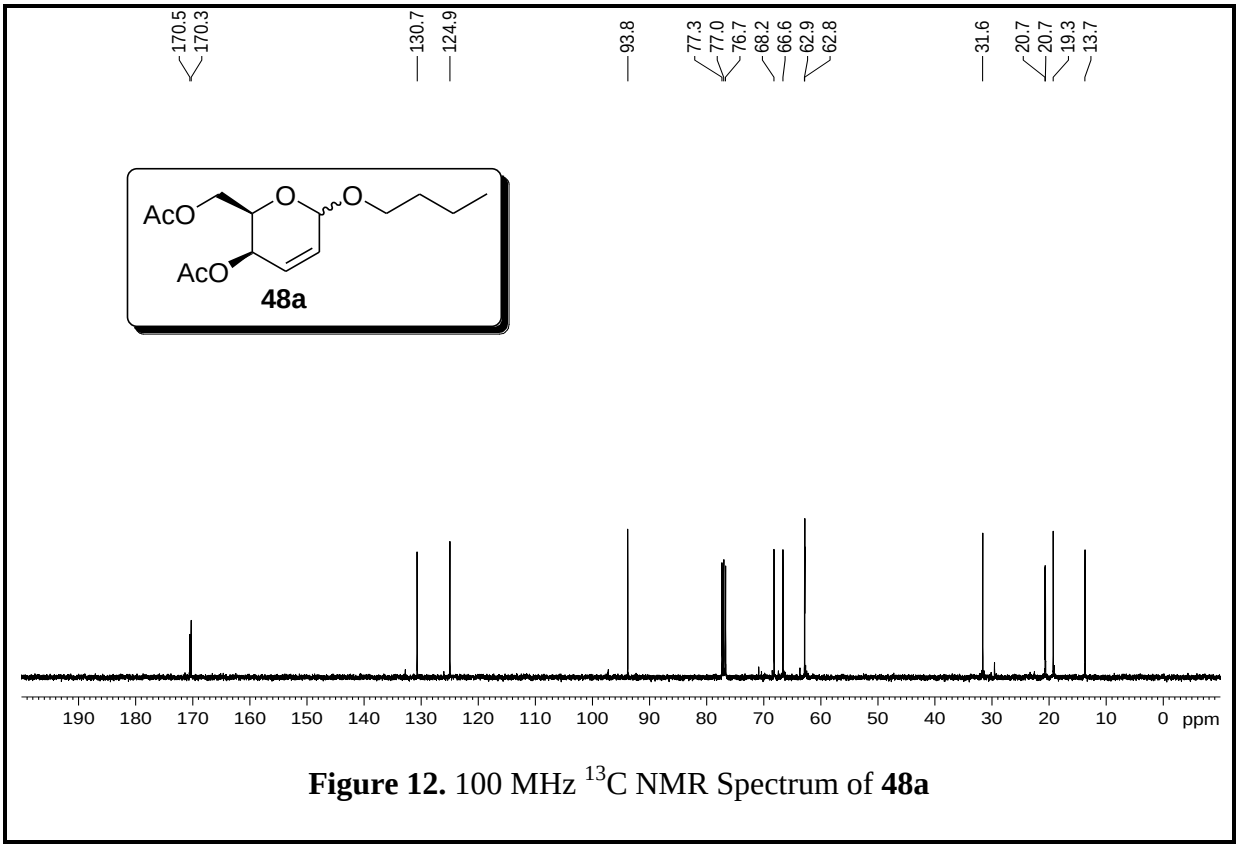


Figure 12. 100 MHz ^{13}C NMR Spectrum of **48a**

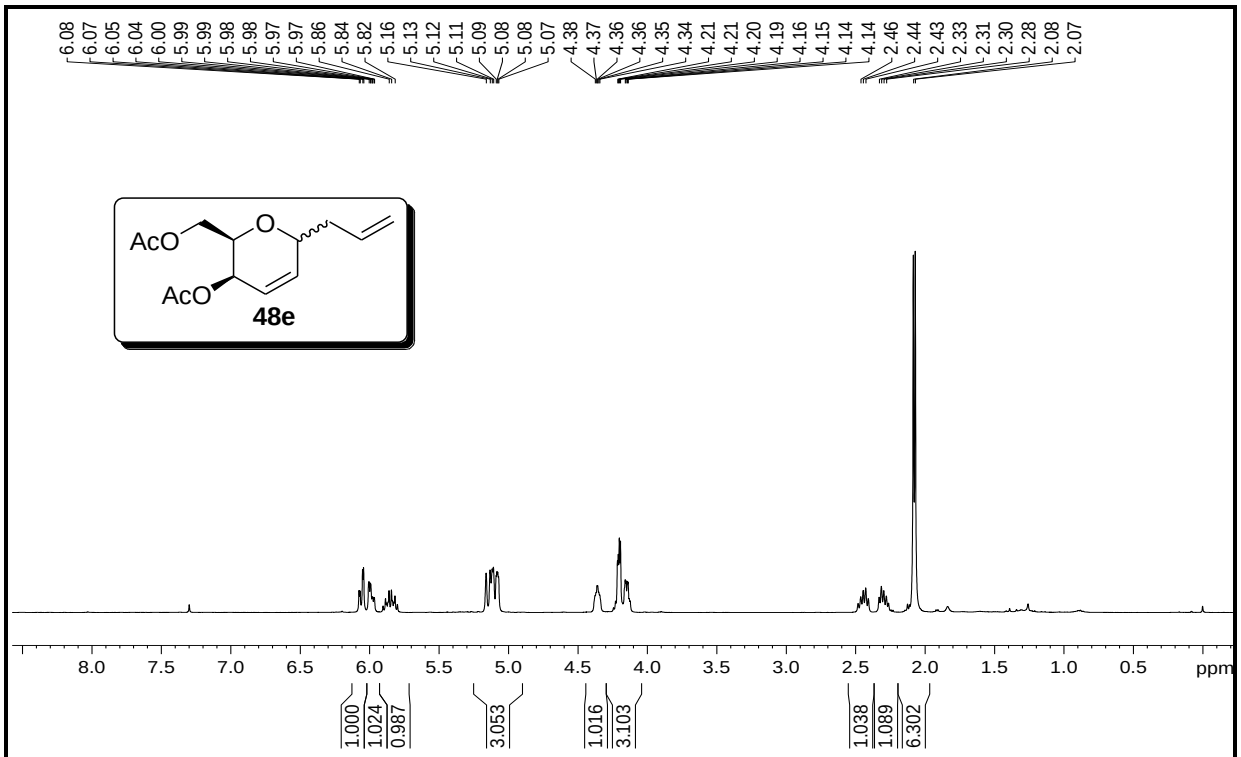


Figure 13. 400 MHz ^{1}H NMR spectrum of compound **48e**

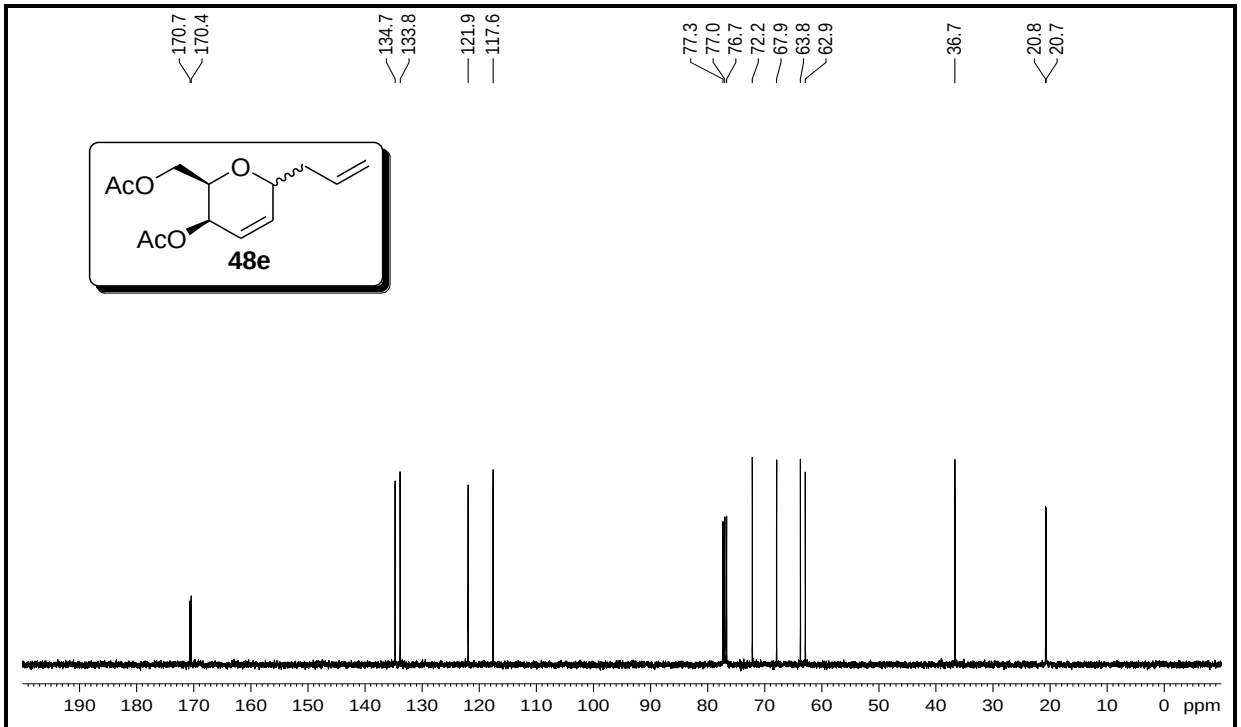


Figure 14. 100 MHz ^{13}C NMR Spectrum of **48e**

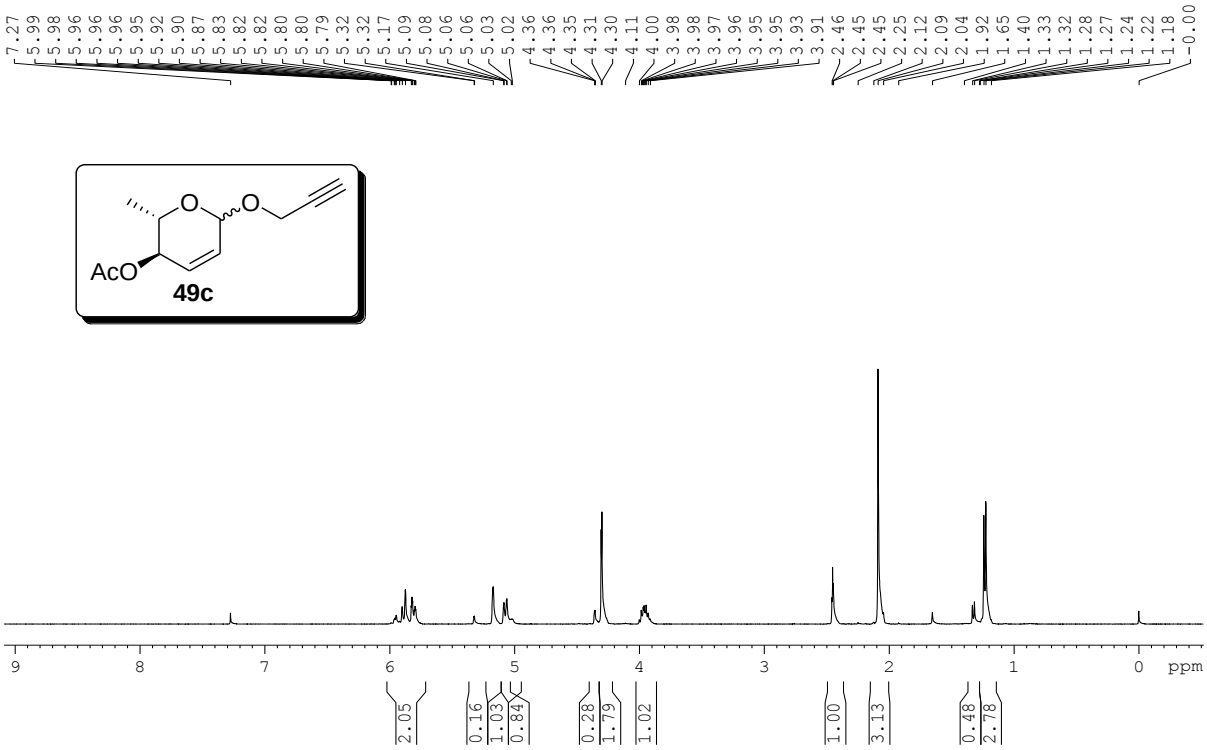


Figure 15. 400 MHz ^{1}H NMR spectrum of compound **49c**

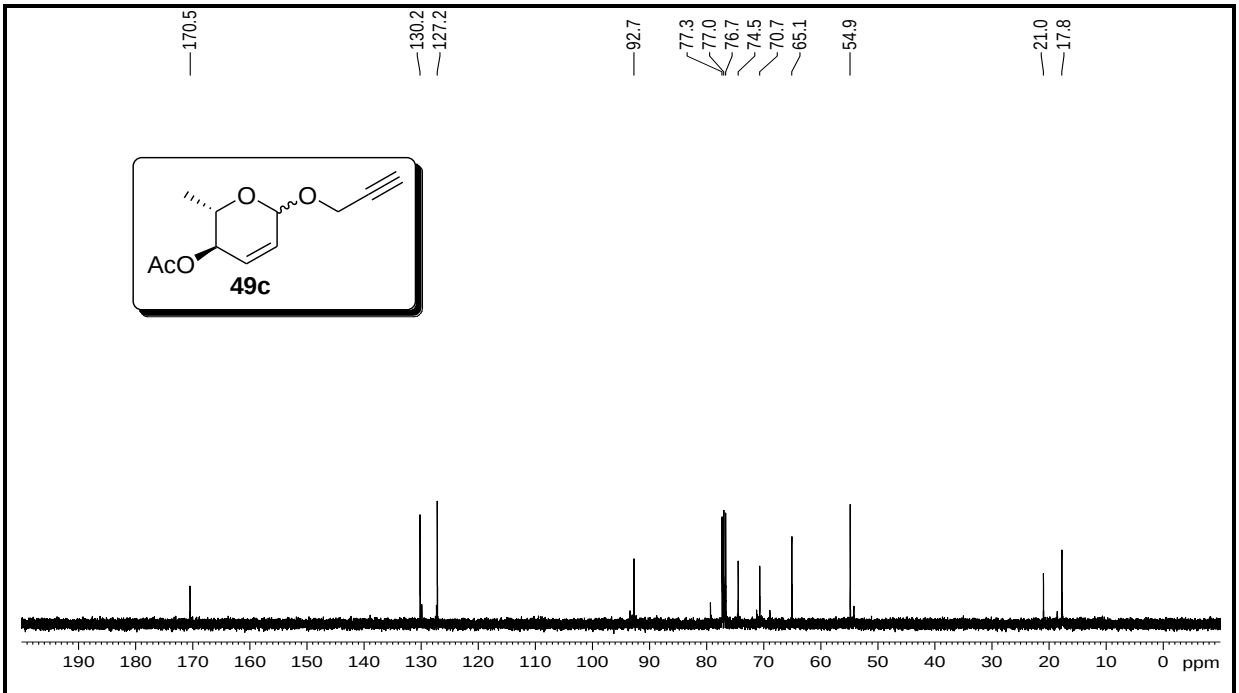


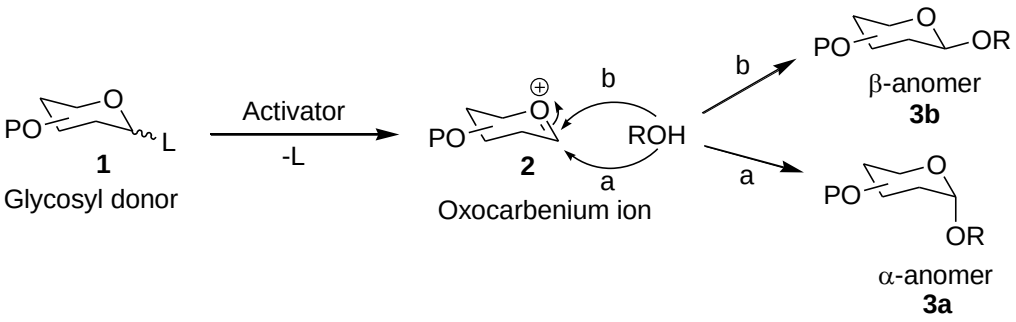
Figure 16. 100 MHz ^{13}C NMR Spectrum of **49c**

Chapter 2

Gold-Catalysed Glycosylation Reaction: Development of an Easily Accessible Glycosyl Donor

2.1 Introduction

Glycosylation reactions play vital role in synthetic carbohydrate chemistry especially in the synthesis of oligosaccharides and glycoconjugates. Glycosylation reactions involve formation of glycosidic bond between a glycosyl donor and a glycosyl acceptor.[1]



Scheme 1. Schematic representation of glycosylation reaction

The mechanism of glycosylation reaction involves activator-assisted departure of leaving group (L) from the donor **1** which results in the formation of oxocarbenium ion **2**. Attack of the nucleophile on to the oxocarbenium ion **2** leads to the formation of glycosylated product (Scheme 1). The stereochemical outcome of the glycosylation reaction *i.e.,* selective formation of either α-anomer or β-anomer depends on several factors including nature of protecting groups, solvent, temperature and promoter.[1] The substituent at 2-position directs the incoming nucleophile by neighboring group participation and subsequently influences the stereochemical outcome of the reaction. Groups such as -OAc and -OBz direct the nucleophile to attack from the β-face by neighboring group participation.[2] Substituents like -OBn and azides cannot involve in neighboring group participation. In these cases, anomeric effect dominates leading to α-selectivity. Participating solvents such as CH_3CN, diethyl ether, THF, nitromethane and acetone can influence the stereoselectivity of chemical glycosylation.[1]

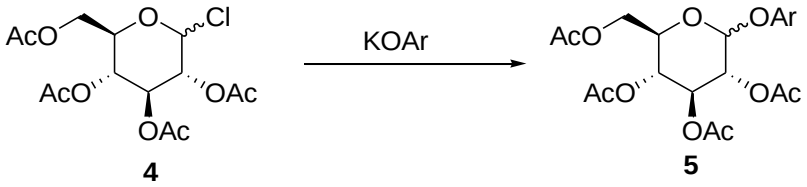
2.1.1 Glycosyl donors

The role of glycosylation in several biological processes like fertilisation, embryogenesis, proliferation of cells leads to enduring search for glycosyl donors and catalyst systems for the chemical synthesis of oligosaccharides.[3] In this regard several glycosyl donors have been developed over the years for the synthesis of oligosaccharides and

glycoconjugates such as glycolipids, glycoproteins.[2] The following sections describe literature on different glycosyl donors. Under each donor one representative example of the glycosylation reactions utilizing the particular donor is presented.

2.1.1.1 Glycosyl halides

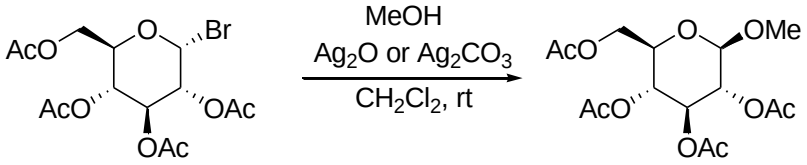
The first glycosylation reaction was reported by Michael in the year 1879. In his attempt, glycosyl chloride **4** was treated with base (potassium aryl alkoxide) to get aryloxy glycoside **5** (Scheme 2).[3]



4 **5**

Scheme 2. Glycosylation with glycosyl chloride **4** as donor

The development of glycosyl donor chemistry involving promoters was started with the activation of glycosyl chlorides **4** or bromides **6** with silver salts by Koenig and Knorr in 1901.[4] Knoeig-Knorr method is the only method which involve Walden inversion type (S_N2) leaving group departure.



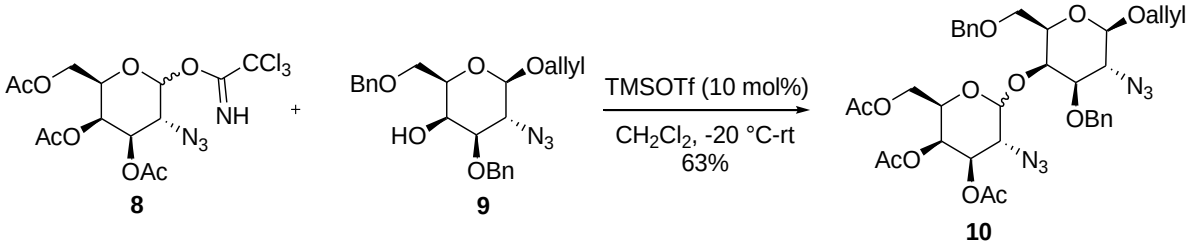
6 **7**

Scheme 3. Glycosylation with glycosyl bromide **6** as donor

This has been demonstrated by treating α-pyranosyl and β-pyranosyl bromides separately with methanol in presence of silver salts. Pure α-pyranosyl resulting in β-glycoside. This might be due to the blockage of α-face with bromide and acetate group. Where as, pure β-anomeric pyranosyl bromide reacted with methanol in presence of silver salt to gave a mixture of anomeric glycosides and orthoester. Activation of glycosyl halides with the mercuric salts was studied by Helferich to form glycosides and is termed as Helferich glycosylation.[5]

2.1.1.2 Trichloroacetimidate donors

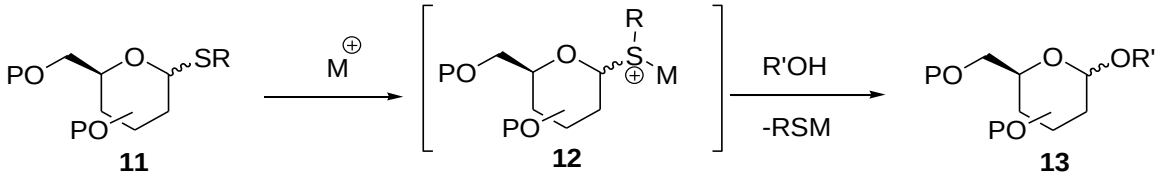
R. R. Schmidt and J. Michael discovered *O*-glycosyl trichloroacetimidate as an efficient glycosyl donor in 1980.[6a] Because of the ease of preparation, these donors have extensively been used in the synthesis of several natural products and other glycoconjugates. These donors can easily be made by reacting sugar lactol with trichloroacetonitrile under basic conditions.[6b] α-Trichloroacetimidates can be prepared by treating sugar lactol with bases such as DBU, KOH and NaH under phase transfer conditions. β-Trichloroacetimidates can be made by treating sugar lactol with bases like K_2CO_3. Several Lewis acids are known to catalyze the glycosylation of glycosyl trichloroacetimidate donors. TMSOTf and $BF_3.Et_2O$ are the preferred ones. This method is particularly useful for making glycosidic linkage between different sugar units. One such example is shown in Scheme 4. 3,4,6-Tri-*O*-acetyl-2-azido galactopyranosyl trichloroacetimidate **8** was treated with acceptor **9** in the presence of catalytic TMSOTf to get the disaccharide **10** (Scheme 4). Here, the trichloroacetimidate leaving group is expelled as trichloroacetamide.[7]



Scheme 4. Synthesis of disaccharide **10** with glycosyl trichloroacetimidate **8** as donor

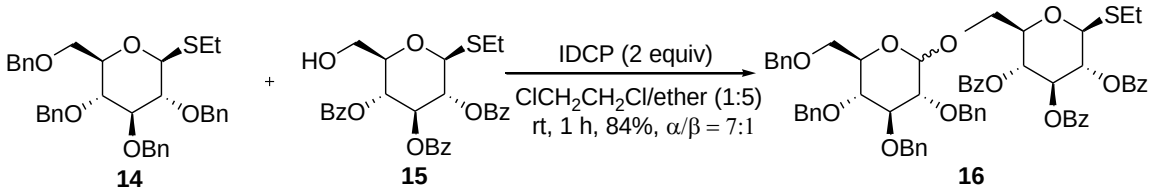
2.1.1.3 Thioglycosides as donors

Thioglycosides can be activated either by direct activation with electrophiles or by indirect activation after transforming into another glycosyl donor by treating with suitable reagent.[8a] Sulfur atom in thioglycosides **11** is soft nucleophile. These can be activated by soft Lewis acids such as heavy metal cations to form sulfonium ions **12**. These sulfonium ions **12** would cleave from sugar moiety due to anomeric stabilisation to deliver oxocarbenium ion **2**. This oxocarbenium ion reacts with nucleophiles to form glycosides **13** (Scheme 5).

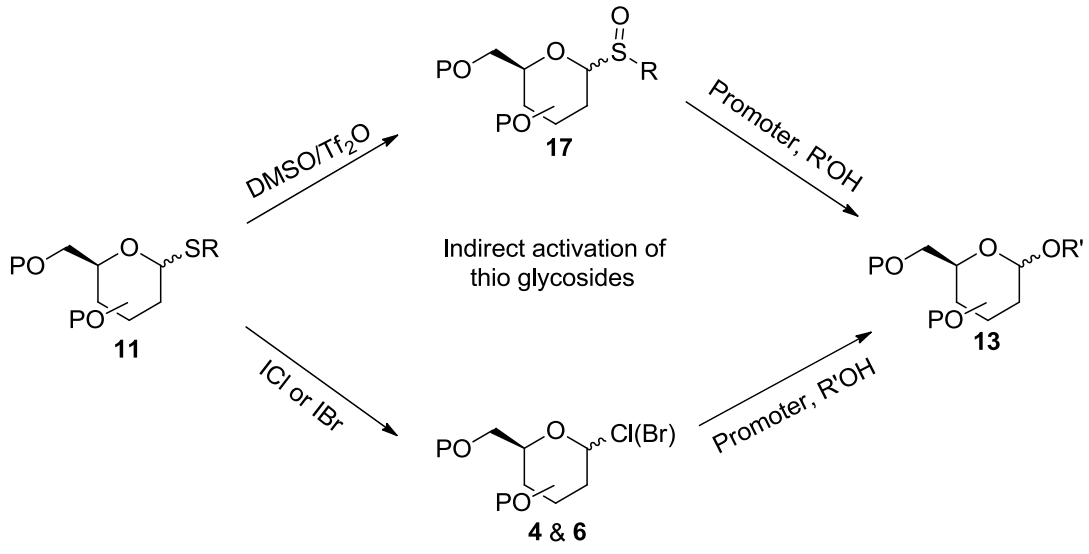


Scheme 5. Activation of thioglycosides **11** with electrophiles for glycosylation

Van Boom and co-workers synthesized the disaccharide **16** by employing ethylthio glycoside **14** as glycosyl donor. It was treated with benzoyl protected acceptor **15** (containing thioglycoside end for further functionalisation) in presence of two equivalents of iodonium dicollidinium perchlorate (IDCP) (Scheme 6). Further, the disaccharide with ethyl thio group at the anomeric position of the reducing sugar **16** was employed in the synthesis of trisaccharide.[8b]



Scheme 6. Synthesis of glycoside **16** by employing thioglycoside as donor



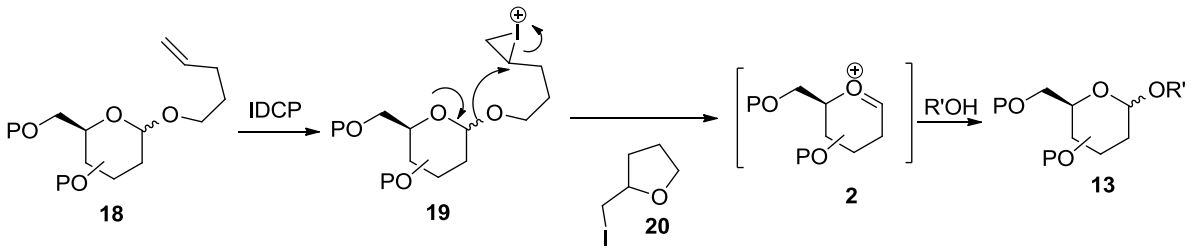
Scheme 7. Synthesis of glycoside **13** by prior activation of thioglycoside **11**

On the other hand, thioglycoside **11** could be converted to other donors like glycosyl chlorides **4**, bromides **6** or glycosyl sulfoxides **17** by treating it with ICl or IBr or

DMSO/Tf_2O respectively (Scheme 7). These secondary donors can be activated by suitable activators to form glycoconjugates **13**.

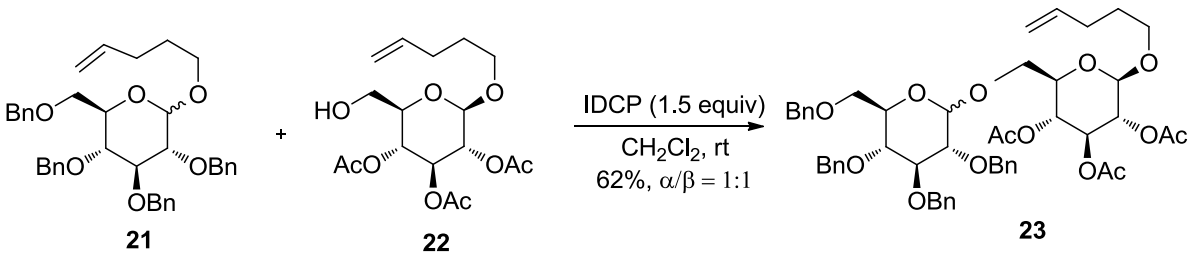
2.1.1.4 *n*-Pentenyl glycosides

n-Pentenyl glycosides can easily be made by the Fischer glycosylation of sugar lactols with *n*-pentenyl alcohol. These donors can be activated with iodonium species conveniently to form glycosides. Iodonium ion coordinates to the double bond of the activator **18** to form epiiodonium intermediate **19**. Further ring oxygen-assisted cleavage of glycosyl bond and subsequent attack of oxygen on to the epiiodonium ion results in oxocarbenium ion **2** and iodomethyl tetrahydrofuran **20**. This oxocarbenium ion **2** reacts with suspended nucleophile to form glycoside **13** (Scheme 8).[1]



Scheme 8. Mechanistic representation of synthesis of glycoside **13** by employing *n*-pentenyl glycoside **18** as donor

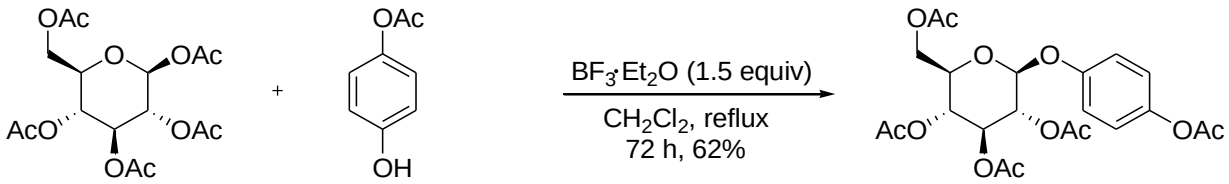
Fraser-Ried and co-workers reported the IDCP-catalysed synthesis of trisaccharide using *n*-pentenyl glycosides as glycosyl donor. Armed-disarmed concept was applied to make the disaccharide fragment. *n*-Pentenyl tetrabenzylglucopyranoside **21** was treated with disarmed acceptor **22** in the presence of IDCP to get disaccharide **23** (Scheme 9).[9]



Scheme 9. Synthesis of glycoside **23** by employing *n*-pentenyl glycoside **21** as donor

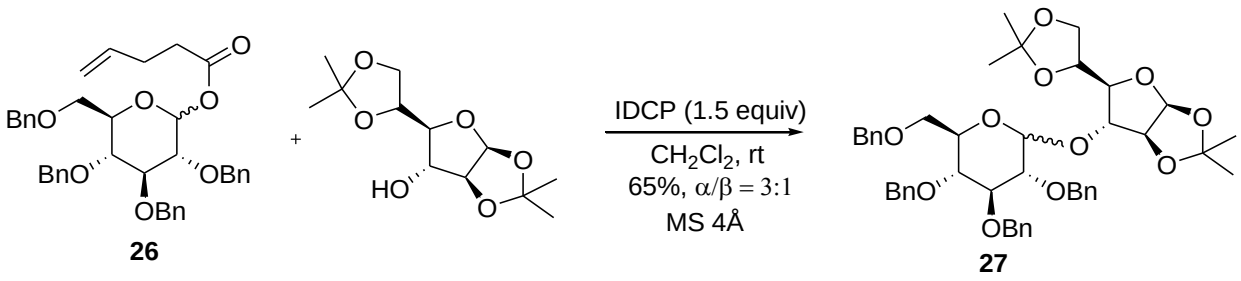
2.1.1.5 Glycosyl esters as donors

Cepanec and co-workers used glycosyl acetates **24** as donors (Helferich glycosylation) in the presence of boron trifloride diethyl etherate as stoichiometric reagent to make aryl glycosides **25** (Scheme 10).[10] This glycosylation methodology was applied for the synthesis of arbutin which is an active pharmaceutical ingredient for the treatment of urinary infections as well as depigmenting agent.



Scheme 10. Synthesis of glycoside **25** by Helferich glycosylation of **24**

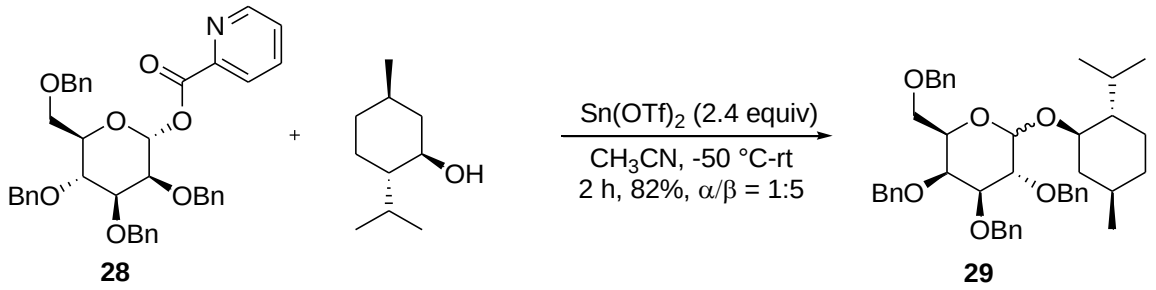
Glycosyl *n*-pentenoic esters **26** have been used by Fraser-Ried and co-workers as donors in the synthesis of disaccharides such as **27** (Scheme 11) and other glycoconjugates under identical reaction conditions as outlined in the case of *n*-pentenyl glycosides in Scheme 8. In this case, activator leaves as iodomethyl γ-butyrolactone derivative.[11]



Scheme 11. Synthesis of glycoside **27** with *n*-pentenoyl ester **26** as donor

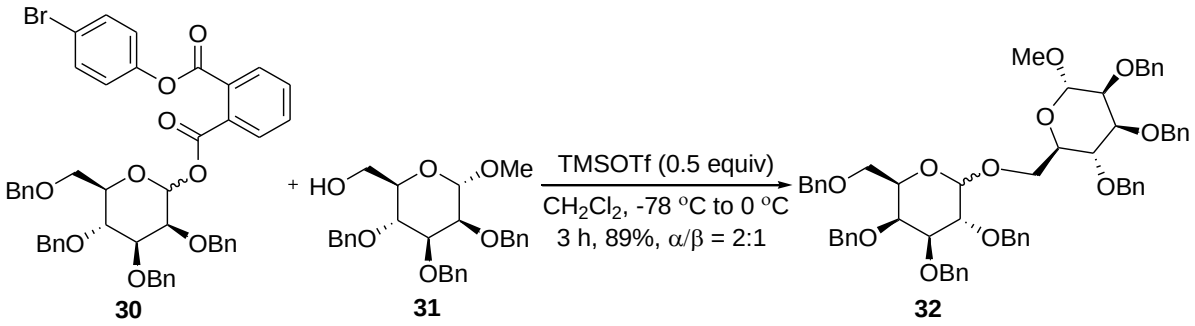
Kobayashi and co-workers developed the glycosyl pyridine-2-carboxylate donors with remote activation strategy.[12a] Here, Lewis acid activates the donor by coordinating to both pyridine nitrogen and ester carbonyl oxygen. These glycosides can be made by treating sugar lactols with picolinoyl chloride in the presence of triethylamine at 0 °C. Pyridine-2-carboxylate donor **28** was reacted with (-)-menthol in the presence of super stoichiometric amounts of $Sn(OTf)_2$ or $Cu(OTf)_2$ in acetonitrile solvent to furnish glycoside **29** in good yield with β-selectivity (Scheme 12).[12b] The same reaction when carried out, in dichloromethane or

ether solvents, it is α-selective (α/β = 5.2:1) due to the absence of solvent participation observed with CH_3CN. The oxocarbenium ion is stabilized from α-position by CH_3CN.



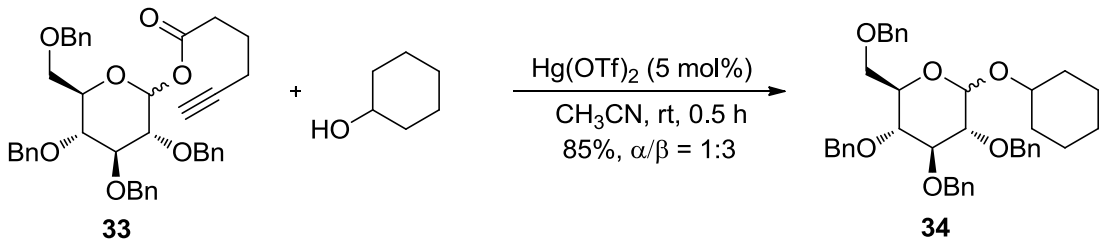
Scheme 12. Synthesis of glycoside **29** with glycosyl pyridine-2-carboxylate **28** as donor

Kim and co-workers reported glycosyl *p*-bromophenylphthalates **30** as efficient donors in the synthesis of glycosides **32** upon activation with Lewis acids like TMSOTf under cryogenic conditions (Scheme 13).[13] Here, the activator *p*-bromophenyl phthalate leaves as phthalic anhydride. Drawback of the methodology is that it requires very low temperature to get good yield and α-selectivity.



Scheme 13. Synthesis of glycoside **32** by employing *p*-bromophenyl phthalate **30** as donor

Imagava *et al.* reported the mercuric triflate-catalysed glycosylation using glycosyl 5-hexynoate donor **33** for synthesizing glycoside **34** (Scheme 14).[14] The authors proposed that, mercury first coordinates to the triple bond of the donor and subsequent ring oxygen-assisted cleavage of leaving group gives oxocarbenium ion. The 5-hexynoate activator leaves as δ-methylene lactone. Glycosyl 4-hexynoates have been made but not explored for glycosylation.



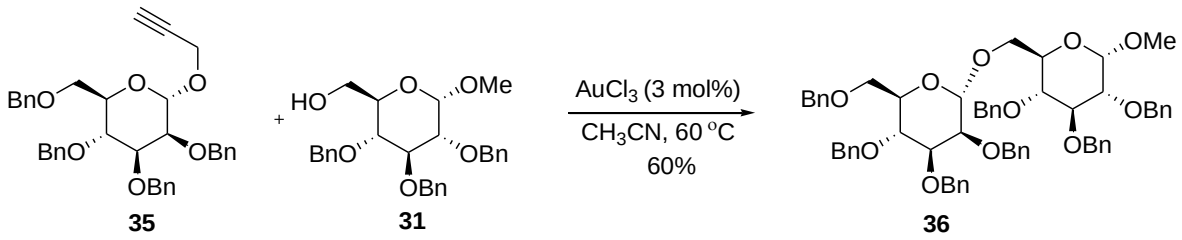
Scheme 14. Synthesis of glycoside **34** with glycosyl 5-hexynoate **33** as donor

2.1.1.6 Gold-catalysed glycosylation reactions

Gold catalysis has been emerging as a field of active research for making interesting molecular scaffolds since last decade.[15] The alkynophilicity of gold has been utilised to a great extent to develop new reactions which find applications in the synthesis of several heterocycles and natural products. Till now, very few reports are only there using gold catalysis in carbohydrate chemistry.[16] A few number of glycosyl donors have been reported in literature for the synthesis of glycoconjugates using gold catalysis.

2.1.1.6.1 Propargyl glycosides as donors

Hotha and co-workers have found the leaving group ability of propargyloxy group under gold-catalytic conditions in glycosylation reactions for the synthesis of glycoconjugates.[17] In mechanistic terms, gold salt initially coordinates with triple bond of propargyloxy group. Further intramolecular attack of the propargyloxy oxygen on to the alkyne followed by the explusion of epoxygold fragment driven by ring oxygen stabilization leads to oxocarbenium ion. This oxocarbenium ion reacts with acceptors to give glycosides in good yield and with a slight β-selectivity. Propargyl mannoside **35** was treated with glucose derived acceptor **31** in the presence of catalytic amount of gold chloride under heating conditions in acetonitrile solvent to get glycoside **36** in moderate yield (Scheme 15).

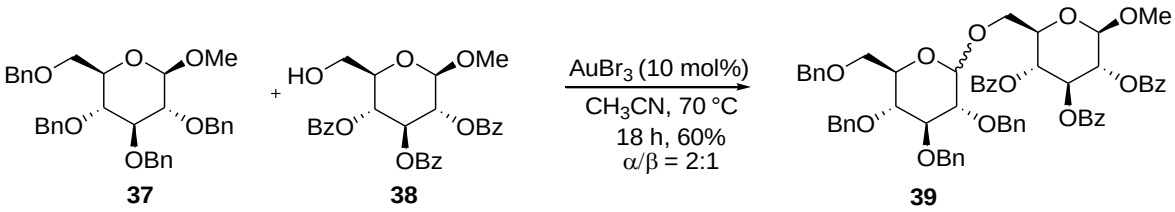


Scheme 15. Propargyl glycoside **35** in the synthesis of disaccharide **36**

2.1.1.6.2 Methyl glycosides as glycosyl donors

Methyl glycosides have been identified as glycosyl donors by Hotha and co-workers for synthesizing disaccharides and oligosaccharides.[18] From catalyst screening experiments, gold(III) bromide was found to be better catalyst in terms of yield. Lewis acids such as $BF_3{\cdot}Et_2O$ and scandium triflate also effected the transformation but failed in affording good yields.

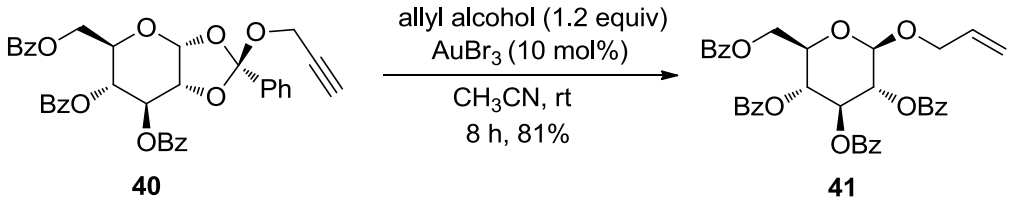
Benzyl protected methyl glycoside **37** was treated with disarmed acceptor **38** in the presence of gold(III) bromide in catalytic amount under vigorous reaction conditions to get disaccharide **39** in moderate yield (Scheme 16). Further, this methodology was extended for the synthesis of tri-and tetrasaccharides.



Scheme 16. Methyl glycoside **37** as donor in the synthesis of disaccharide **39**

2.1.1.6.3 Propargyl 1,2-orthoesters as donors

Glycosyl 1,2-orthoesters in absence of acceptor undergo acid-catalysed rearrangement which involve transfer of alkoxy group to anomeric center lead to 2-acyloxy glycosides. Propargyl 1,2-orthoester donor **40** and allyl alcohol were subjected to gold(III) bromide-catalysed glycosylation conditions at room temperature to give allylglycoside **41** and trace amount of rearranged propargyl glycoside.[19]



Scheme 17. Propargyl 1,2-ortho ester **40** as glycosyl donor

2.1.1.6.4 Glycosyl *ortho*-alkynyl benzoates as donors

Yu and co-workers reported glycosyl *ortho*-alkynylbenzoates as glycosyl donors under cationic Au(I)-catalysed conditions.[20] The *ortho*-alkynyl benzoate activator was made by palladium-catalysed coupling of alkyne to the 2-iodo methylbenzoate followed by base hydrolysis. Using this activator, a wide range of glycoconjugates have been synthesized like disaccharides, glycopeptides. In the presence of participating neighboring groups like -OAc, -OBz at 2-position of the donor, β-selectivity was observed where as 2-deoxy donors gave selectively α-anomers. Further, the efficacy of this methodology was demonstrated by synthesising complex cyclic triterpene glycoside saponin. The proposed isochromen-4-yl gold(I) intermediate **42** was successfully isolated and characterised by X-ray analysis (Figure 1).[21] Groups that cannot involve in neighboring group participation such as benzyl at C-2 position forms the product with α-selectivity. Tetrabenzoyl glycosyl *ortho*-hexynylbenzoate **43** when treated with phenol derivative under gold(I)-catalysed conditions gave aryloxy glycoside **44** in good yield with β-selectivity (Scheme 18).

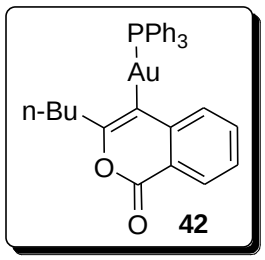
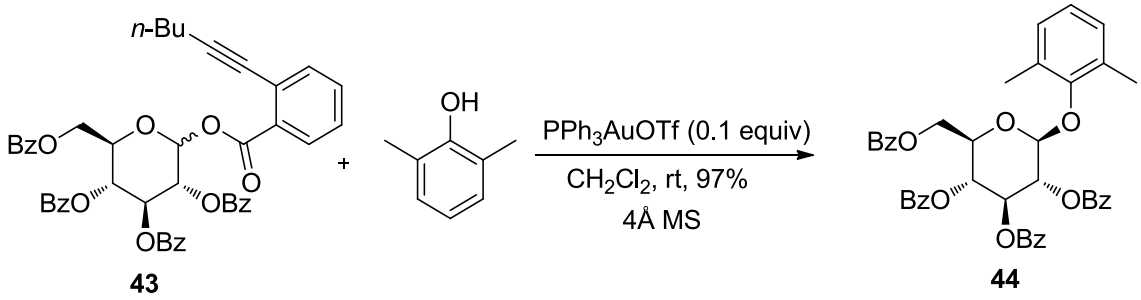


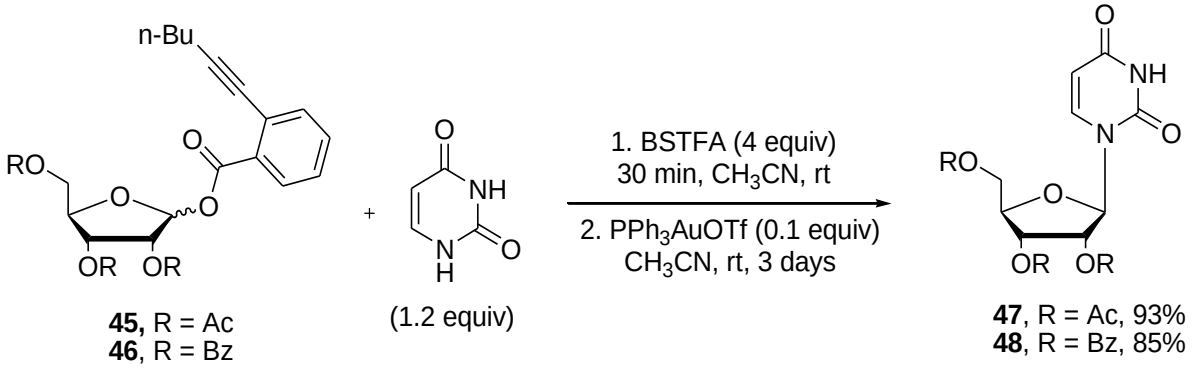
Figure 1



Scheme 18. Glycosyl *ortho*-hexynylbenzoate **43** as glycosyl donor

This methodology was applied in the synthesis of nucleosides under different reaction condition as compared to Scheme 18. Since pyrimidines are less nucleophilic, silylated pyrimidines were employed in the reaction. Initially, pyrimidines were treated with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) in acetonitrile to form silylated pyrimidines which were employed in the *in situ* glycosylation to yield nucleosides. On the other hand, purines were employed directly without prior silylation to form nucleosides. Glycosyl *ortho*-hexynylribofuranoside donor **45** or **46** and uracil were treated with BSTFA (4 equiv) to form

silylated uracil (Scheme 19).[22] Then, the reaction mixture was reacted with gold(I) catalyst to get nucleoside **47** or **48** in good yield but after stirring for three days.

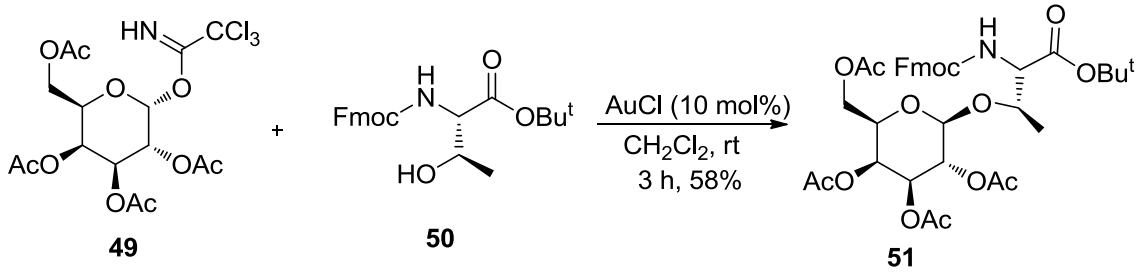


Scheme 19. Synthesis of nucleosides **47** and **48** using glycosyl *ortho*-hexynylbenzoate **45** and **46** as glycosyl donors

The scope of this methodology was extended to the next level by demonstrating the synthesis of Kaempferol 3-*O*-[2″,3″- and 2″,4″-di-*O*-(*E*)-*p*-coumaroyl]-α-L-rhamnopyranosides, two acylated flavonol 3-*O*-glycosides with strong inhibitory activity against methicillin-resistant *Staphylococcus aureus* by employing cyclopropyl alkynyl benzoates as glycosyl donors for assembling the required fragments.[23]

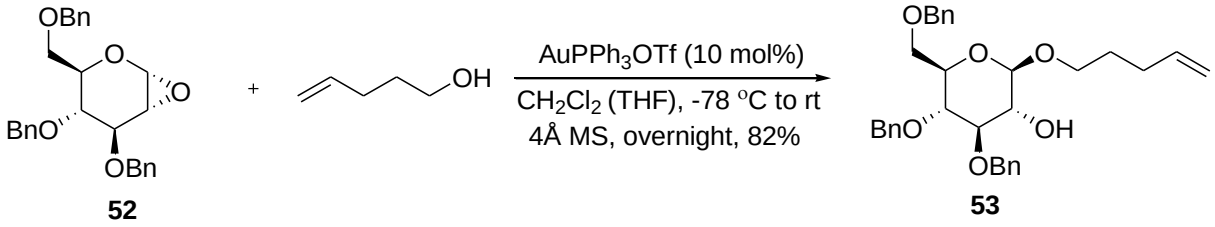
2.1.1.6.5 Gold-catalysed activation of known donors

Kunz and co-workers reported the activation of glycosyl halides and trichloroacetimidates by gold(I) chloride as the catalyst under ambient conditions.[24] Tetraacetyl galactotrichloroacetimidate **49** and amino alcohol **50** were treated with gold(I) chloride to get glycoconjugate **51** in good yield. Due to neighboring group participation of -OAc at 2-position β–anomer formed selectively (Scheme 20).



Scheme 20. Gold-catalysed activation of glycosyl trichloroacetimidate **49**

Glycosyl epoxides have been studied as donors under gold(I)-catalysed ambient conditions. Glycosyl epoxides can easily be made by treating protected glycals with DMDO in acetone solvent. By using this glycosylation protocol, 2-hydroxy sugars can be made easily which are very useful in constructing 2-linked oligosaccharides such as saponins. One interesting aspect of this reaction is that glyosyl epoxide **52** gave, in most of the cases, the β-anomer exclusively by S_N2 nucleophilic attack (Scheme 21).[25]

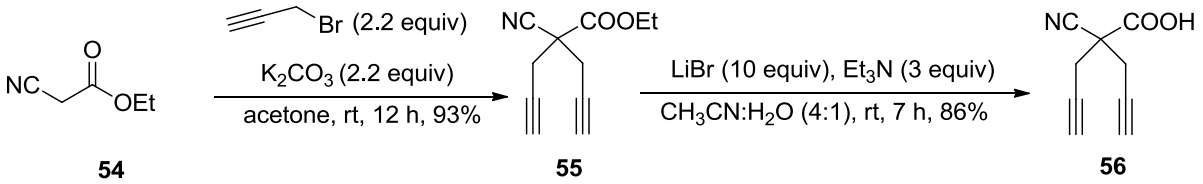


Scheme 21. Gold-catalysed activation of glycosyl epoxides **52** to synthesise 2-hydroxy glycosides **53**

2.2 Results and discussion

2.2.1 Preparation of starting materials

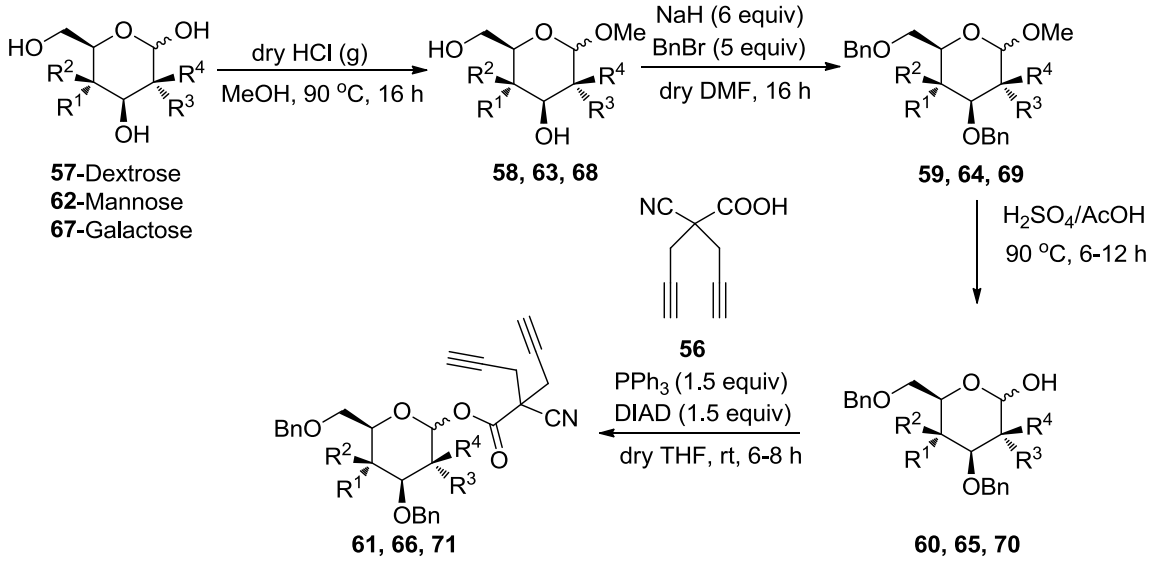
Dipropargyl ethyl ester **55** was made by alkylating ethyl cyanoacetate **54** with propargyl bromide using potassium carbonate as base. This ester **55** was hydrolysed under basic conditions to get the acid fragment **56** (Scheme 22).



Scheme 22. Synthesis of carboxylic acid fragment **56**

Methyl glucoside **58**, mannoside **63** and galactoside **68** were synthesized from commercially available dextrose **57**, mannose **62** and galactose **67** respectively by treating them separately with methanolic HCl solution (dry HCl gas was produced by dropwise addition of 35 % HCl onto the $CaCl_2$ granules placed in a separate dry chamber). These methyl glycosides on benzylation using NaH/BnBr gave methyl tetra-*O*-benzylglucoside **59**, mannoside **64** and galactoside **69** respectively. Lactols of gluco **60**, manno **65** and galacto **70** derivatives were made by heating the corresponding methyl tetra-*O*-benzylglycosides with H_2SO_4/AcOH system. These lactols were coupled with dipropargylcyanoacetic acid **56** to

furnish respective glycosyl esters of gluco **61**, manno **66** and galacto **71** derivatives (Scheme 23).

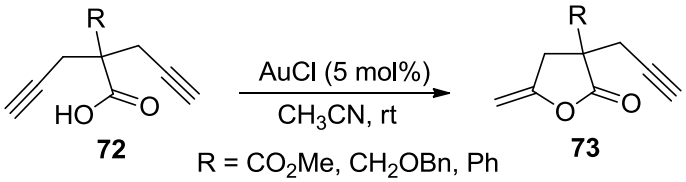


gluco series: $R^1 = R^3 = OBn$; $R^2 = R^4 = H$; **58**, (commercially avialable); **59**, 87%; **60**, 61%; **61**, 97%
manno series: $R^1 = R^4 = OBn$; $R^2 = R^3 = H$;(manno-): **63**, 90%; **64**, 55%; **65**, 52%; **66**, 78%
galacto series: $R^2 = R^3 = OBn$; $R^1 = R^4 = H$; (galacto-): **68**, 85%; **69**, 51%; **70**, 60%; **71**, 78%

Scheme 23. Synthesis of glycosyl esters starting from corresponding commercially available sugars

2.2.2 Activator design

Having utilized $AuCl_3$ in efficient Ferrier reaction of glycals (Chapter 1), we wished to develop an efficient Au(III)-catalysed glycosylation reaction.[26] For this purpose, we planned for an activator which will generate oxocarbenium ion upon treatment with gold catalysts. Genin *et al.* have reported gold-catalysed cyclisation of 4-alkynyl carboxylic acid **72** to make γ-methylene lactone **73** (Scheme 24).[27]



Scheme 24. Gold-catalysed synthesis of γ-methylene lactone **73**

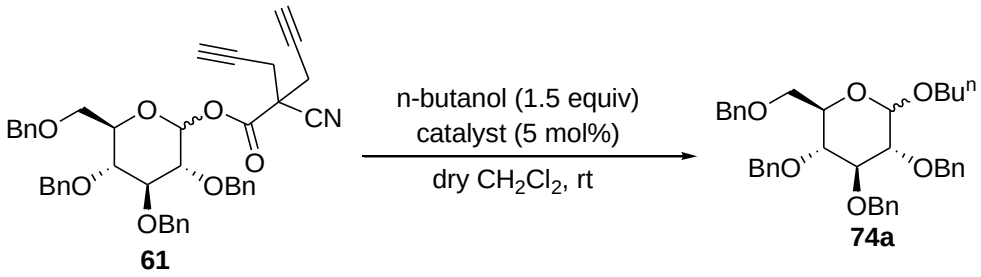
We planned to employ this simple methodology in the glycosylation reaction to cleave the activator from the glycosyl counterpart under gold catalysis to deliver

oxocarbenium ion for further functionalisation. We aspired to make the activator from commercially available ethyl cyanoacetate. We choose ethyl cyanoacetate to make the activator for two reasons. First is, it can easily be propargylated. The second and important reason is, it has CN group which can assist the cleavage of the activator by giving nucleophilic assistance or stabilise the formed oxocarbenium ion from axial side so that it can direct the incoming nucleophile from the equatorial side. However, chance for the nucleophilic participation to facilitate the cleavage of the activator from the anomeric carbon is less as the orientation of the lone pair on N is along the C-N triple bond direction. Although the activator in the substrate will be in the form of glycosyl ester, unlike the acid which involved in the study by Genet and co-workers, it is expected that the ring oxygen can participate in effecting the activator to cyclize. Although only one propargyl group is required for the cyclization, it is difficult to make mono propargylated derivative as the reaction resulted in the dipropargyl derivative.

2.2.3 Optimization of reaction conditions

The proposed glycosylation reaction was evaluated using glycosyl donor **61** and *n*-BuOH using different gold as well as other transition metal catalysts. We started investigating glycosylation reaction by treating 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dipropargylcyanoacetic ester **61** with *n*-butanol (1.5 equiv) in the presence of gold catalysts at room temperature. With $AuCl_3$ alone as the catalyst, the glycosylation proceeded but gave the desired product in low yield (28%) and 0.6:1 α/β ratio (Table 1, entry 1). $AgSbF_6$ resulted in 50% yield of the product (entry 2). When the reaction was carried out in the presence of $AuCl_3$ and $AgSbF_6$ the yield improved to 78% (entry 3). $AuCl_3$ with either AgOTf or $AgBF_4$ were comparatively less effective (entry 4 & 5). With $AuPPh_3Cl$, the glycosylation reaction did not proceed (Table 1, entry 6). $AuPPh_3Cl/AgSbF_6$ and $AuPPh_3Cl$/AgOTf systems also worked well but slightly less effective in terms of yield (Table 1, entry 7 & 8). Among the catalysts screened $AuCl_3/3AgSbF_6$ was found to give good yield of *n*-butyl 2,3,4,6-tetrabenzylglucopyranoside **74a** (Table 1, entry 3).

Table 1. Results of catalyst optimisation for gold-catalysed glycosylation



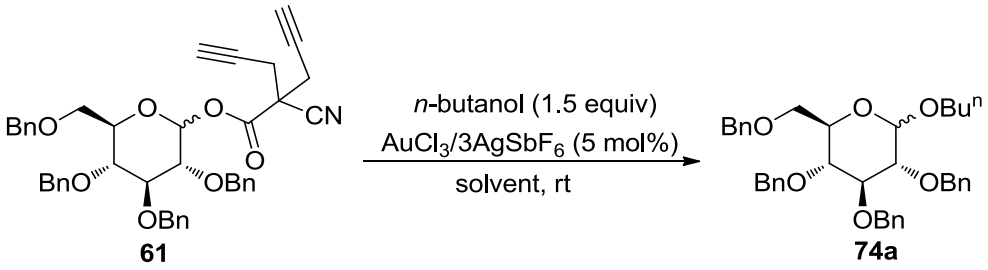
61 **74a**

Entry	Catalyst (5 mol%)	Time (h)	Yield (%)[a]	α/β[b,c]
1	$AuCl_3$	48	28	0.6:1
2	$AgSbF_6$	48	50	1:1
3	**$AuCl_3$/3$AgSbF_6$**	**12**	**78**	**1.2:1**
4	$AuCl_3$/3AgOTf	24	66	1.1:1
5	$AuCl_3$/3$AgBF_4$	24	22	1.1:1
6	Au(PPh_3)Cl	48	NR	-
7	Au(PPh_3)Cl/$AgSbF_6$	24	69	1.8:1
8	Au(PPh_3)Cl/AgOTf	24	44	1.3:1
9	Au(PPh_3)Cl/$AgBF_4$	24	12	1.3:1
10	$PtCl_4$/4$AgSbF_6$	24	30	1.4:1
11	Cu$(OTf)_2$	24	5	1.3:1

[a]Isolated yields. [b]Ratio is based on the ^{1}H NMR integration. [c]α/β ratio of **61** is 1.3:1.

Then, a set of reactions were carried out in different solvents using $AuCl_3$/3$AgSbF_6$ to find the best solvent. Among the solvents screened, CH_2Cl_2, DCE and CH_3CN were found to be good for the glycosylation reaction (Table 2, entry 2, 3 & 4). The selectivity observed is different for different solvents. More β-selectivity is observed in CH_3CN, THF and acetone might probably due to the coordination of solvents to the oxocarbenium ion from α-face (Table 2, entry 1, 4 & 7). In DMF solvent, the glycosylation reaction not at all occurred (Table 2, entry 6). Based on these experiments, $AuCl_3$/3$AgSbF_6$ system in CH_2Cl_2 was chosen for the investigation of substrate scope. 2,3,4,6-Tetra-*O*-benzylglucosyl ester **61** was treated with various acceptors to get glucosides 7**4a-74f** as a mixture of anomers (Scheme 25).

Table 2. Results of solvent optimisation for gold-catalysed glycosylation



S.No	Solvent	Time (h)	Yield (%)[a]	α:β[b,c]
1	THF	48	23	0.8:1
2	**CH_2Cl_2**	**12**	**78**	**1.2:1**
3	$ClCH_2CH_2Cl$	48	66	1.1:1
4	CH_3CN	36	67	0.6:1
5	Dioxane	48	trace	-
6	DMF	48	NR	-
7	Acetone	48	19	0.6:1

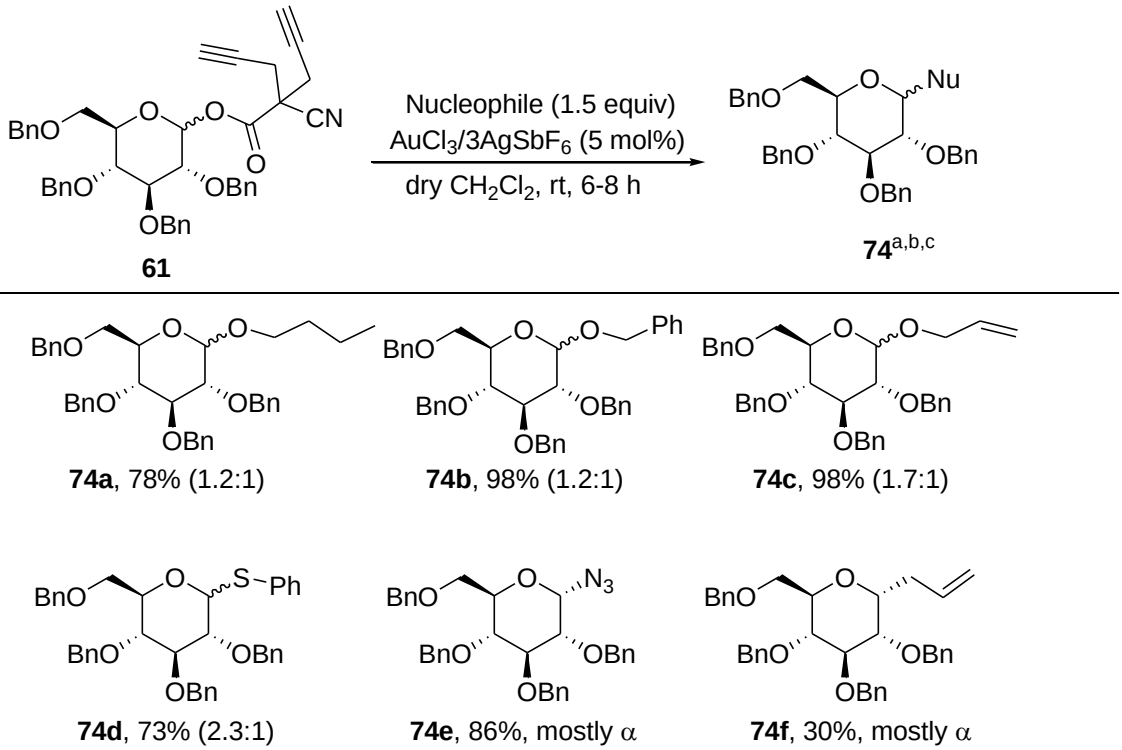
[a]Isolated yields. [b]Ratio is based on the ^{1}H NMR integration. [c]α/β ratio of **61** is 1.3:1.

Acceptors such as *n*-butyl, benzyl and allyl alcohols reacted smoothly to give the corresponding *n*-butyl, benzyl and allyl glycosides 7**4a-74c** respectively in very good yields and as a mixture of anomers with marginal α-selectivity. Thiophenol also reacted with glucosyl donor **61** to give thioglucoside 7**4d** in 73% yield. Because of growing number of applications of azides in click chemistry,[28] we attempted the glycosylation with $TMSN_3$. To our delight we were successful in getting 1-azido-2,3,4,6-tetra-*O*-benzylglucose 7**4e** in good yield with α-selectivity. However, when allyltrimethylsilane was used as nucleophile the yield was poor.

We then studied the glycosylation of 2,3,4,6-tetra-*O*-benzylmannopyranosyl ester **66** with several nucleophiles under the optimized gold-catalysed conditions (Scheme 26). Oxygen-based nucleophiles like, benzylalcohol, *n*-butanol, isopropanol and allyl alcohol reacted smoothly to give respective mannosides **75a-75d** in excellent yields and with exclusively α-selectivity. Next, we attempted the glycosylation with $TMSN_3$, and found the formation of 1-azidomannoside **75e** stereoselectively in 69% yield. Interestingly, hydride donor Et_3SiH reacted well with sugar donor **66** to furnish 1,5-anhydromannitol **75f** in good

yield. Benzyl mercaptan and thiophenol were also reacted with mannosyl ester **66** to get the corresponding thiomannosides **75g** and **75h** in moderate yields. Slightly decreased yields in the reaction using sulphur nucleophiles might be due to the possible coordination of sulphur with gold. Like in the case of glucosides, reaction with allyl trimethylsilane with substrate **66** resulted in poor yield. In all the cases, mannosides **75a-75i** were obtained as pure α-anomer.

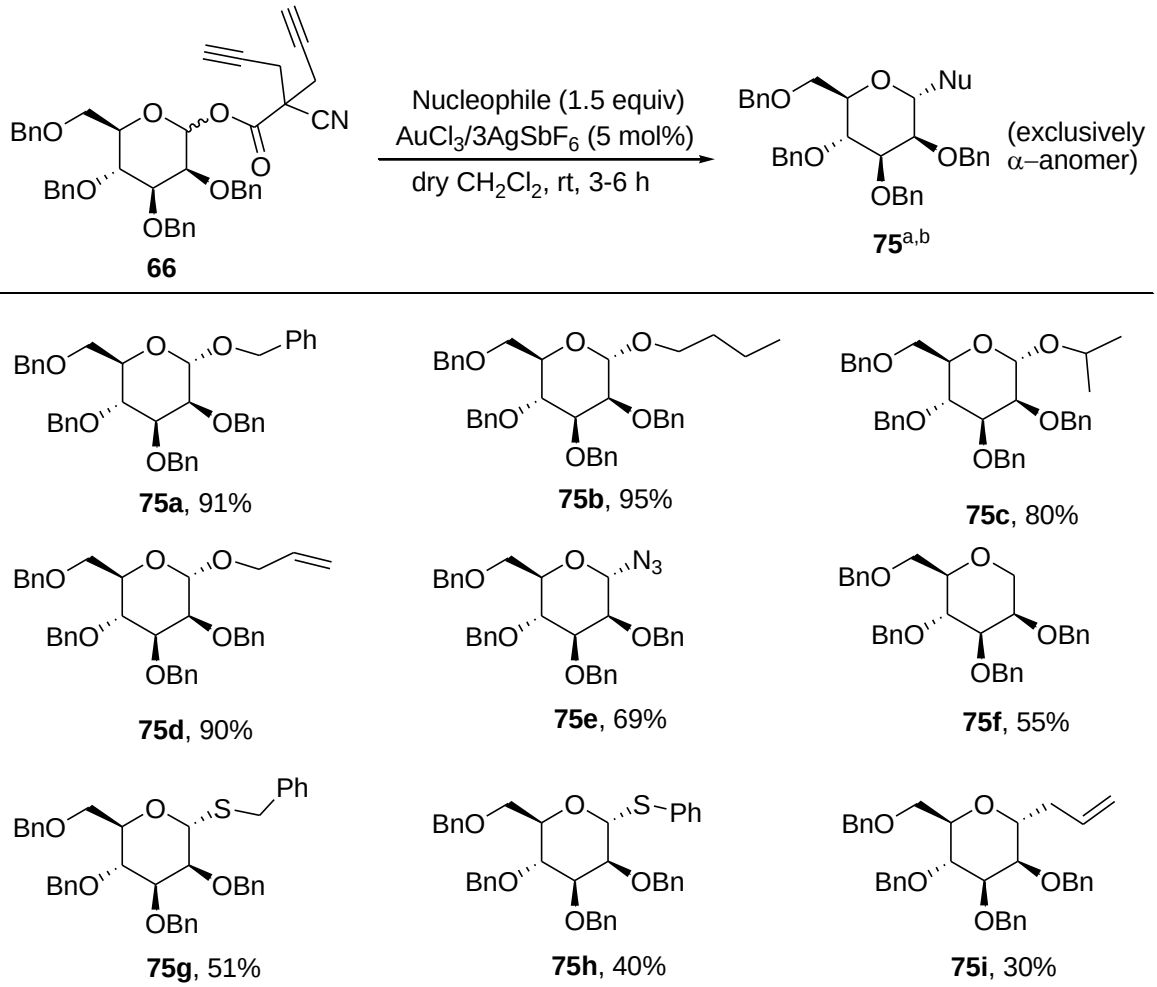
Scheme 25. Synthesis of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides



[a]Isolated yields. [b]Values in parantheses represents the α/β ratio based on ^{1}H NMR integration. [c]α/β ratio of starting glycosyl ester is 1.3:1.

Gold-catalysed glycosylation reaction was checked using galactosyl donor **71** as well (Scheme 27). Glycosylation reaction using galactosyl donor **71** with *n*-propanol and allyl alcohol yielded corresponding galactosides **76a-76b** in excellent yields and with slight α-selectivity. With $TMSN_3$ and thiophenol, 1-azidogalactoside **76c**, thiogalactoside **76d** were obtained in 61%, 57% yields respectively with good α-selectivity.

Scheme 26. Synthesis of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosides

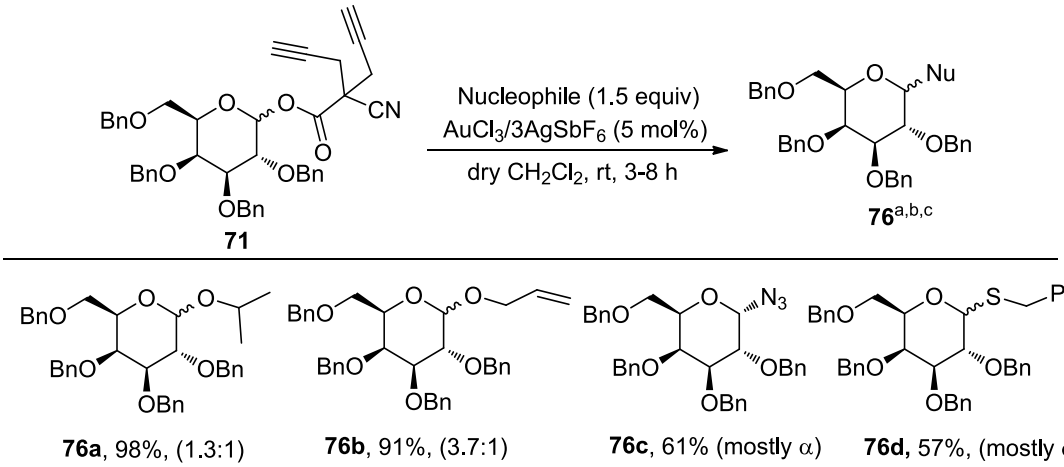


[a]Isolated yields. [b]α/β ratio of **66** is 1.9:1 and for reactions involving **75a**, **75b** and **75h**, α/β ratio of **66** is 25:1.

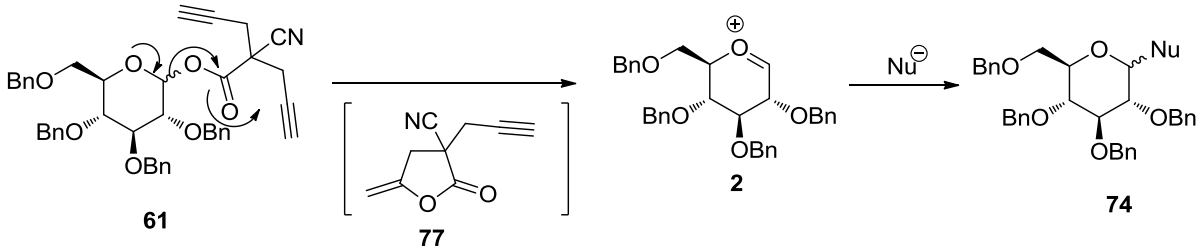
From the mechanistic insight, we hypothesise that gold(III) first coordinates to the triple bond of the alkyne activator. Further attack of the carbonyl oxygen of the activator onto the alkyne in 5-*exo*-*dig* fashion give γ-methylene lactone **77** and sugar oxocarbenium ion **2**. This oxocarbenium ion reacts with the nucleophiles to form anomeric glycosides **74**. From any of the glycosylation reactions, we could not isolate the γ-methylene lactone **77**. We wished to check the lactone formation in the cases of both simple propargyl cyanoacetic acid and its ethyl ester. When we treated dipropargylcyano ethyl ester under optimised $AuCl_3/3AgSbF_6$ conditions in dichloromethane solvent, we didn't observe the formation of γ-

methylene lactone derivative **77**. This outcome suggests the role of sugar ring oxygen in the expulsion of the leaving group. However, dipropargylcyanoacetic acid gave the α-methylene lactone **77** which was isolated under identical reaction conditions in an yield of 22%.

Scheme 27. Synthesis of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosides



[a]Isolated yields. [b]Ratio is based on the ^{1}H NMR integration. [c]Pure α-glycosyl ester.

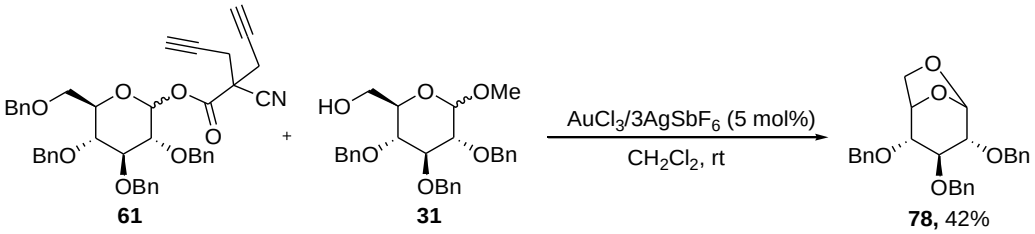


Scheme 28. Plausible mechansim for gold-catalysed glycosylation reaction

2.2.4 Attempts to make disaccharide

Several attempts were made for the preparation of disaccharide derived from glycosyl donor **61** and acceptor **31**, but we failed to get the desired product. We observed the decomposition of donor **61** under the reaction conditions and acceptor **31** underwent intramolecular glycosylation reaction to provide 1,6-anhydrosaccharide **78**. Then, we attempted the glycosylation reaction with 4-hydroxy free sugar. Here also we failed to get the desired disaccharide but most of the acceptor has been recovered from the reaction. These

results indicate the strong acidic glycosylation conditions which might not fit for less nucleophilic and acid sensitive acceptors.



Scheme 29. Attempted disaccharide formation with glucosyl donor **61**

2.3 Conclusions

Gold-catalysed glycosylation strategy has been developed using an easily accessible activator derived from commercially available ethyl cyanoacetate. Several nucleophiles such as *O*-, *S*-, and *C*-based nucleophiles, azides and hydrides have been employed in the glycosylation reaction. Glucosyl **74a-74f**, mannosyl **75a-75i** and galactosyl **76a-76d** pyranosides were formed under the optimised reaction conditions in moderate to good yields. Ring oxygen is responsible for the effective leaving of the activator. Mannosides **75a-75i** were formed exclusively as α-anomers. Glucosides **74a-74f** and galactosides **76a-76d** were formed as a mixture of anomers. Disaccharide formation was attempted but the outcome was not fruitful.

2.4 Experimental section

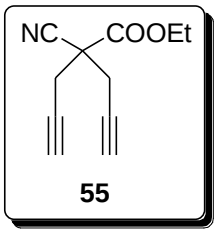
General information

Refer chapter 1 for general information.

Synthesis of carboxylic acid fragment 56

Preparation of dipropargyl ethylcyanoacetate 55[29]

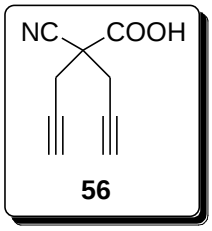
To a solution of ethyl cyanoacetate **54** (3 g, 24.3 mmol) and distilled acetone (70 mL) in a 100 mL round bottom flask, K_2CO_3 (8.4 g, 60.9 mmol) was added. After stirring for 30 min, propargyl bromide (5.5 mL, 60.9 mmol) was added drop wise. The reaction mixture was stirred at



55

room temperature. After 12 h, the resulting solution was concentrated, and diluted with ethyl acetate. The organic fraction was washed with saturated NH_4Cl solution several times to remove base. The organic layers were combined and washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography to get compound **55 (**4.6 g**)** as clear liquid. Yield: 93%; IR (neat, cm^{-1}): 3294, 1747, 1242, 1217, 659; ^1H NMR (400 MHz, $CDCl_3$): δ 4.34 (q, *J* = 7.2 Hz, 2H), 2.94 (d, *J* = 2.4 Hz, 4H), 2.23 (t, *J* = 2.4 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 117.0, 76.0, 73.6, 63.5, 47.1, 25.6, 13.8; HRMS (ESI) m/z calcd for $C_{11}H_{11}NO_2$ $[M+Na]^+$ = 212.0687, found = 212.0702.

Preparation of acid derivative 56[30]



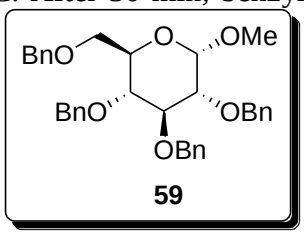
56

Dipropargyl cyano ester **55** (1.57 g, 9.35 mmol) was dissolved in a mixture of CH_3CN and H_2O (4:1) solvent. To this solution, triethylamine (2.83 g, 28 mmol) was added followed by addition of LiBr (8.12 g, 93.5 mmol). The reaction mixture was stirred vigorously at room temperature for 7 h. The reaction progress was monitored by TLC, and the reaction mixture was quenched by adding AcOH carefully. The reaction mixture was washed with ethyl acetate to remove any unreacted ester. This ethyl acetate layer was drained off. After that the p^H of the reaction mixture (aqueous layer from ethyl acetate washing) was taken to 6 by adding 2N HCl carefully before doing work up. Now again the aqueous acidic solution was washed with ethyl acetate several times. The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The pasty acid **56 (**1.3 g) was used for the next step without any further purification. Yield: 85%; IR (KBr, cm^{-1}): 3298, 1741, 1253, 663; ^1H NMR (400 MHz, $CDCl_3$): δ 9.76 (br s, 1H), 2.99-2.98 (m, 4H), 2.29 (t, *J* = 2.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 116.4, 75.7, 74.1, 47.5, 25.6; HRMS (ESI) m/z calcd for $C_9H_7NO_2$ $[M+Na]^+$ = 184.0374, found = 184.0377.

Synthesis of glucosyl ester 61

Preparation of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 59[31]

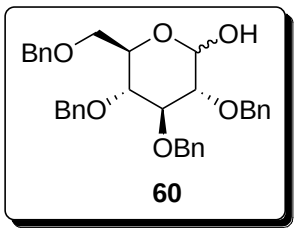
To a solution of methyl glucoside **58** (2.00 g, 10.29 mmol) in dry DMF (75 mL) sodium hydride (3.52 g, 88.1 mmol) was added portion wise at 0 °C. After 30 min, benzyl bromide (8.3 mL , 70.8 mmol) was added drop wise. The reaction was monitored by TLC, after completion of the reaction, the brown colored reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was washed with NH_4Cl solution and brine solution. The organic fraction was concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/EtOAc = 5/1) to get methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **59** (4.9 g) as colourless oily liquid. Yield = 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.25 (m, 18H), 7.13-7.11 (m, 2H), 4.97 (d, *J* = 10.4 Hz, 1H), 4.83-4.78 (m, 3H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.62-4.48 (m, 2H), 4.47-4.45 (m, 2H), 3.98 (t, *J* = 9.8 Hz, 1H), 3.75-3.70 (m, 2H), 3.64-3.60 (m, 2H), 3.55 (dd, *J* = 9.6, 2.6 Hz, 1H), 3.37 (s, 3H).



59

Preparation of 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranose 60[31]

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside **59** (3 g, 5.5 mmol) was dissolved in a mixture of glacial acetic acid (60 mL) and aqueous H_2SO_4 (2M, 30 mL). The reaction mixture was heated to 90 °C for 12 h. After completion of the reaction, the reaction mixture was diluted with cold water (70 mL) and ethyl acetate (70 mL). The organic layer was washed several times with water to remove AcOH and then with aqueous $NaHCO_3$. The organic fraction was concentrated to give syrup. The syrup was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1) to get 2,3,4,6-tetra-*O*-benzyl-glucopyranose **60** (1.8 g) as a white solid. Yield = 61%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.26 (m, 18H), 7.14-7.12 (m, 2H), 5.22 (d, *J* = 3.5 Hz, 1H), 4.94 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 10.8 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.48 (d, *J* = 12.2 Hz, 1H),

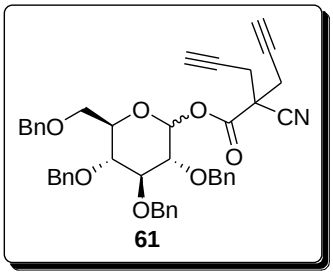


60

4.05-4.01 (m, 1H), 3.96 (t, *J* = 9.1 Hz, 1H), 3.70 (dd, *J* = 10.4, 3.4 Hz, 1H), 3.63 (dd, *J* = 7.7, 2.1 Hz, 2H), 3.59-3.52 (m, 1H).

Coupling reaction of 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranose 60 and 2-cyano-2-(prop-2-ynyl)pent-4-ynoic acid 56

2,3,4,6-Tetra-*O*-benzyl-glucopyranose **60** (1.96 g, 3.6 mmol) was dissolved in dry THF (15 mL) in an oven dried 100 mL round bottom flask. A solution of cyano carboxylic acid derivative **56** (0.878 g, 5.45 mmol) in dry THF was added. To this reaction mixture, triphenylphosphine (1.43 g, 5.45 mmol), diisopropyl azodicarboxylate (1.1 g, 5.45 mmol) were added successively. The reaction mixture was stirred at room temperature under N_2 atmosphere. After 6 h, the resulting solution was concentrated and diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution several times to remove acid. It was washed with brine solution and dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure. The residue was purified by column chromatography to get glucosyl ester **61** (2.3 g) as a mixture of anomers. Yield = 97%; $[\alpha]_D^{25}$ +39.2 (c, 2.5, $CHCl_3$); IR (KBr, cm^{-1}): 3290, 2920, 1759, 1093, 1070, 738, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.24 (m, 37H), 7.18-7.14 (m, 4H), 6.38 (d, *J* = 3.0 Hz, 1H), 5.66 (d, *J* = 7.02 Hz, 1H), 4.94-4.90 (m, 1.7H), 4.88-4.87 (m, 1H), 4.85-4.83 (m, 3H), 4.80-4.78 (m, 1.6H), 4.65 (m, 2H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 11.1 Hz, 1H), 3.97-3.92 (m, 2H), 3.79-3.69 (m, 6H), 3.63 (d, *J* =11.4 Hz, 2H), 2.98-2.83 (m, 7H), 2.17 (t, *J* = 2.3 Hz, 1.7H), 2.10 (t, *J* = 2.1 Hz, 1H), 2.04-2.03 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 164.6, 138.3, 138.2, 137.9, 137.8, 137.7, 137.5, 128.4, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 116.7, 96.5, 93.6, 84.4, 81.2, 80.3, 78.6, 76.0, 75.9, 75.7, 75.6, 75.2, 75.0, 74.9, 74.3, 74.0, 73.8, 73.7, 73.5, 73.4, 68.1, 67.9, 47.5, 26.0, 25.8, 25.5; HRMS (ESI) m/z calcd for $C_{43}H_{41}NO_7$ $[M+Na]^+$ = 706.2781, found = 706.2781.



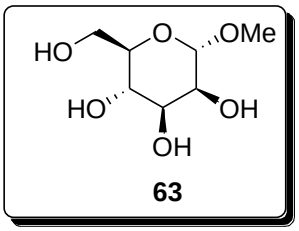
61

Synthetic route for making 2,3,4,6-tetra-*O*-benzylmannosyl ester 66

Preparation of methyl-α-D-mannopyranoside 63

D-Mannose **62** (3 g, 16.67 mmol) was dissolved in dry methanol (100 mL) and dry HCl gas was passed through the reaction mixture (dry HCl gas was produced by dropwise

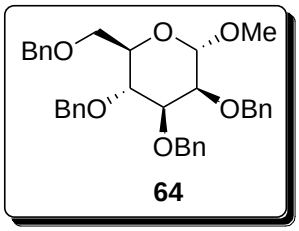
addition of 35% HCl onto the $CaCl_2$ granules in a separate dry chamber). After complete passage of dry HCl through the reaction mixture, it was refluxed at 90 °C. After 16 h, a light brown solution was formed which was cooled to room temperature. The resulting solution was neutralized with $PbCO_3$ (s). The resulting white slurry was filtered to remove inorganic salts. The solvent was removed under reduced pressure and thus yielded in a creamy solid of methyl α-D-mannopyranoside **63** (2.9 g) which was used directly in the next step without any further purification. Yield = 90%.



63

Preparation of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside 64[32]

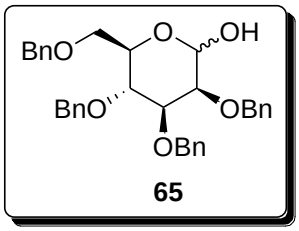
To a solution of methyl mannoside **63** (2.8 g, 14.6 mmol) in dry DMF (75 mL), sodium hydride (3.52 g, 88.1 mmol) was added at 0 °C. After 30 min, benzyl bromide (8.3 mL, 70.8 mmol) was added dropwise at 0 °C. The reaction mixture was stirred overnight. After completion of the reaction, the white cloudy reaction mixture was poured into water and extracted with ethyl acetate and washed with NH_4Cl and brine solution. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes/EtOAc = 5/1) to get methyl 2,3,4,6-tetra-*O*-benzyl-D-mannopyranoside **64** (4.4 g) as colourless oily liquid. Yield = 55%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.25 (m, 18H), 7.16–7.14 (m, 2H), 4.88 (d, *J* = 11.1 Hz, 1H), 4.77-4.73 (m, 3H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.60 (m, 2H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 3.97 (t, *J* = 9.6 Hz, 1H), 3.88 (dd , *J* = 9.3, 3.1 Hz, 1H), 3.80–3.72 (m, 4H), 3.32 (s, 3H).



64

Preparation of 2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranose 65[33]

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside **64** (2 g, 3.6 mmol) was dissolved in a mixture of glacial acetic acid (55 mL) and aqueous H_2SO_4 (1M, 18 mL). The reaction mixture was heated to 90 °C with vigorous stirring for 3 h. After completion of the reaction, the reaction mixture was diluted with cold water (70 mL) and ethyl acetate (70 mL). The organic layer was separated and washed

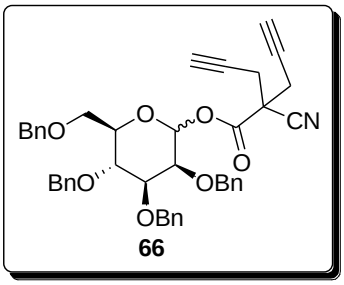


65

several times with water to remove excess AcOH, and then with aqueous $NaHCO_3$ followed by water. The solution was concentrated to get syrup. The syrup was purified by column chromatography to get 2,3,4,6-tetra-*O*-benzyl-mannopyranose **65** (1.0 g) as dense liquid. Yield = 52%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.24 (m, 18H), 7.16–7.14 (m, 2H), 5.24 (m, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.74 (d, *J* = 12.3 Hz, 1H), 4.69 (d, *J* = 12.3 Hz, 1H), 4.60-4.59 (m, 2H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.02 (m, 1H), 3.95 (dd, *J* = 9.3, 3.0 Hz, 1H), 3.87-3.82 (m, 1H), 3.81-3.78 (m, 1H), 3.73-3.69 (m, 1H), 3.65 (dd, *J* = 10.2, 6.4 Hz, 1H).

Coupling of 2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranose 65 with 2-cyano-2-(prop-2-ynyl)pent-4-ynoic acid 56

2,3,4,6-Tetra-*O*-benzyl-mannopyranose **65** (1 g, 1.66 mmol) was dissolved in dry THF (15 mL) in an oven dried 100 mL round bottom flask. Cyano carboxylic acid derivative (0.402 g, 2.49 mmol) in dry THF was added. To this reaction mixture, triphenylphosphine (0.653 g, 2.49 mmol), diisopropyl azodicarboxylate (0.5037 g, 2.49 mmol) were added in tandem. The reaction mixture was stirred at room temperature under N_2 atmosphere. After 6 h, the resulting solution was concentrated and diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution several times to remove acid. It was washed with brine solution and dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure. The residue was purified by column chromatography to get mannosyl ester **66** (0.9 g) as the mixture of anomers. Yield = 78%; $[\alpha]_D^{25}$ +10.24 (c, 1.3, $CHCl_3$); IR (KBr, cm^{-1}): 3288, 2870, 1759, 1319, 1028; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.36 (m, 2H), 7.33–7.24 (m, 16H), 7.20–7.17 (m, 2H), 6.25 (d, *J* = 2.0 Hz, $1H^{\alpha}$), 5.87 (d, *J* = 1.65 Hz, $1H^{\beta}$) 4.87 (d, *J* = 11.5 Hz, 1H), 4.74 (br s, 2H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H) 4.13–4.08 (m, 1H), 4.03–3.98 (m, 1H), 3.91–3.85 (m, 1H), 3.79– 3.74 (m, 2H), 3.68 (d, *J* = 11.2 Hz, 1H), 2.86–2.82(m, 4H), 2.16–2.13 (m, 1H), 2.07(t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 137.9, 137.8, 137.3, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.5, 116.4, 94.8, 78.6, 75.8, 75.7, 75.1, 75.0, 74.1, 73.9, 73.8, 73.4, 73.3, 73.1, 72.7, 72.4, 68.4, 47.5, 25.6; HRMS (ESI) m/z calcd for $C_{43}H_{41}NO_7$ $[M+Na]^+$ = 706.2781, found = 706.2781.

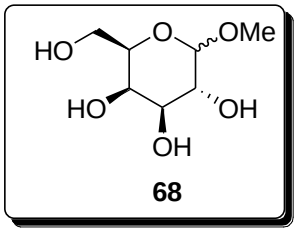


66

Synthesis of galactosyl ester 71

Preparation of methyl-α/β-D-galactopyranoside 68

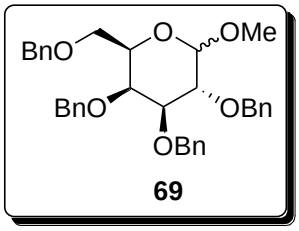
Galactose **67** (5 g, 27.7 mmol) was dissolved in dry methanol (35 mL) and dry HCl gas was passed through the reaction mixture (dry HCl gas was produced by dropwise addition of 35 % HCl onto the $CaCl_2$ granules in a separate dry chamber). After complete passage of dry HCl through the reaction mixture, it was refluxed at 90 °C. After 14 h, a clear solution formed which was cooled to room temperature. The resulting solution was neutralized with $PbCO_3$ (s). The resulting white slurry was filtered to remove inorganic salts. Solvent was removed under reduced pressure. The resulting brown syrup was used directly for the next step without any further purification. Yield: 4.5 g, 84%.



68

Preparation of methyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranoside 69[32]

Methyl α-D-galactopyranoside **68** (4.49 g, 23.14 mmol) was dissolved in dry DMF (75 mL). Sodium hydride (60% dispersion in mineral oil) (5.2 g, 139 mmol) was added portion-wise to the solution at 0 °C under N_2 atmosphere. After 1 h, benzyl bromide (19.25 mL, 115.9 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched by adding methanol carefully. The solution was diluted with ethyl acetate, the organic layer was washed with water several times to remove DMF. The organic layers were combined and washed with brine solution and dried over anhydrous Na_2SO_4. Solvents was evaporated under reduced pressure. The residue was purified by column chromatography to get methyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside **69** (6.5 g) as a clear liquid. Yield: 51%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.24 (m, 37H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 11.8 Hz, 1H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.72 (d, *J* = 10.7 Hz, 1H), 4.71-4.66 (m, 3H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H),

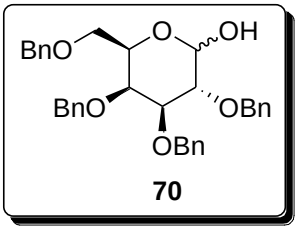


69

4.38 (d, *J* = 11.9 Hz, 1H), 4.05-3.98 (m, 1H), 3.94 (m, 2H), 3.92-3.87 (m, 2H), 3.82-3.76 (m, 1H), 3.79-3.68 (m, 1H), 3.61-3.58 (m, 1H), 3.54-3.50 (m, 2H), 3.36 (s, 3H).

Preparation of 2,3,4,6-tetra-*O*-benzylgalactopyranose 70[34]

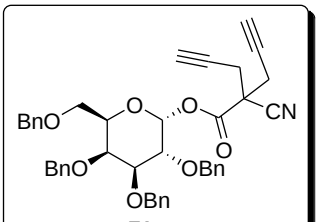
Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside **69** (5.8 g, 10.46 mmol) was dissolved in a mixture of glacial acetic acid (60 mL) and aqueous sulfuric acid (3M, 9 mL). The reaction mixture was heated to 90 °C with good stirring. The mixture was diluted with cold water (70 mL) and ethyl acetate (70 mL) was added to it. The layers were separated and the organic layer was first washed with water to remove excess of AcOH, followed by aqueous $NaHCO_3$, dried over anhydrous sodium sulfate. The solution was concentrated to get a syrup. The crude syrup was purified by column chromatography to get 2,3,4,6-tetra-*O*-benzyl-galactopyranose **70** (3.4 g) as a syrup. Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 20H), 5.27 (d, *J* = 3.5 Hz, 1H), 4.95-4.90 (m, 1H), 4.83-4.68 (m, 4H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.17-4.13 (m, 1H), 4.03 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.95-3.87 (m, 2H), 3.55-3.44 (m, 2H).



70

Preparation of galactosyl ester 71

2,3,4,6-Tetra-*O*-benzyl-galactopyranose **70** (2 g, 3.7 mmol) was dissolved in dry THF (20 mL) in a dry 100 mL round bottom flask. Cyanocarboxylic acid derivative **56** (0.896 g, 5.56 mmol) was added as a solution in dry THF. To this mixture triphenylphosphine (1.46 g, 5.56 mmol) and diisopropyl azodicarboxylate (1.12 g, 5.56 mmol) were added. The reaction mixture, was stirred at room temperature under N_2 atmosphere. The reaction was monitored by TLC. After 5 h, The resulting solution was concentrated and diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution several times to remove acid then with brine solution and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography to get galactosyl ester **71** (1.9 g) as pure α-anomer. Yield: 78%; $[\alpha]_D^{25}$ +39.8 (c, 0.7, $CHCl_3$); IR (KBr, cm^{-1}): 3290, 2924, 1759, 1211, 1105, 698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.21 (m, 20H), 6.39 (d, *J* = 3.3



71

Hz 1H$_\alpha$), 4.94 (d, *J* = 11.3 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 11.9 Hz 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.19-4.09 (m, 2H), 4.03 (br s, 1H), 3.94 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.52 (d, *J* = 5.6 Hz, 2H), 2.86 (qd, *J* = 17.0, 2.6 Hz, 2H), 2.80-2.71 (m, 2H), 2.11 (t, *J* = 2.5 Hz, 1H), 2.03 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 138.1, 137.8, 137.6, 128.4, 128.2, 128.2, 127.9, 127.8, 127.8, 127.7, 127.6, 116.8, 94.3, 77.9, 76.0, 75.8, 75.0, 74.9, 74.1, 73.9, 73.8, 73.4, 73.3, 72.9, 72.6, 68.1, 47.6, 25.9, 25.5; HRMS (ESI) m/z calcd for $C_{43}H_{41}NO_7$ $[M+Na]^+$ = 706.2781, found = 706.2781.

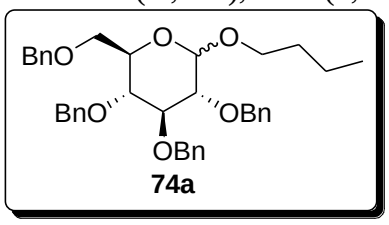
General procedure for gold-catalysed glycosylation reaction

To a stirred solution of glycosyl ester (0.1 g, 0.146 mmol) in dry dichloromethane (2 mL), nucleophile (1.5 equiv) was added. To this reaction mixture $AuCl_3$ (5 mol%)/3$AgSbF_6$ (15 mol%) were added successively under inert atmosphere and the reaction mixture was stirred at room temperature. After completion of the reaction as revealed by TLC analysis, dichloromethane was evaporated. The concentrated reaction mixture was directly loaded on to the silica gel column and purified using EtOAc/hexanes as eluents.

Characterisation data for the glycosides

***n*-Butyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranoside 74a**[35]

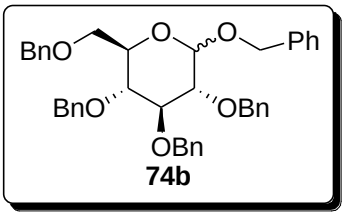
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 18H), 7.16-7.12 (m, 2H), 4.92 (d, *J* = 10.8 Hz, 1H), 4.82 (d, *J* = 10.8 Hz, 1H), 4.81 (d. *J* = 11.3 Hz, 1H), 4.75 (t, *J* = 3.7 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.00-3.94 (m, 1H), 3.79-3.68 (m, 2H), 3.67-3.58 (m, 3H), 3.56-3.51 (m, 1H), 3.46-3.39 (m, 1H), 1.71-1.58 (m, 2H), 1.46-1.34 (m, 2H), 0.92 (q, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 138.7, 138.5, 138.3, 138.2, 138.0, 129.6, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 120.6, 115.3, 103.7, 96.9, 84.8, 82.3, 82.2, 80.2, 78.0, 77.8, 77.3, 75.7, 75.1, 75.0, 74.9, 73.5, 73.2, 70.1, 69.8, 69.1, 68.6, 67.9, 31.9, 31.5, 29.7.



74a

Benzyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranoside 74b[36]

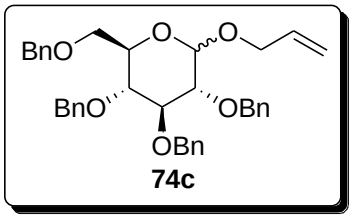
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (m, 44H), 7.18-7.11 (m, 4H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.98 (d, *J* = 11.8 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.92 (d, *J* = 10.9 Hz, 1H), 4.85-4.80 (m, 3H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 4.69-4.62 (m, 3H), 4.59-4.52 (m, 4H), 4.50-4.45 (m, 2H), 4.04 (t, *J* = 9.2 Hz, 1H), 3.80 (m, 1H), 3.76 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.72-3.71 (m, 1H), 3.69-3.67 (m, 1H), 3.65-3.61 (m, 2H), 3.59-3.57 (m, 1H), 3.56-3.54 (m, 1H), 3.49-3.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.6, 138.4, 138.2, 138.1, 138.1, 137.9, 137.4, 137.1, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 102.6, 95.6, 84.7, 82.3, 82.1, 79.9, 77.8, 77.3, 77.7, 75.7, 75.0, 75.0, 74.9, 74.9, 73.4, 73.0, 71.1, 70.3, 69.1, 68.9, 68.4.



74b

Allyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranoside 74c[33]

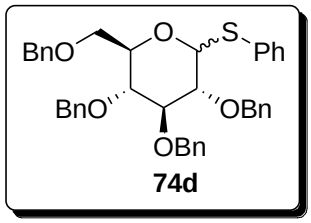
Mixture of anomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.25 (m, 18H), 7.17-7.12 (m, 2H), 6.02-5.87 (m, 1H), 5.36-5.27 (m, 1H), 5.20 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.97 (t, *J* = 11.1 Hz, 1H), 4.92 (d, *J* = 11.1 Hz, 1H), 4.84-4.75 (m, 3H), 4.73-7.51 (m, 2H), 4.47-4.41 (m, 2H), 4.14 (ddd, *J* =12.6, 5.4, 1.1 Hz, 1H), 4.03-3.96 (m, 1H), 3.82-3.68 (m, 2H), 3.67-3.64 (m, 1H), 3.62-3.55 (m, 1H), 3.50-3.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.6, 138.4, 138.2, 138.1, 138.0, 137.9, 134.0, 133.7, 128.3, 128.2, 128.1, 127.9, 127.9, 127.7, 127.7, 127.6, 118.2, 117.2, 102.7, 95.7, 84.7, 82.3, 82.1, 79.9, 77.9, 77.7, 75.7, 75.0, 74.9, 73.5, 73.2, 70.3, 70.2, 69.0, 68.4, 68.2.



74c

Phenyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-thio glucopyranoside 74d[37]

Mixture of anomers; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.14 (m, 38H), 5.64 (d, *J* = 4.3 Hz, 1H), 4.99 (d, *J* = 10.9 Hz, 1H), 4.91-4.77 (m, 4H), 4.74-4.65 (m, 3H), 4.61-4.55 (m, 2H), 4.49 (d, *J* = 10.3 Hz, 1H), 4.40 (d, *J* = 11.1 Hz, 1H), 4.34-4.31 (m, 1H), 3.90-3.88 (m, 2H), 3.80-3.72 (m, 2H), 3.70-3.65 (m, 2H), 3.60 (dd, *J* = 10.5, 1.6 Hz, 1H);

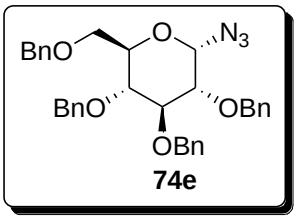


74d

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.4, 138.3, 138.2, 138.0, 137.9, 137.7, 134.5, 132.0, 131.6, 128.9, 128.5, 128.4, 128.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.1, 87.4, 87.0, 82.6, 80.8, 79.8, 79.1, 77.8, 75.8, 75.4, 75.1, 73.4, 72.6, 71.2, 69.0, 68.5.

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl azide 74e[38]

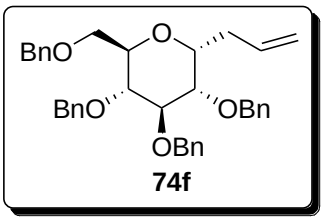
IR (KBr, cm^{-1}): 2916, 2866, 2112, 1093; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.21 (m, 18H), 7.13-7.11 (m, 2H), 5.21 (d, *J* = 4.2 Hz, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 4.83-4.78 (m, 2H), 4.75 (d, *J* = 10.9 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 3.88-3.82 (m, 1H), 3.73-3.71 (m, 1H), 3.66-3.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.3, 137.6, 137.7, 128.7, 128.5, 128.2, 128.1, 128.0, 127.8, 127.8, 88.1, 81.7, 79.4, 77.3, 75.1, 73.8, 73.6, 73.5, 72.5, 68.1.



74e

Prop-1-en-3-yl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside 74f[32]

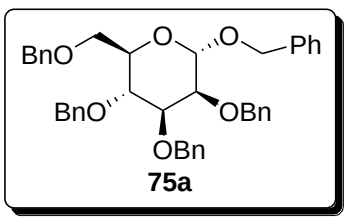
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.24 (m, 18H), 7.13-7.10 (m, 2H), 5.86-5.76 (m, 1H), 5.12-5.05 (m, 2H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.81 (d, *J* = 10.5 Hz, 2H), 4.69 (d, *J* = 11.6 Hz, 2H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.46 (d. *J* = 11.9 Hz, 2H), 4.13 (m, 1H), 3.82-3.73 (m, 2H), 3.70 (m, 1H), 3.66-3.58 (m, 3H), 2.55-2.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.3, 138.2, 138.1, 134.8, 128.5, 128.4, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 117.0, 82.5, 80.1, 78.2, 75.5, 75.2, 73.8, 73.5, 73.2, 71.2, 69.0, 29.9.



74f

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside 75a[39]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 22H), 7.16-7.15 (m, 3H), 4.97 (s, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.72 (m, 3H), 4.70 (d, *J* = 11.3 Hz, 1H), 4.60 (m, 2H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.50 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 10.6 Hz, 1H), 4.01 (t, *J* = 9.2 Hz, 1H), 3.95 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.85-3.77 (m, 3H), 3.70 (dd, *J* = 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.4, 138.2, 137.3, 128.4,

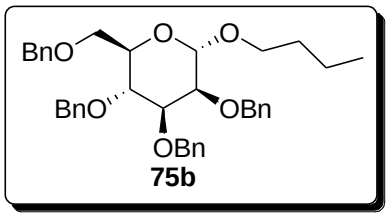


75a

128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 97.2, 80.2, 77.3, 75.2, 74.9, 74.6, 73.4, 72.5, 72.2, 72.0, 69.2, 68.9.

_n_-Butyl 2,3,4,6-tetra-_O_-benzyl-α-D-mannopyranoside 75b[40]

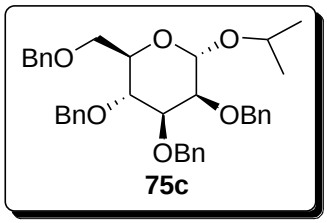
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.23 (m, 18H), 7.16-7.14 (m, 2H), 4.87 (d, *J* = 10.7 Hz, 2H), 4.75 (d, *J* = 12.4 Hz, 1H), 4.71 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.62 (m, 2H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 3.98 (t, *J* = 9.4 Hz, 1H), 3.90 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.80-3.71 (m, 4H), 3.68-3.63 (m, 1H), 3.38-3.32 (m, 1H), 1.53-1.46 (m, 2H), 1.35-1.23 (m, 2H), 0.88 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 97.7, 80.3, 75.2, 74.9, 74.7, 73.3, 72.5, 72.1, 71.7, 69.2, 67.3, 31.5, 19.3, 13.9.



75b

Isopropyl 2,3,4,6-tetra-_O_-benzyl-α-D-mannopyranoside 75c[39]

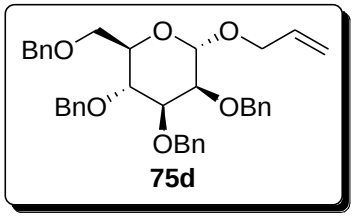
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.23 (m, 18H), 7.16-7.14 (m, 2H), 4.96 (d, *J* = 1.8 Hz, 1H), 4.87 (d, *J* = 10.6 Hz, 1H), 4.77 (d, *J* = 12.5 Hz, 1H), 4.70 (d, *J* = 12.6 Hz, 1H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.63 (m, 2H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 3.99 (t, *J* = 9.3 Hz, 1H), 3.93-3.91 (m, 1H), 3.90-3.86 (m, 1H), 3.84-3.77 (m, 2H), 3.74-3.70 (m, 2H), 1.15 (d, *J* =6.2 Hz, 3H), 1.05 (d, *J* = 6.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.6, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 127.5, 95.9, 80.5, 75.3, 75.2, 73.4, 72.7, 72.2, 71.8, 69.4, 68.9, 23.3, 21.3.



75c

Allyl 2,3,4,6-tetra-_O_-benzyl-α-D-mannopyranoside 75d[33]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (m, 18H), 7.16-7.14 (m, 2H), 5.88-5.79 (m, 1H), 5.20 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.14 (dd, *J* = 10.3, 1.3 Hz, 1H), 4.92 (d, *J* = 1.7 Hz, 1H), 4.88 (d, *J* = 10.7 Hz, 1H), 4.75 (d, *J* = 12.6 Hz, 1H), 4.71 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.62 (s, 2H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.50

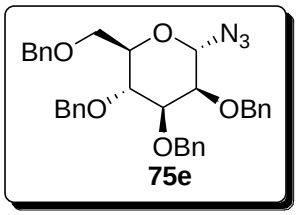


75d

(d, *J* = 10.7 Hz, 1H), 4.17 (ddt, *J* = 13.0, 4.9, 1.4 Hz, 1H), 4.02-3.91 (m, 3H), 3.81-3.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.4, 138.3, 133.7, 128.3, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 117.2, 97.0, 80.2, 75.1, 74.9, 74.6, 73.3, 72.5, 72.1, 71.8, 69.2, 67.8.

2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl azide 75e[41]

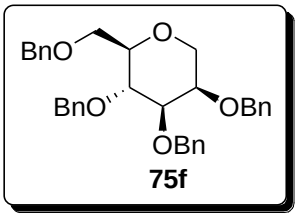
IR (KBr, cm^{-1}): 3030, 2916, 2112; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 18H), 7.17-7.15 (m, 2H), 5.39 (d, *J* = 2.0 Hz, 1H), 4.86 (d, *J* = 10.9 Hz, 1H), 4.73 (d, *J* = 12.3 Hz, 1H), 4.70-4.65 (m, 2H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.58-4.49 (m, 3H), 4.02 (t, *J* = 9.2 Hz, 1H), 3.89-3.86 (m, 1H), 3.82-3.77 (m, 2H), 3.73 (dd, *J* = 10.9, 1.7 Hz, 1H), 3.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 138.2, 137.9, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 88.1, 79.1, 75.2, 74.6, 74.4, 74.0, 73.5, 72.8, 72.5, 68.9.



75e

1,5-Anhydro-2,3,4,6-tetra-*O*-benzyl-α-D-manno-hexitol 75f[42]

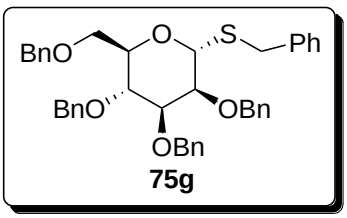
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.39 (d, *J* = 7.1 Hz, 2H), 7.35-7.24 (m, 16H), 7.17-7.16 (m, 2H), 4.91 (d, *J* = 10.8 Hz, 1H), 4.78 (d, *J* = 12.6 Hz, 1H), 4.69-4.52 (m, 6H), 4.13 (dd, *J* = 12.8, 2.1 Hz, 1H), 3.88 (t, *J* = 9.4 Hz, 1H), 3.75-3.73 (m, 2H), 3.68 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.56 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.41 (m, 1H), 3.28 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 138.3, 138.2, 128.3, 128.0, 128.0, 127.9, 127.7, 127.6, 127.5, 82.8, 79.8, 75.3, 73.5, 72.4, 71.5, 71.0, 69.7, 66.8.



75f

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-manno-thiopyranoside 75g[43]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.16 (m, 25H), 5.28 (s, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.55-4.47 (m, 5H), 4.11 (dd, *J* = 9.9, 4.7 Hz, 1H), 4.02 (t, *J* = 9.4 Hz, 1H), 3.90-3.78 (m, 2H), 3.77-3.72 (m, 2H), 3.69 (m, 1H), 3.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5,

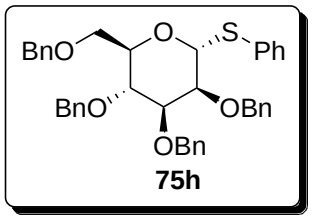


75g

138.4, 138.2, 137.8, 129.0, 128.5, 128.3, 127.9, 127.8, 127.6, 127.5, 127.1, 80.8, 80.4, 75.7, 75.1, 75.0, 73.3, 72.3, 71.9, 71.7, 69.1, 34.7.

Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-manno-thiopyranoside 75h[44]

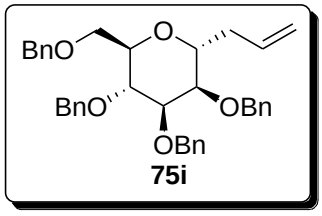
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H), 7.35-7.18 (m, 23H), 5.61 (s, 1H), 4.90 (d, *J* = 10.1 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.66-4.56 (m, 4H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.28 (m, 1H), 4.07 (t, *J* = 9.8 Hz, 1H), 3.99 (m, 1H), 3.87-3.82 (m, 2H), 3.76-3.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 138.4, 138.2, 137.9, 134.4, 131.7, 129.1, 128.5, 128.4, 128.3, 128.0, 128.0, 127.9, 127.8, 127.7, 127.7, 127.5, 127.4, 85.7, 80.2, 76.2, 75.3, 75.0, 73.3, 72.8, 72.1, 71.9, 69.2.



75h

3-C-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-1-propene 75i[44]

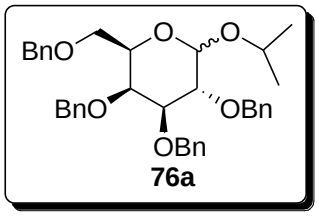
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (m, 18H), 7.23-7.19 (m, 2H), 5.82-5.66 (m, 1H), 5.05-4.99 (m, 2H), 4.75-4.68 (m, 2H), 4.63-4.52 (m, 6H), 4.05 (q, *J* = 7.0 Hz, 1H), 3.90-3.83 (m, 2H), 3.81-3.77 (m, 2H), 3.74-3.69 (m, 1H), 3.65-3.63 (m, 1H), 2.42-2.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 138.3, 138.2, 138.1, 134.3, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.4, 117.2, 77.2, 76.9, 75.1, 74.9, 73.8, 73.7, 72.3, 73.3, 72.0, 71.5, 69.1, 34.6.



75i

Isopropyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranoside 76a[34]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.24 (m, 30H), 4.96-4.91 (m, 3H), 4.84 (d, *J* = 11.4 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.74-4.71 (m, 2H), 4.66 (dd, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.42-4.38 (m, 2H), 4.03-4.00 (m, 2H), 3.98-3.95 (m, 2H), 3.93-3.86 (m, 1H), 3.87-3.85 (m, 1H), 3.81-3.76 (m, 1H), 3.58-3.55 (m, 1H), 3.54-3.48 (m, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 4.8 Hz, 3H), 1.21 (d, *J* = 4.8 Hz, 3H), 1.17 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.8, 138.7, 138.6, 138.6, 138.0, 137.9, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1. 128.0, 127.8, 127.7, 127.6, 127.5,

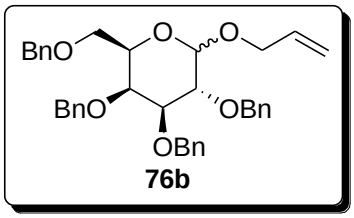


76a

127.4, 102.4, 95.4, 82.4, 79.6, 79.2, 77.2, 76.4, 75.2, 75.1, 74.7, 74.4, 73.5, 73.4, 73.3, 73.2, 73.1, 73.1, 72.1, 69.1, 69.0, 23.6, 23.2, 22.1, 21.2.

Allyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranoside 76b[33]

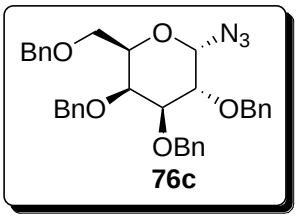
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.24 (m, 20H), 5.98-5.87 (m, 1H), 5.34-5.26 (m, 1H), 5.19-5.15 (m, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.88-4.79 (m, 2H), 4.77-4.72 (m, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.43-4.38 (m, 2H), 4.15 (dd, *J* = 13.1 Hz, 4.8 Hz, 1H), 4.06-3.94 (m, 4H), 3.88-3.82 (m, 1H), 3.52-3.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.7, 138.6, 138.0, 137.9, 134.2, 134.0, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 118.0, 117.1, 103.0, 96.3, 82.2, 79.6, 79.2, 76.5, 75.3, 75.2, 74.8, 74.5, 73.5, 73.4, 73.3, 73.1, 70.2, 69.4, 69.0, 68.9, 68.3.



76b

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl azide 76c[38]

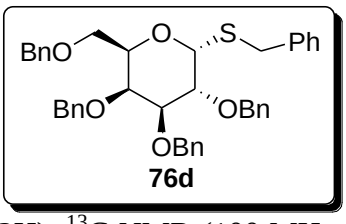
IR (KBr, cm^{-1}): 3030, 2914, 2114, 1452, 1095; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 20H), 5.31 (d, *J* = 4.2 Hz, 1H), 4.94 (d, *J* = 11.5 Hz. 1H), 4.86 (d, *J* = 11.6 Hz, 1H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.41 (d, *J* = 12.1 Hz, 1H), 4.13 (dd, *J* = 10.0, 4.7 Hz, 1H), 4.03 (t, *J* = 6.5 Hz, 1H), 3.97 (m, 1H), 3.81 (dd, *J* = 9.7, 2.6 Hz, 1H), 3.56-3.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 138.4, 138.0, 137.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 88.9, 78.9, 76.0, 74.9, 74.6, 74.0, 73.6, 73.2, 71.7, 60.5.



76c

Benzyl 2,3,4,6-tetra-*O*-benzyl-α-D-galacto-thiopyranoside 76d[42]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 25H), 5.26 (d, *J* = 5.3 Hz, 1H), 4.92 (d, *J* = 11.1 Hz, 1H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.53-4.38 (m, 4H), 4.31 (m, 1H), 4.27-4.19 (m, 1H), 3.92 (m, 1H), 3.84-3.70 (m, 2H), 3.63 (d, *J* = 11.8 Hz, 1H), 3.51-3.49 (m, 2H); ^{13}C NMR (100 MHz,



76d

$CDCl_3$): δ 138.8, 138.6, 138.2, 138.1, 129.2, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.5, 126.9, 83.2, 82.2, 798, 76.2, 75.9, 75.0, 74.8, 73.5, 72.0, 69.9, 69.2, 33.0.

2.5 References

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Chapter 2

2.6 Representative ^{1}H NMR and ^{13}C NMR spectra

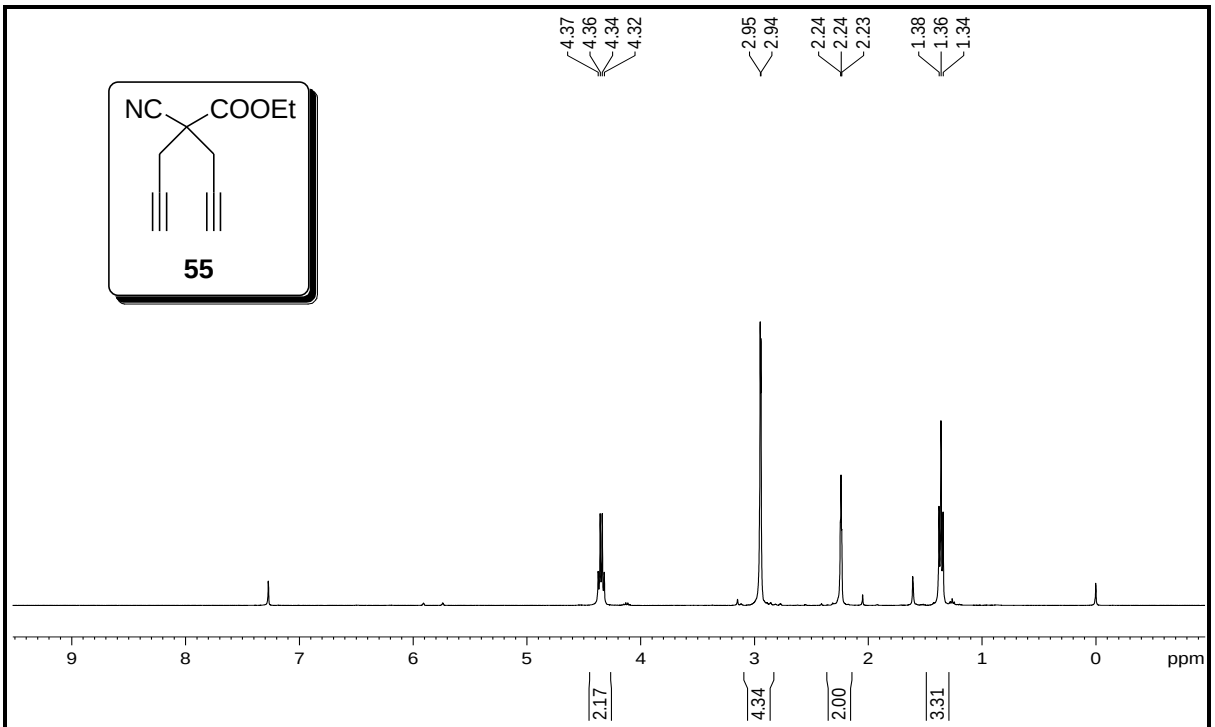


Figure 2. 400 MHz ^{1}H NMR spectrum of compound **55**

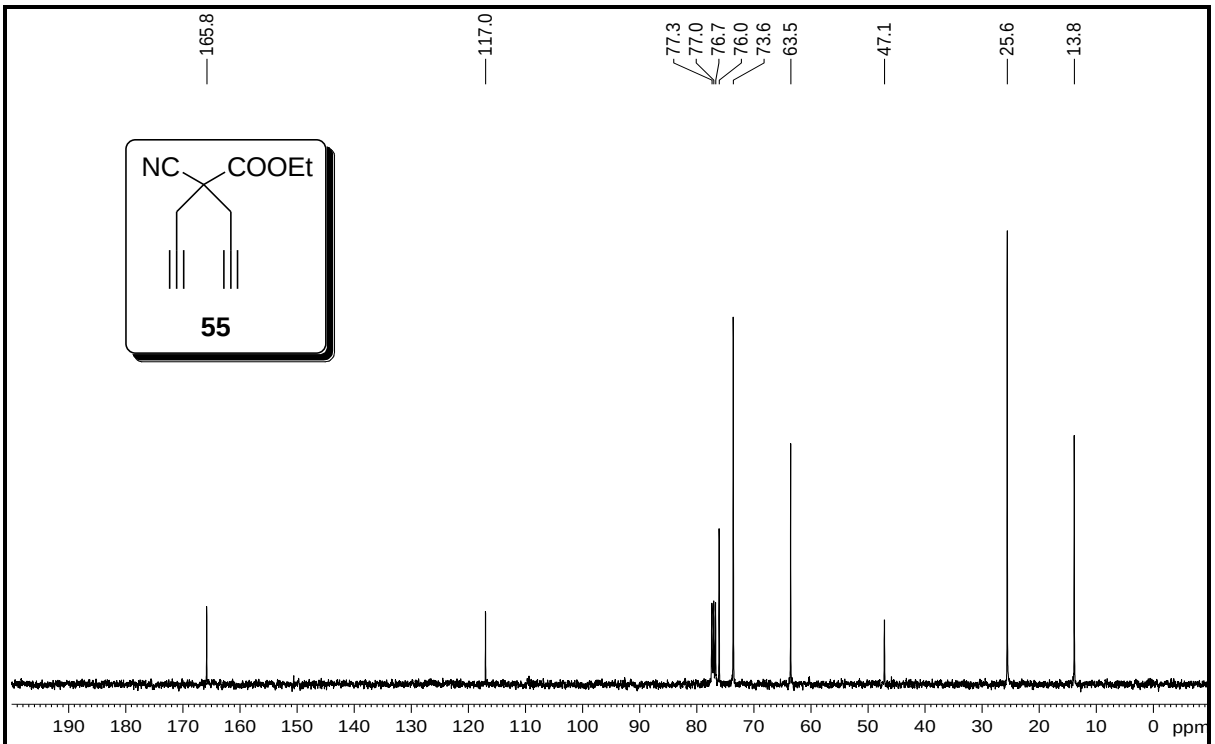


Figure 3. 100 MHz ^{13}C NMR Spectrum of **55**

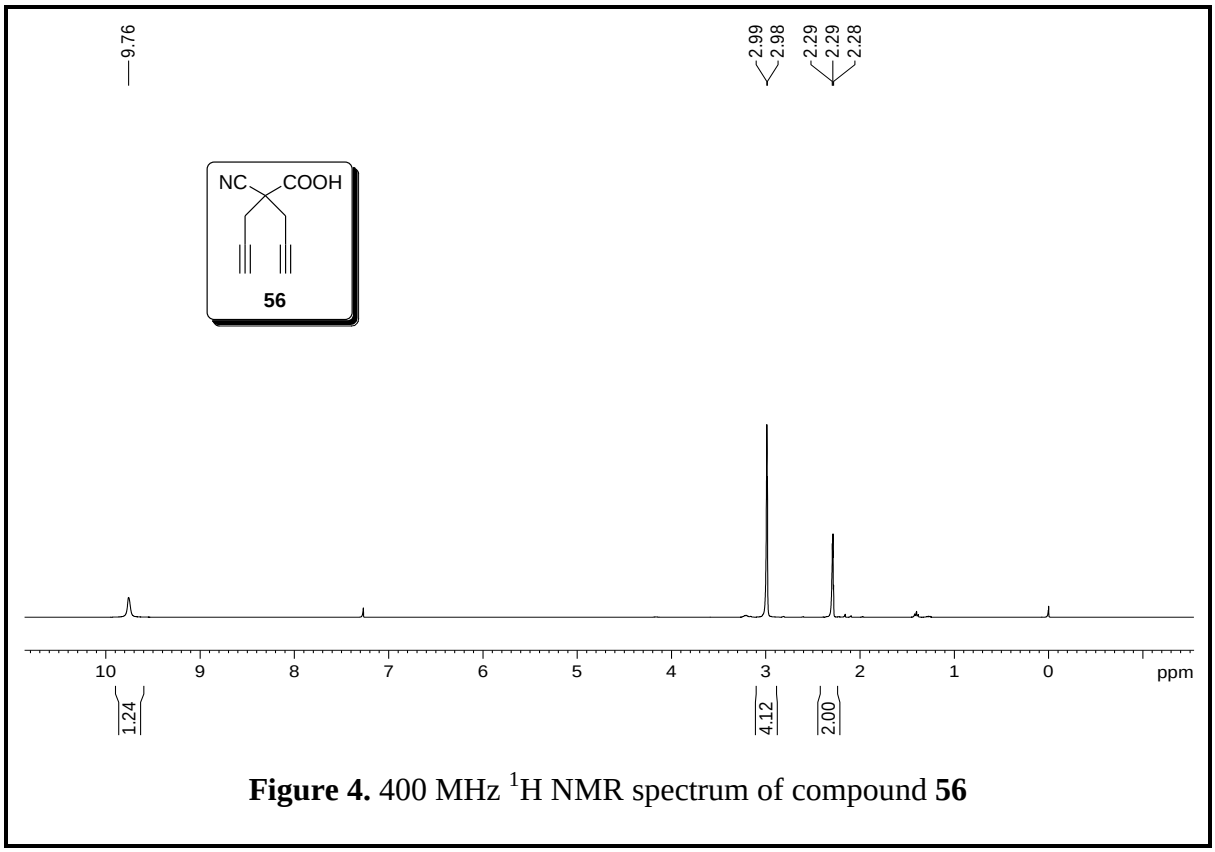


Figure 4. 400 MHz ^{1}H NMR spectrum of compound **56**

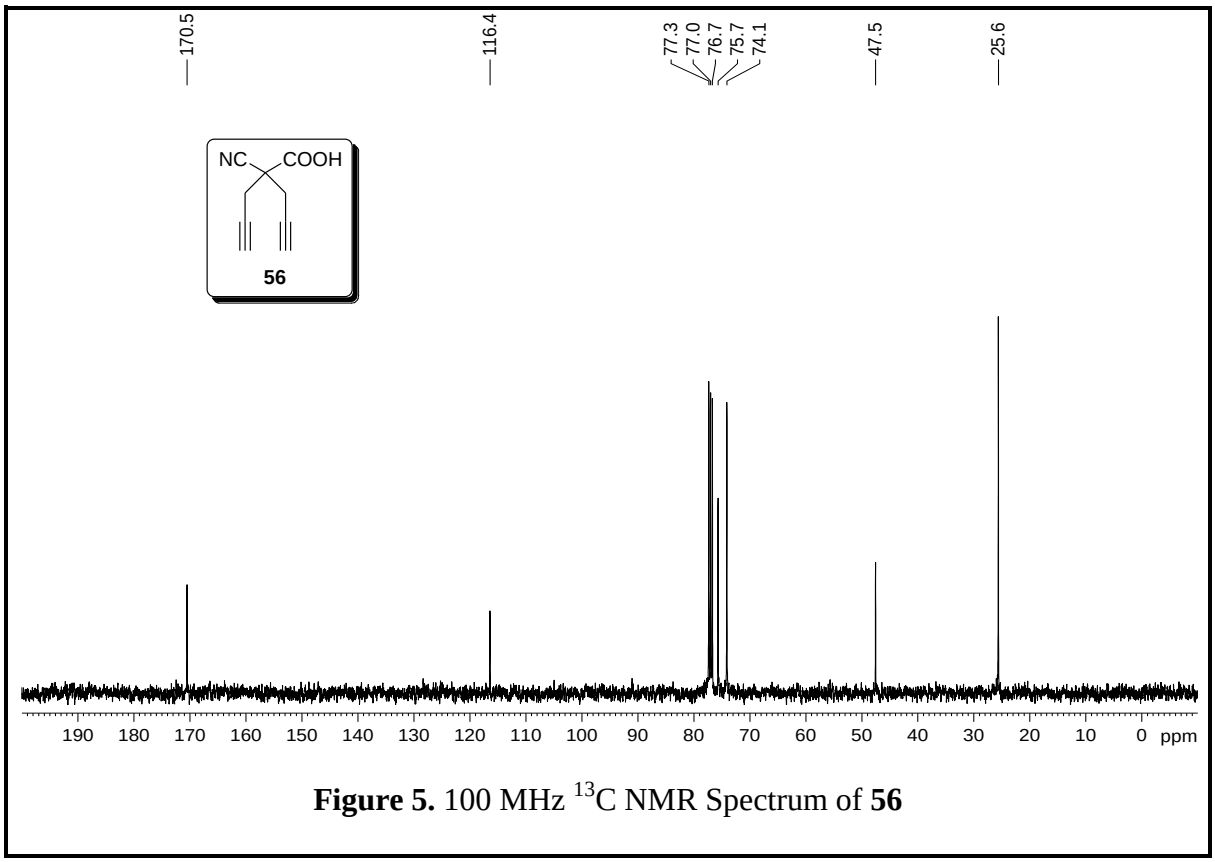


Figure 5. 100 MHz ^{13}C NMR Spectrum of **56**

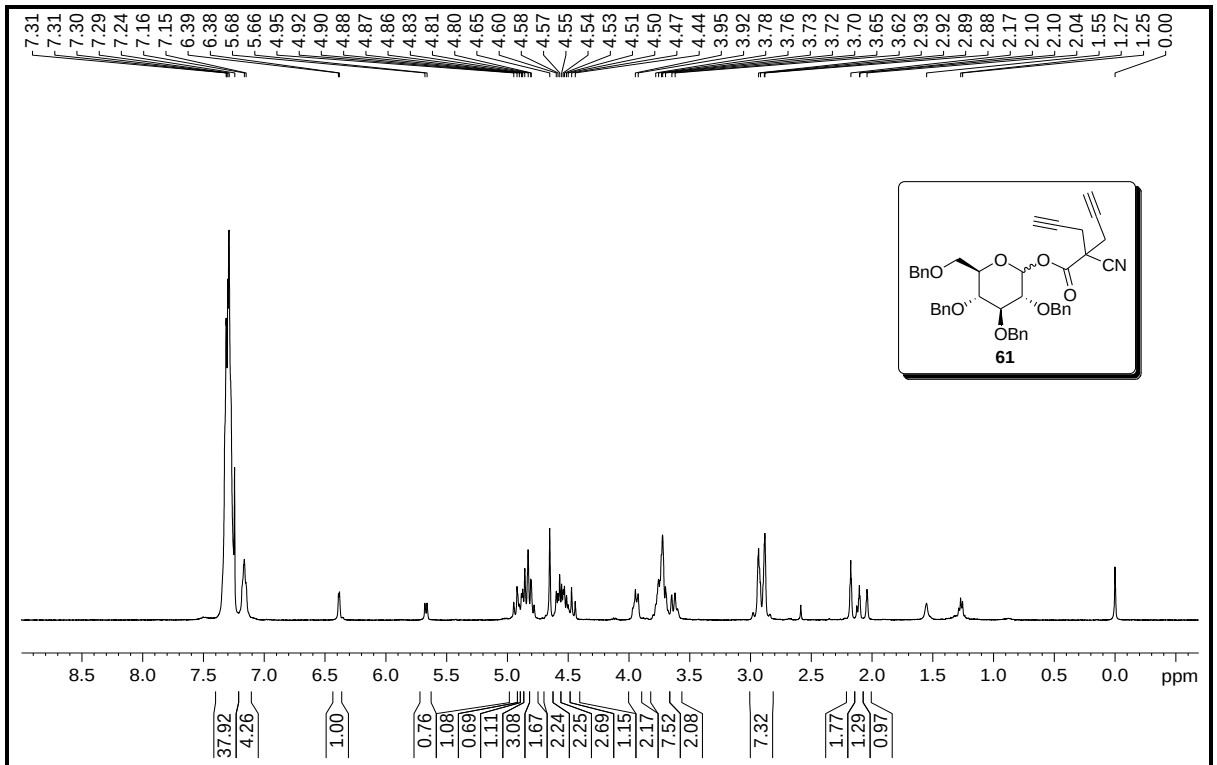


Figure 6. 400 MHz ^{1}H NMR spectrum of compound **61**

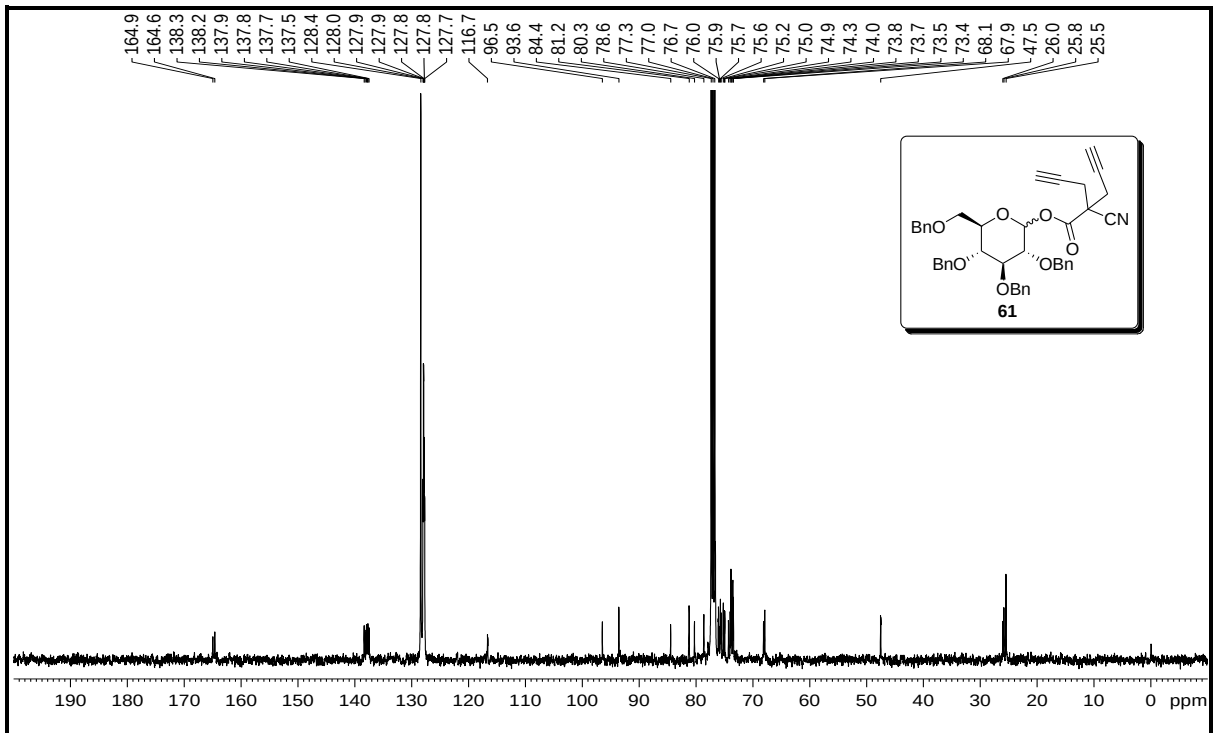


Figure 7. 100 MHz ^{13}C NMR Spectrum of **61**

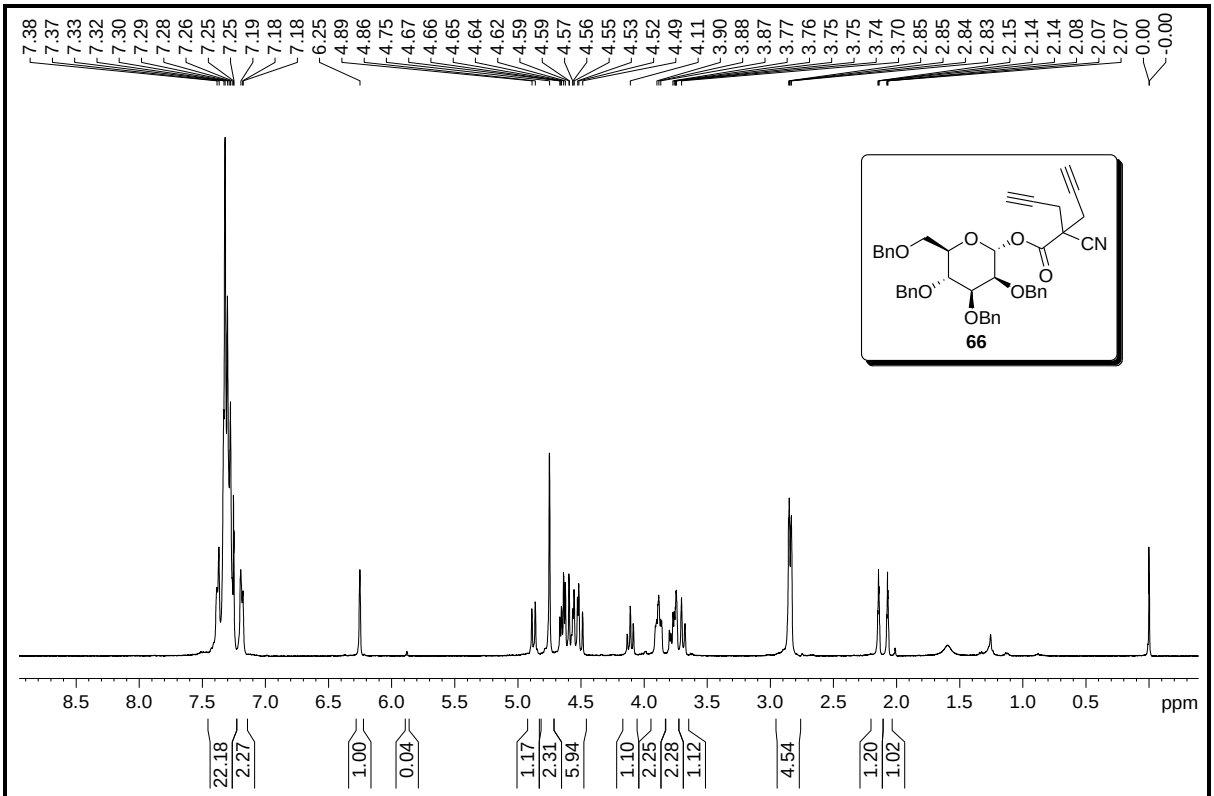


Figure 8. 400 MHz ^{1}H NMR spectrum of compound **66**

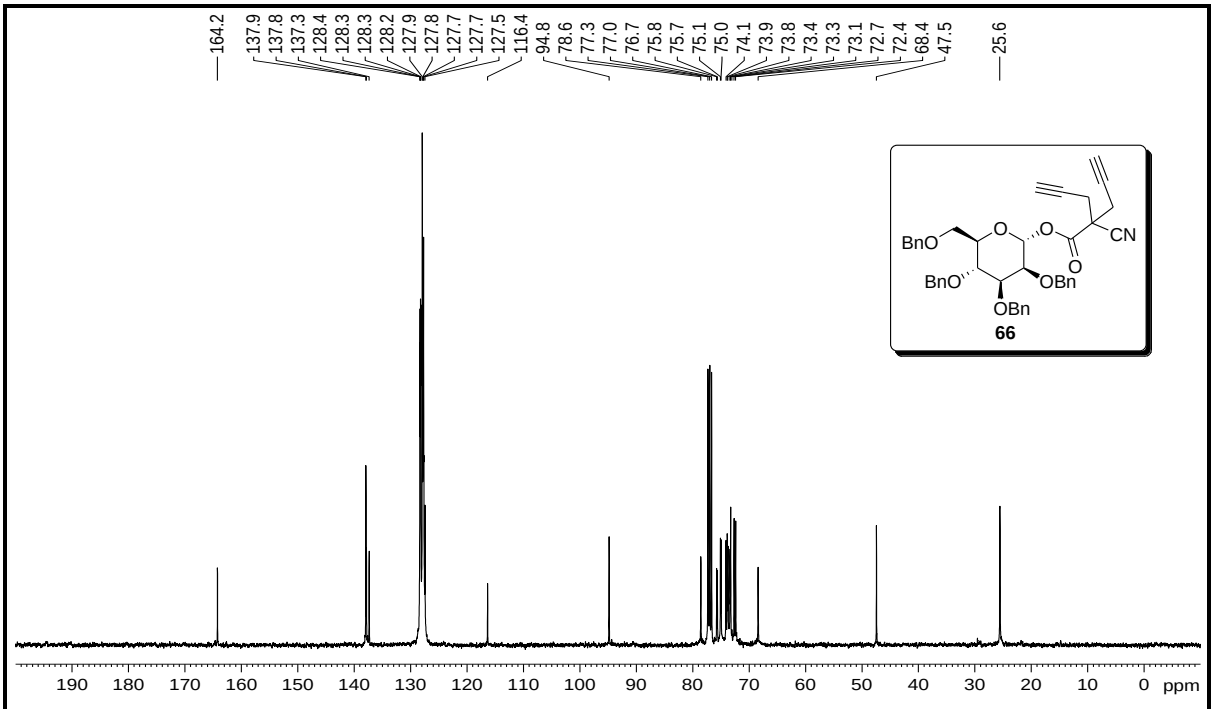


Figure 9. 100 MHz ^{13}C NMR Spectrum of **66**

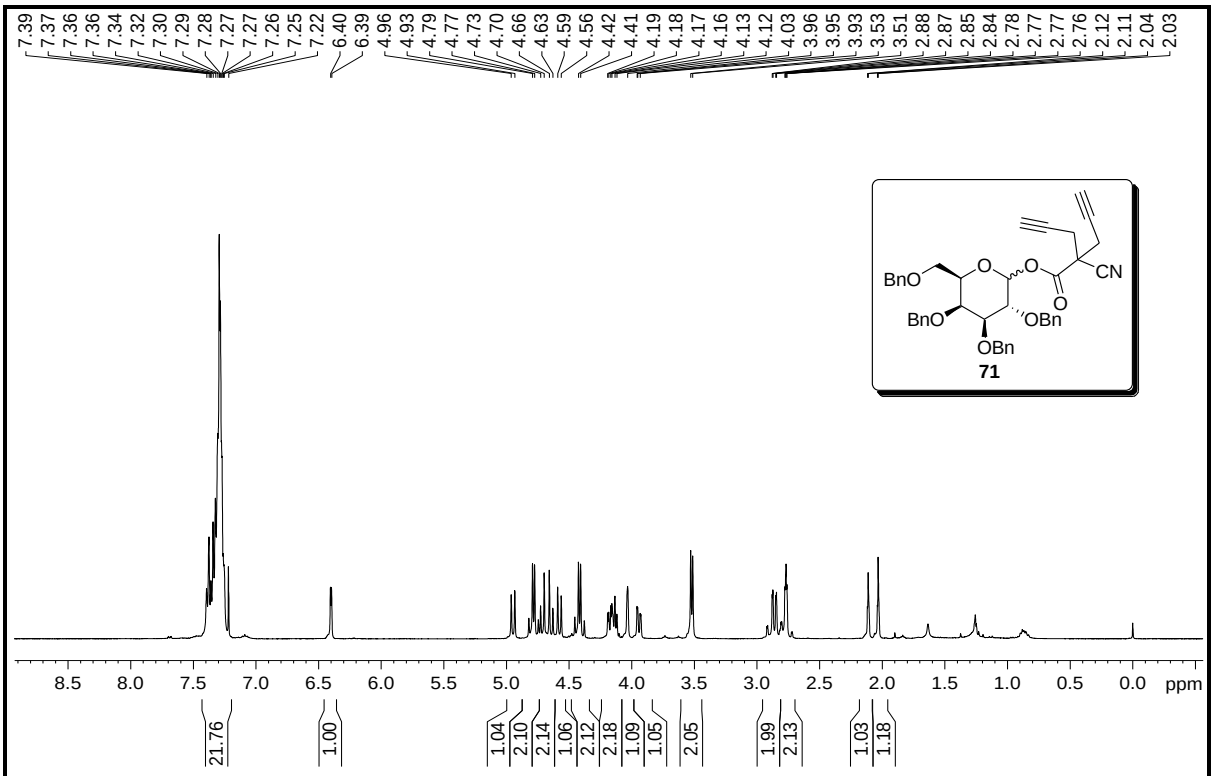


Figure 10. 400 MHz ^{1}H NMR spectrum of compound **71**

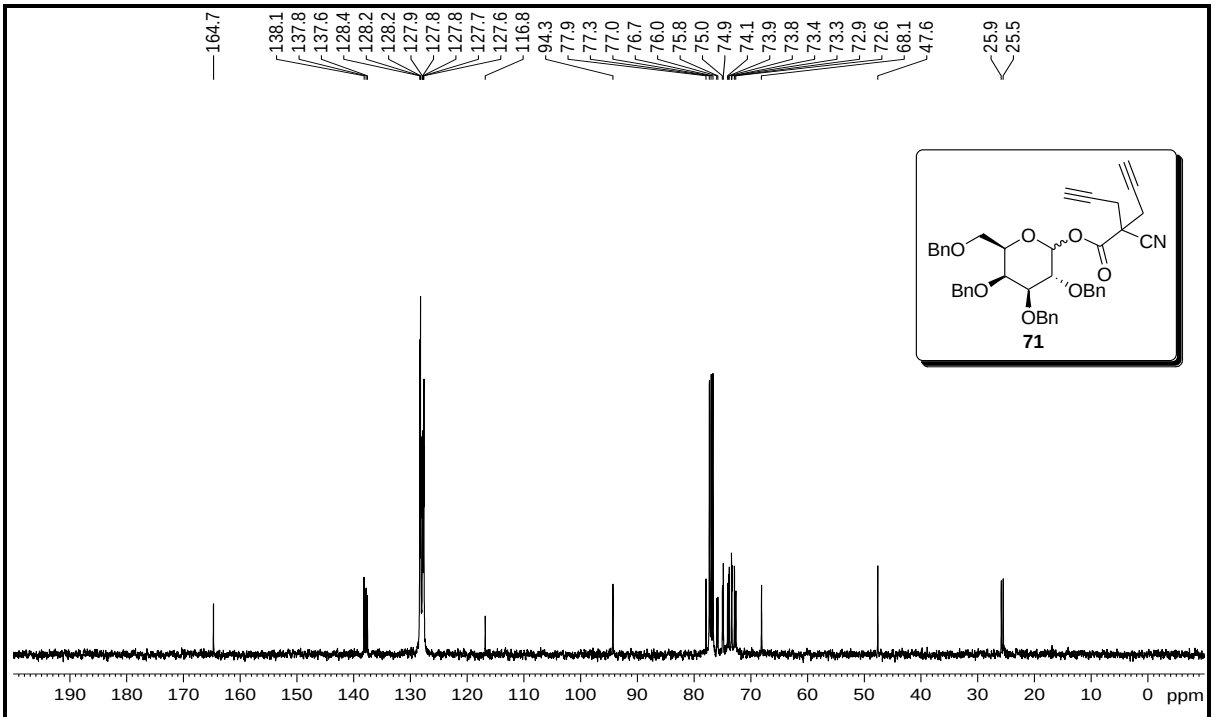


Figure 11. 100 MHz ^{13}C NMR Spectrum of **71**

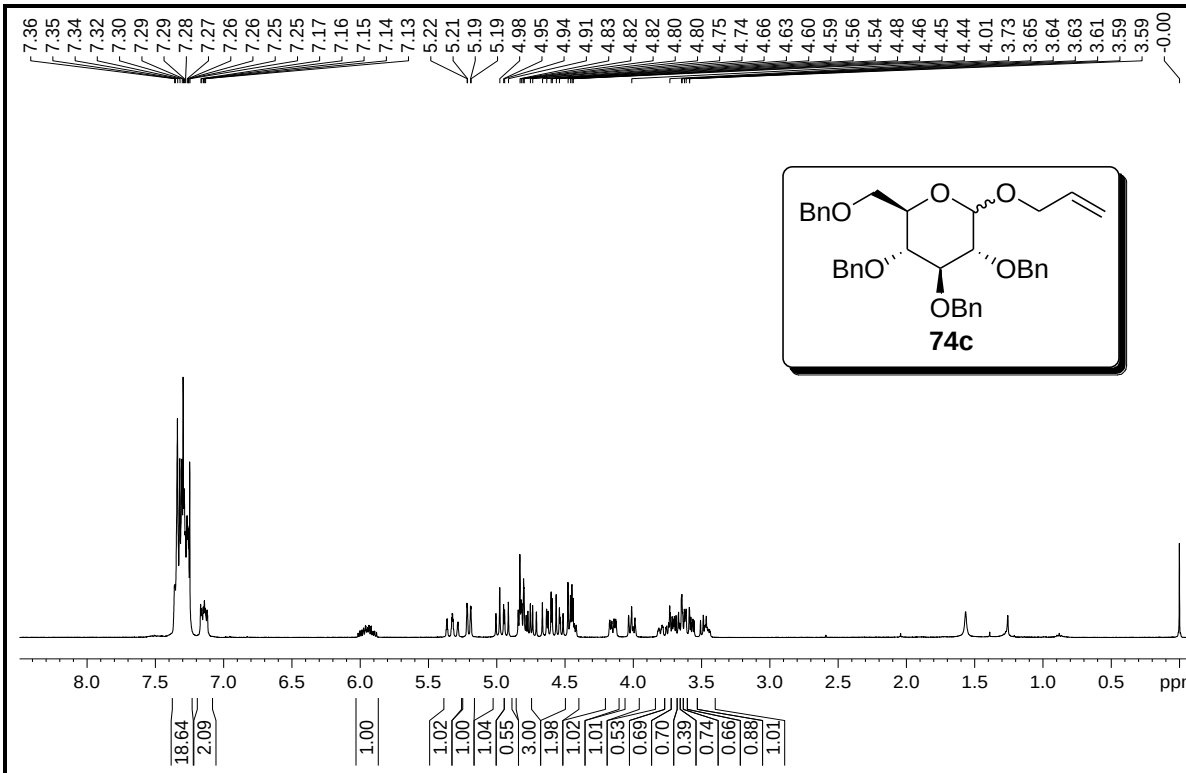


Figure 12. 400 MHz ^{1}H NMR spectrum of compound **74c**

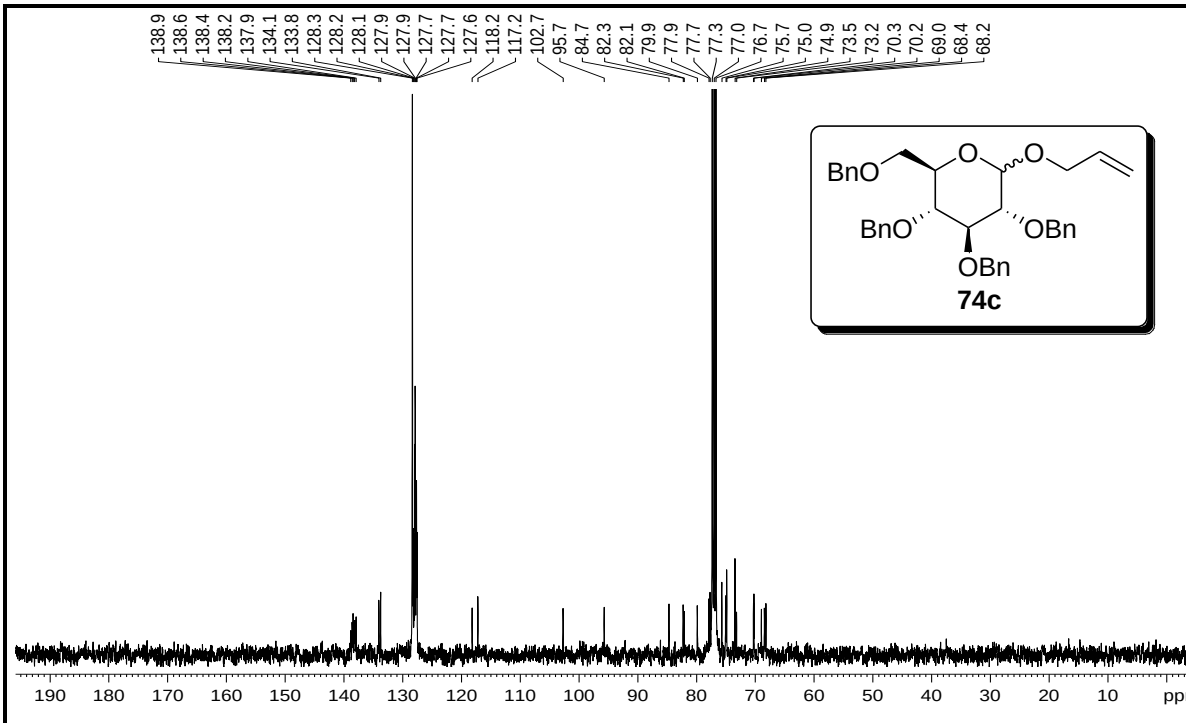


Figure 13. 100 MHz ^{13}C NMR Spectrum of **74c**

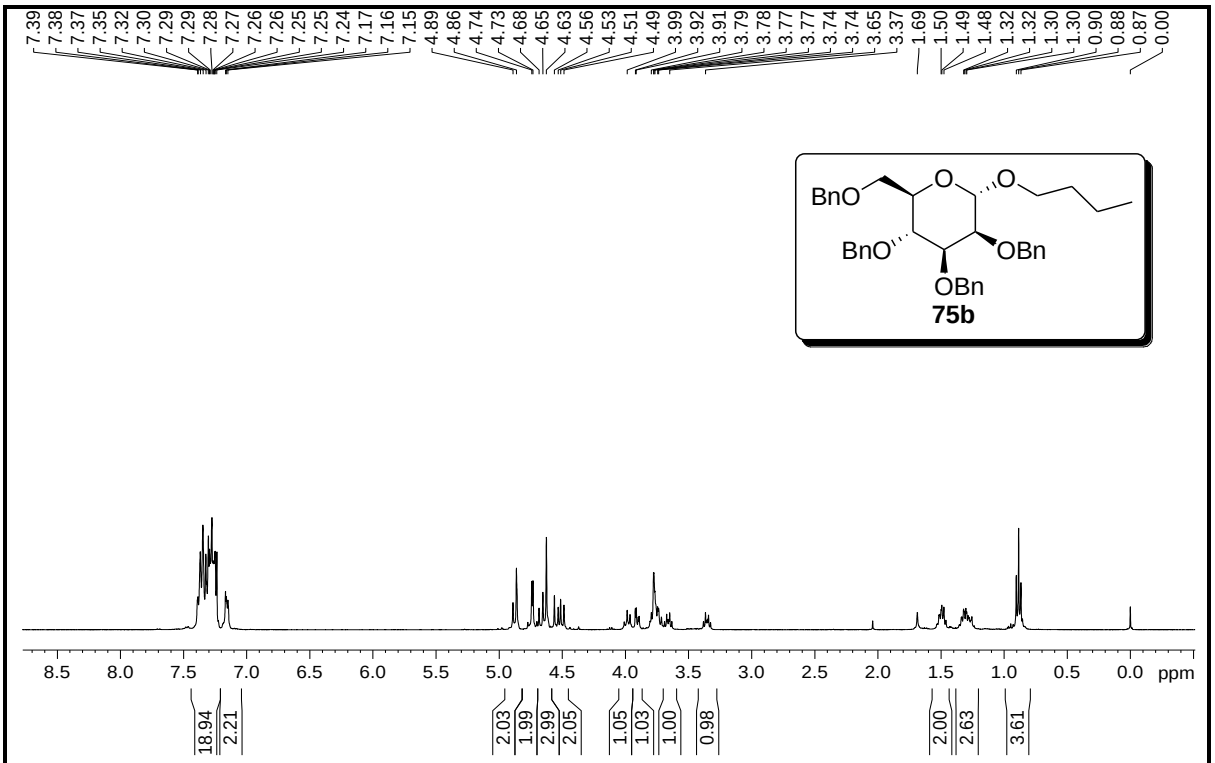


Figure 14. 400 MHz ^{1}H NMR spectrum of compound **75b**

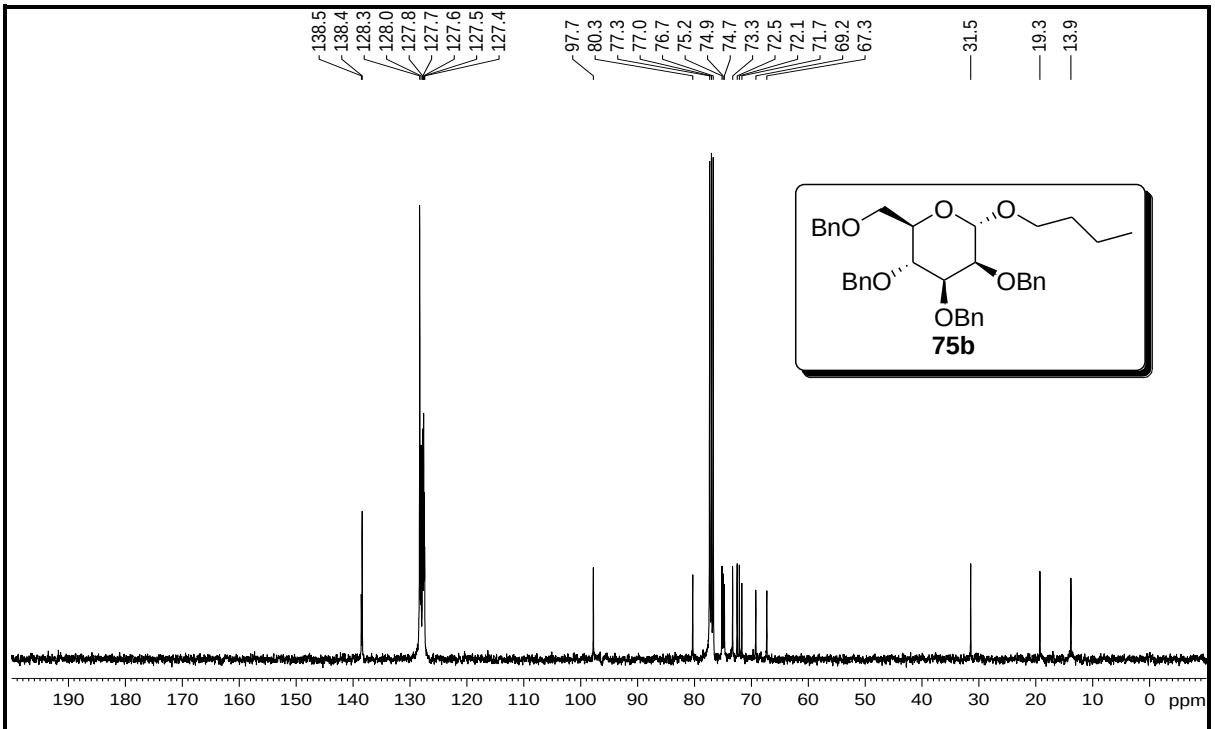


Figure 15. 100 MHz ^{13}C NMR Spectrum of **75b**

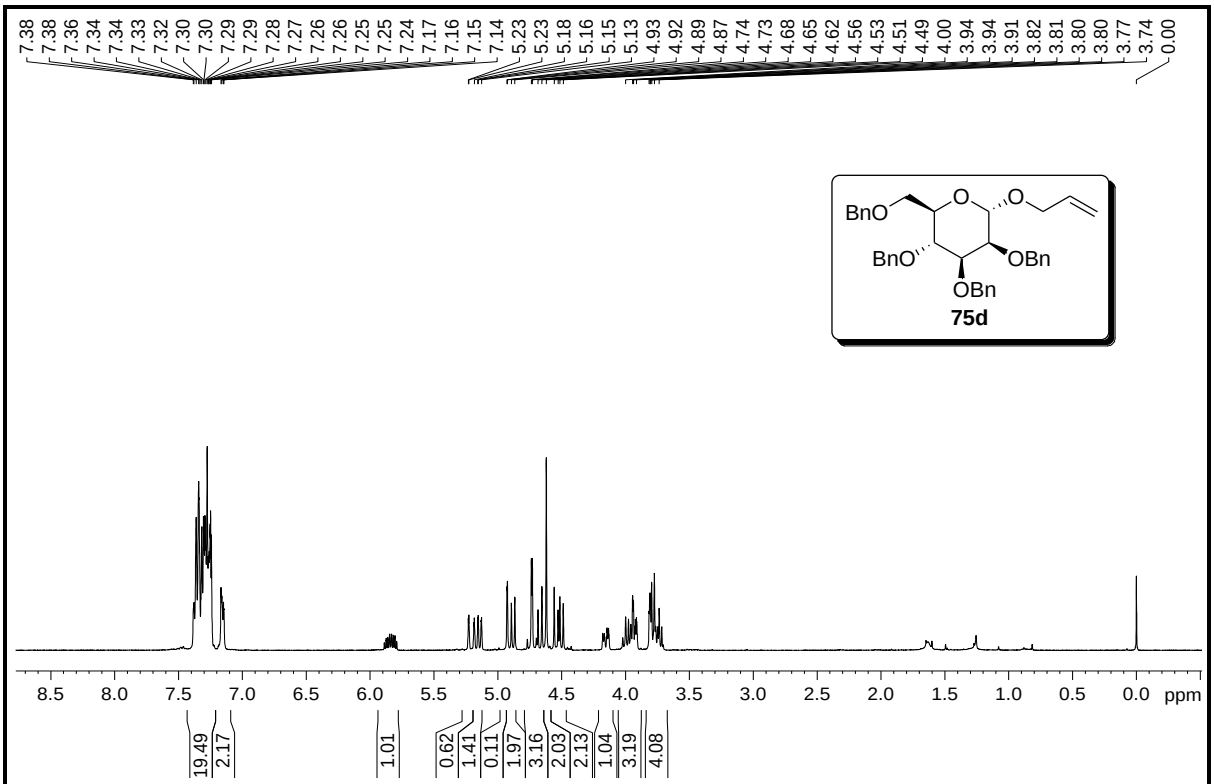


Figure 16. 400 MHz ^{1}H NMR spectrum of compound **75d**

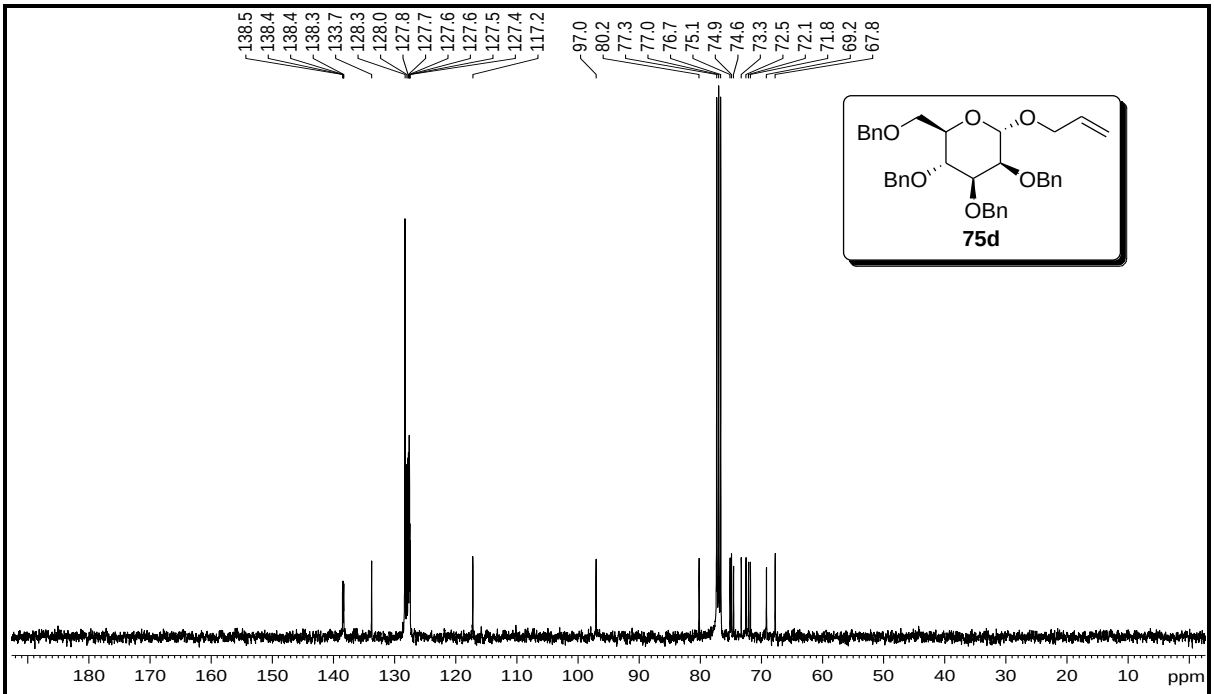


Figure 17. 100 MHz ^{13}C NMR Spectrum of **75d**

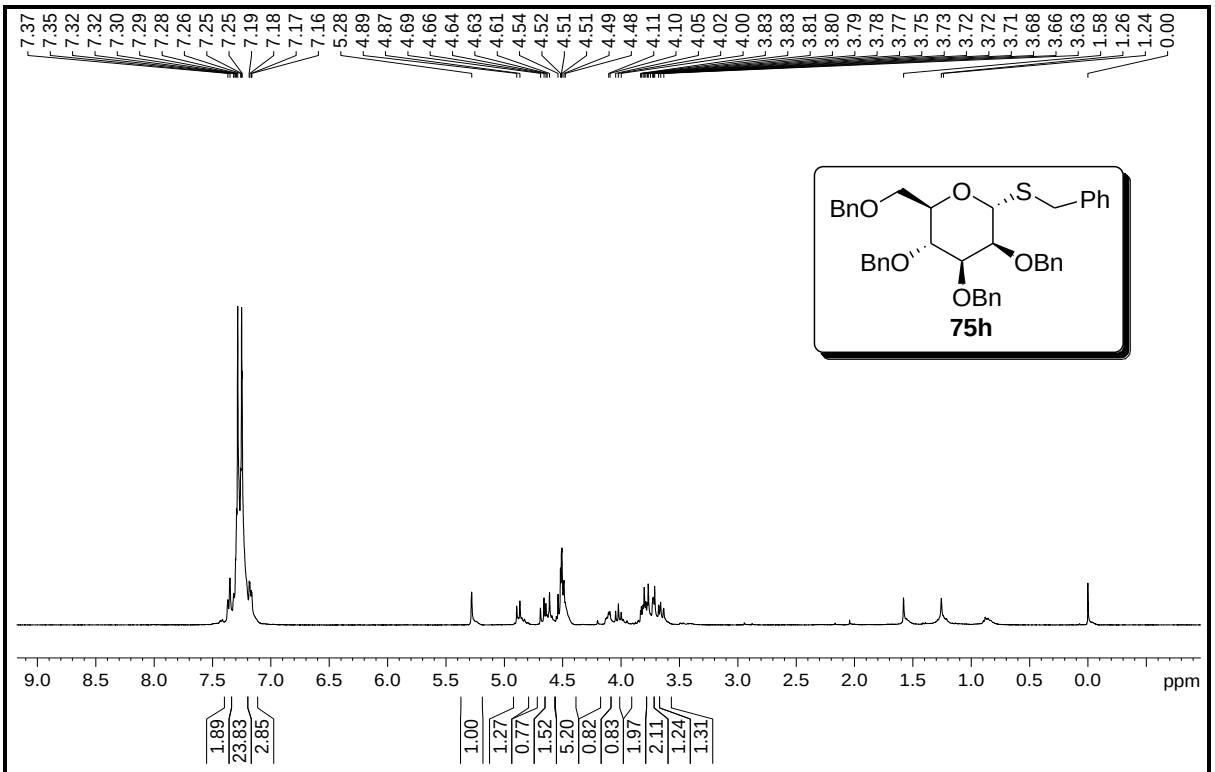


Figure 18. 400 MHz ^{1}H NMR spectrum of compound **75h**

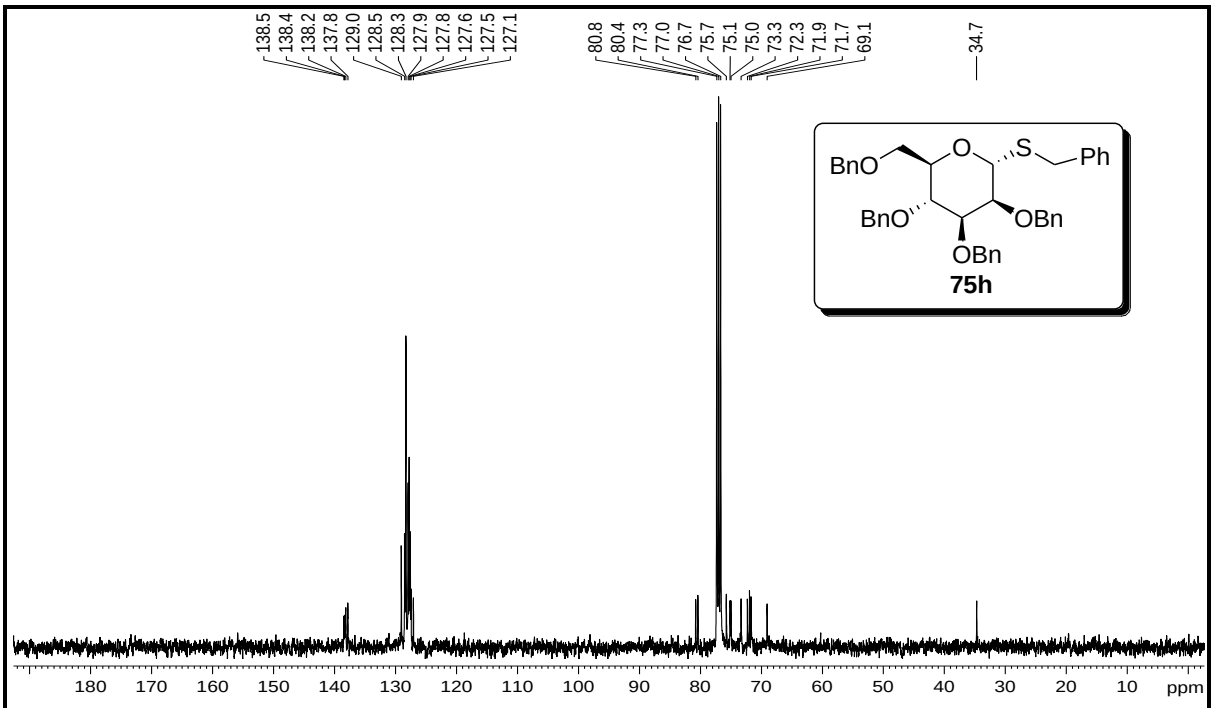


Figure 19. 100 MHz ^{13}C NMR Spectrum of **75h**

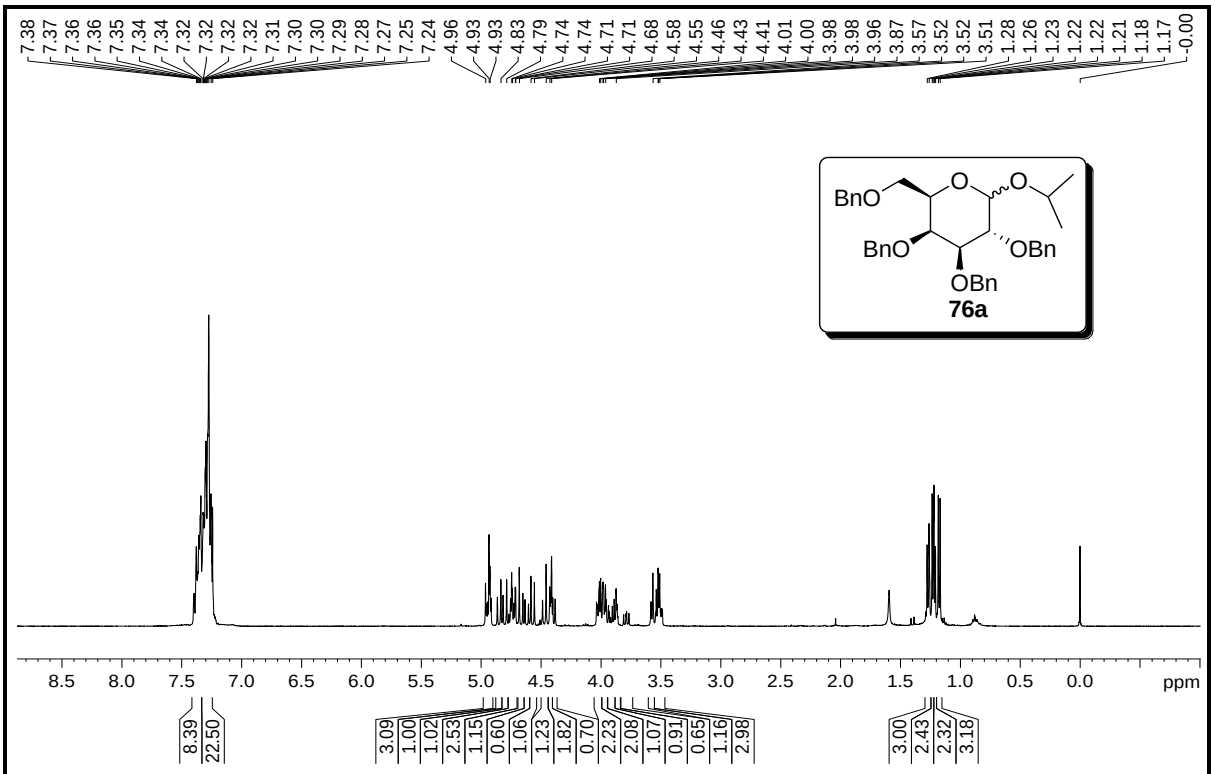


Figure 20. 400 MHz ^{1}H NMR spectrum of compound **76a**

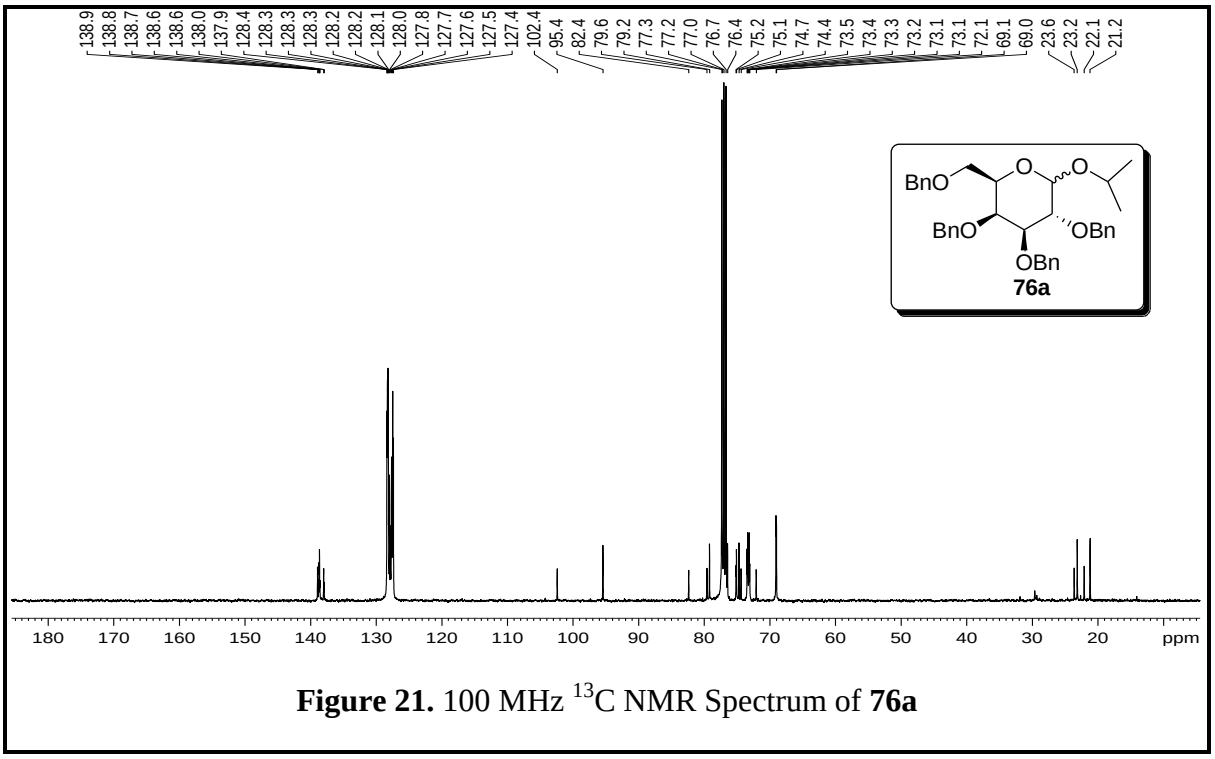


Figure 21. 100 MHz ^{13}C NMR Spectrum of **76a**

Part-B

TfOH-Promoted α-Functionalization of Unactivated Ketones

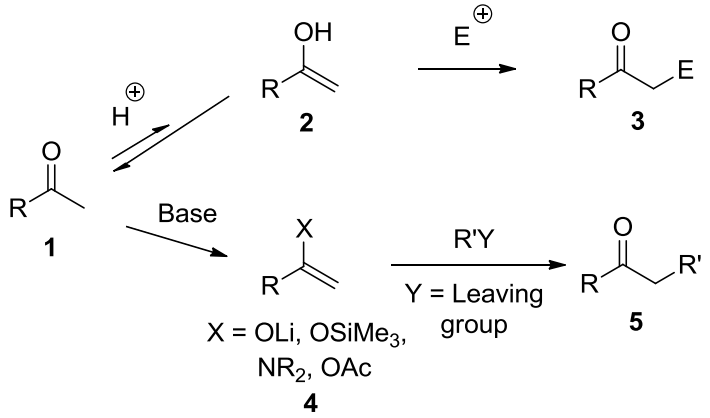
Chapter 3

Triflic Acid-Promoted and Lewis Acid-Catalysed Direct α-Alkylation of Unactivated Ketones

3.1 Introduction

Alkylation at the α-carbon of carbonyl compound is one of the fundamental reaction to form a C-C bond. In recent years, there has been considerable interest in carrying out α-alkylation using unactivated substrates directly without any prior activation like converting carbonyl compounds into enolate equivalents and attaching good leaving groups to the electrophile. The initial development witnessed in this area was significantly through enols, enolates and enamines. The nucleophilicity follows the order enolates > enamine > enol in the alkylation reactions.[1-4]

3.1.1 Traditional methods for alkylation



Scheme 1. Schematic representation of traditional methods of alkylation of ketones

Ketones can exist in equilibrium with its enol form under acidic conditions. This enol form **2** can act as nucleophile under suitable reaction conditions and reacts with electrophiles to form the alkylated product **3**. Acid-catalysed aldol reaction and its variants come under this category. As we know, enolates have been employed in various basic reactions of carbonyl compounds like aldol, Michael, Mannich, Claisen condensation and so on. Under basic reaction conditions, enolates are generated from the ketone **1**. This enolate on treatment with electrophiles with good leaving groups furnish the product **5**. By doing direct alkylation using alcohols we can avoid products of inorganic waste. Enamines can be prepared by reacting the ketone or aldehyde with secondary amine in the presence of strong dehydrating agent or on aziotropic distillation of water. The β-carbon of enamine is more nucleophilic

because of resonance stabilization. Enamines can react with electrophiles to form the alkylated products.

3.1.2 Direct alkylation of carbonyl compounds

In the above discussed classical alkylation reactions, both the carbonyl compound and the electrophile are to be activated first by converting into enolates/enamines and attaching good leaving group respectively. Eventually, the reaction will generate equimolar amounts of waste such as salts. In this regard, there has been quite interest in carrying out α-alkylation of carbonyl compounds directly without prior activation. Also, using alcohols as electrophiles has great advantage as the by product is water. In the following section, direct alkylation using alcohols as electrophiles is described.

3.1.2.1 Direct alkylation of 1,3-diketones

As compared to simple ketones ($pK_a \approx 18$-20), 1,3-diketones ($pK_a \approx 9$-14) contain more acidic protons which can easily be deprotonated (Figure 1**)**.[5] Several Lewis acids and Brønsted acids are known to catalyse the alkylation of 1,3-diketones with benzylic, allylic alcohols, propargylic alcohols, alkenes and indoles. In most of the reactions, under extreme heating conditions, good reaction outcome was observed.

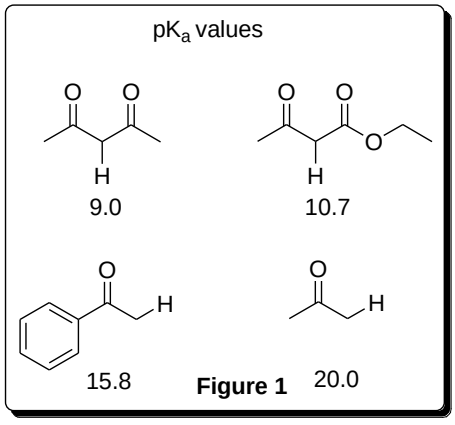
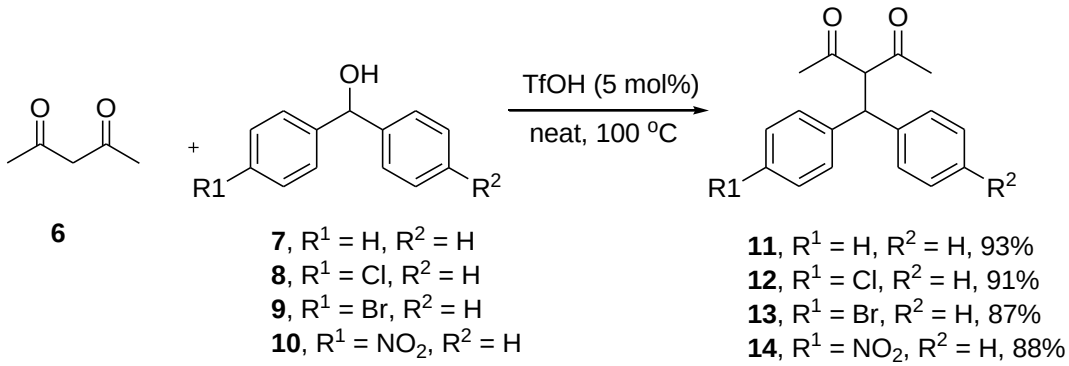


Figure 1

3.1.2.1.1 Brønsted acid-catalysed alkylation of 1,3-diketones

Sanz and co-workers reported the triflic acid-catalysed alkylation of β-dicarbonyl compounds at high temperatures with benzhydrols and 1-arylethanols.[6] Interestingly, with 1-arylethanols, excellent yields of alkylated products were observed in nitromethane solvent where as, with benzhydrol no alkylation product was formed in the same solvent as the diaryl methanol disproportionates into benzophenone and diarylmethane. At neat reaction conditions, benzhydrols **7-10** reacted smoothly to give alkylated diketones **11-14** with excellent yields (Scheme 2). A wide range of Brønsted acids were reported to catalyse the

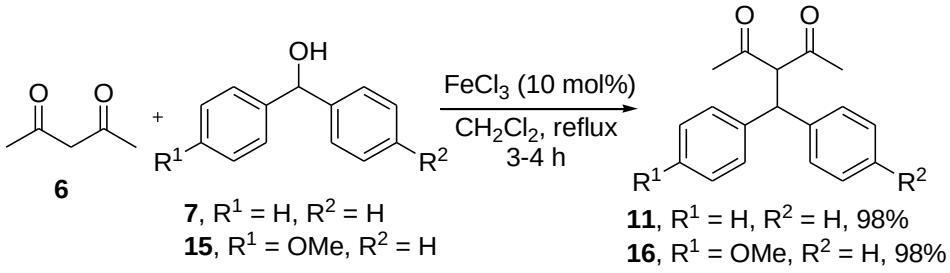
alkylation of β-dicarbonyl compounds which comprise $H_5CoW_{12}O_{40}$ supported on nano silica from rice husk ash,[7] H-montmorillonite,[8] Phosphomolybdic acid supported on silica gel (PMA/SiO_2),[9] triflic acid supported on silica gel,[10] H_2O,[11] perchloric acid,[12] BINSA[13] and dodecyl benzene sulfonic acid,[14] phosphotungstic acid,[15] EMIOTf[16] and so on.



Scheme 2. Triflic acid-catalysed alkylation of 1,3-diketone **6**

3.1.2.1.2 Lewis acid-catalysed alkylation of 1,3-diketones

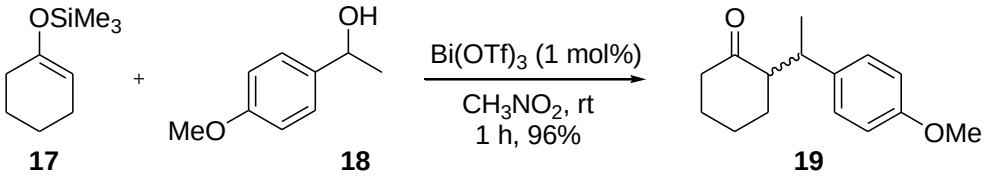
Iron(III) chloride-catalysed direct alkylation of 1,3-diketones with benzyl and allylic alcohols was reported under reflux conditions.[17] A wide variety of 1,3-diketones were employed in the reaction including diethyl malonate, ethyl acetoacetate and 1-ethoxycarbonyl cyclopentanone which reacted smoothly under iron-catalysed reaction conditions to give the products in excellent yields. Several other Lewis acid catalysts such as $Cu(OTf)_2$,[18] $Yb(OTf)_3$,[19] $InCl_3$,[20] $Bi(OTf)_3$,[21] $B(C_6F_5)_3$,[22] Ir-Sn bimetallic catalyst,[23] Zn based ionic liquid,[24] Ru complex[25] and $Hf(OTf)_4$[26] have also been reported for catalyzing this transformation.



Scheme 3. Iron(III)-catalysed alkylation of 1,3-diketone **6**

3.1.2.2 Alkylation *via* silyl enol ethers

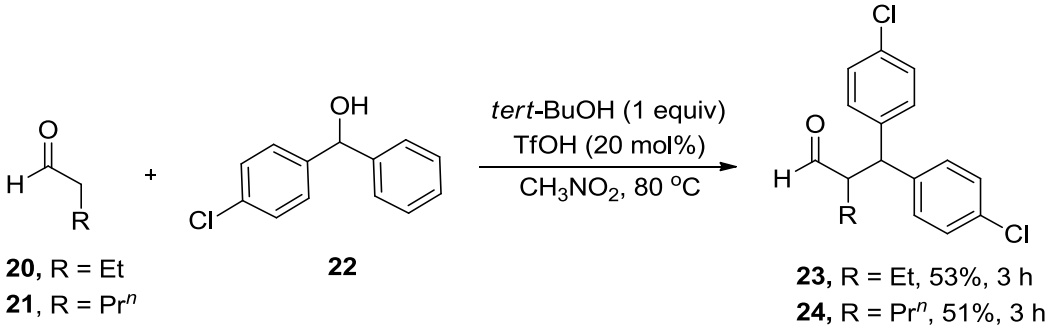
Silyl enol ethers have been extensively employed as nucleophiles in the reactions such as Mukaiyama-aldol,[27] Michael[28] and Mannich[29] reactions. These silyl enol ethers can be made by treating the parent ketone with trimethylsilyl chloride under basic conditions at elevated temperatures. Bach and co-workers reported the bismuth(III) triflate-catalysed direct alkylation of silyl enol ethers with benzyl alcohols and their acetates at room temperature. The methodology is limited only to *p*-methoxy benzyl alcohols (Scheme 4**)**.[30]



Scheme 4. Bismuth(III)-catalysed alkylation *via* silyl enolates

3.1.2.3 α-Alkylation of aldehydes

Chi and co-workers reported the Brønsted acid-catalysed α-alkylation of aldehydes with benzhydrols and allylic alcohols (Scheme 5**)**.[31] To avoid the self-condensation of benzhydrols under strong acidic conditions, in most of the cases, stoichiometric amount of *tert*-butanol was added which suppresses the tetrabenzyl ether formation and subsequent disproportionation into benzophenone along with diphenylmethane.

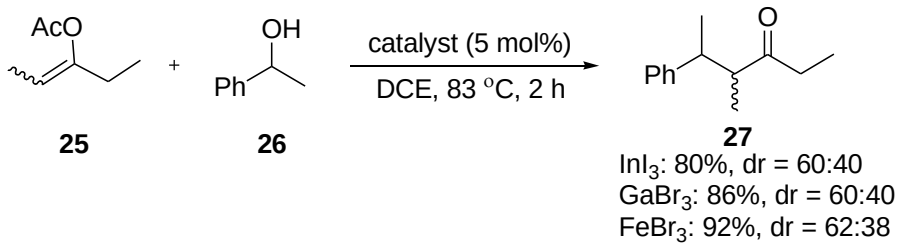


Scheme 5. α-Alkylation of aldehydes catalysed by triflic acid

3.1.2.4 Enol acetates as enol equivalents

Baba and co-workers reported the alkylation of enol acetates with alcohols under Lewis acidic conditions.[32] Among the various Lewis acids screened for the alkylation

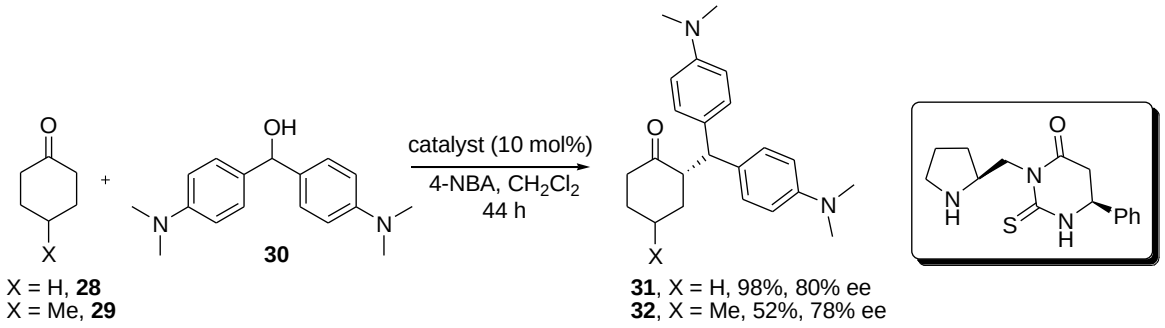
reaction, InI_3, $GaBr_3$ and $FeBr_3$ were successful in obtaining good yields. 2-Butanone derived enol acetate **25** was treated with 1-phenylethanol **26** in the presence of mild Lewis acids such as InI_3, $GaBr_3$ and $FeBr_3$ under reflux conditions to give diastereomeric mixture of alkylated products **27** (Scheme 6).



Scheme 6. Intermolecular α-alkylation through enol acetate **25**

Strong Lewis acids like $BF_3{\cdot}Et_2O$, $TiCl_4$ and $AlCl_3$ failed to give the alkylated product due to their more oxophilic nature which lead to the formation of undesired products such as products of dehydration and transesterification. It was believed that the successful outcome in the cases of Lewis acids such as InI_3, $GaBr_3$ and $FeBr_3$ is due to their mild oxophilicity and reaction tolerance.

3.1.2.5 α-Alkylation of ketones

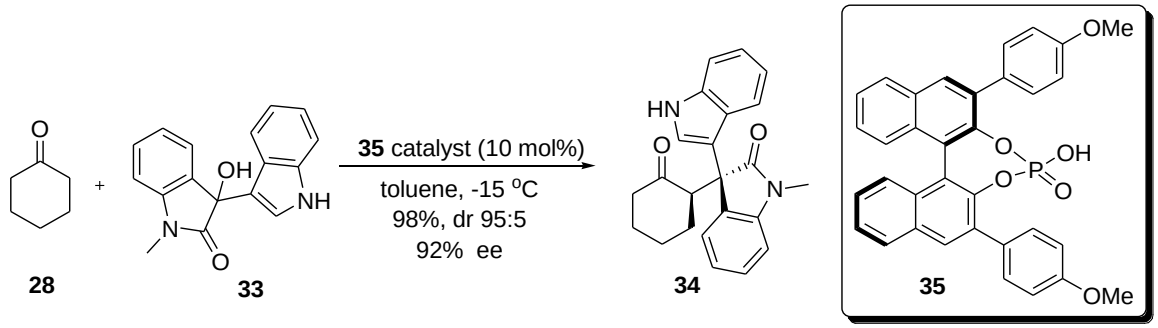


Scheme 7. α-Alkylation of ketone catalysed by organocatalyst

Kokotos and co-workers reported the reaction of cyclohexanone derivatives with *N*,*N*-dimethyl substituted diaryl methanol **30** in the presence of proline derived organocatalyst which furnished the alkylated ketones (Scheme 7).[33] Few other organocatalysts are also reported for the alkylation reactions.[34]

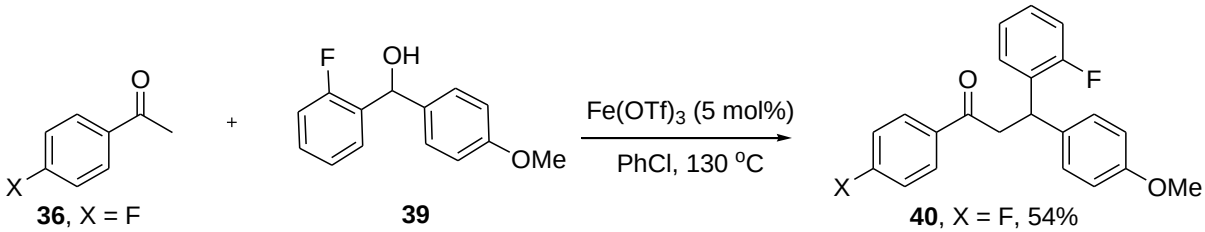
Song *et al.* developed an asymmetric α-alkylation of unactivated aliphatic ketones with substituted 3-hydroxy-3-indolyloxindoles **33** under chiral phosphoric acid **35** catalysis

(Scheme 8).[35] The reaction requires excess of ketone (5 equiv), long reaction times, low temperatures (around -15 °C) and toluene as the solvent to get good yield and enantioselectivity.



Scheme 8. α-Alkylation of cyclohexanone **28** catalysed by organocatalyst **35**

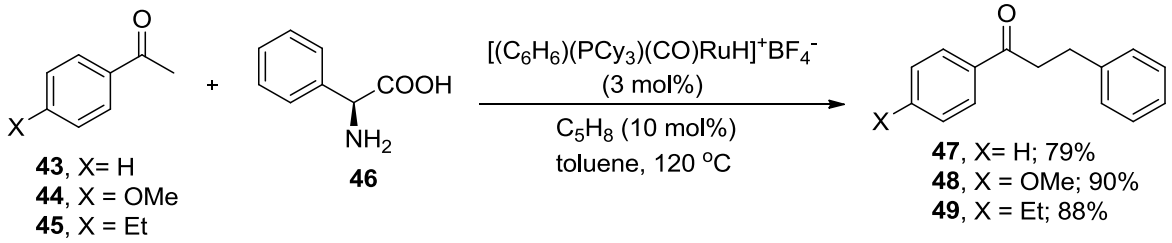
Gu and co-workers have reported the iron(III) triflate-catalysed direct benzylation of unactivated ketones with benzhydrols by heating them in chlorobenzene at 130 °C.[36] However, it was found that the reaction occurred only when one of the aryls in diarylmethanol had methoxy group. This methodology suffers from high substrate loading and harsh reaction conditions.



Scheme 9. $Fe(OTf)_3$-catalysed direct α-alkylation

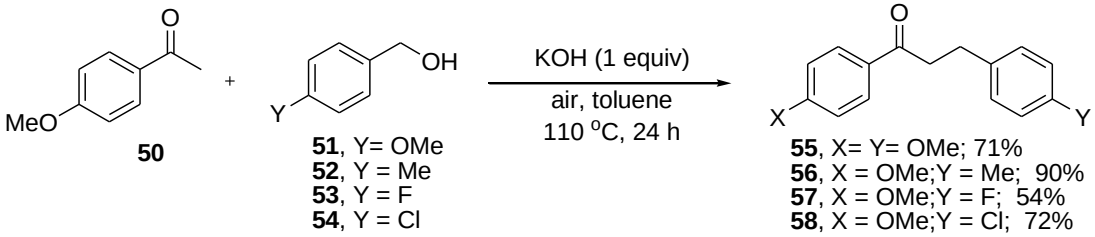
As an extention to this protocol, synthesis of 4H-chromones was achieved from salicylaldehyde, dimidone and unactivated ketone. However, the reaction requires excess of ketone to get good yield.

Kalutharage and Yi have developed a cationic ruthenium hydride complex-catalysed α-alkylation of ketones using amino acids under reflux in toluene (Scheme 10). During the reaction, amino acid degrades by releasing carbon dioxide and ammonia.[37] A wide range of substrates were employed in the reaction like α-, β-aminoacids.



Scheme 10. Ru-catalysed direct α-alkylation with aminoacids as electrophiles

The latest report for the direct α-alkylation of ketones involve catalyst free heating of ketones with alcohols in the presence of stoichiometric amount of KOH at 110 °C (Scheme 11**)**.[38] This reaction involving interesting redox pathway is, however, limited to aryl ketones and benzylic primary alcohols.

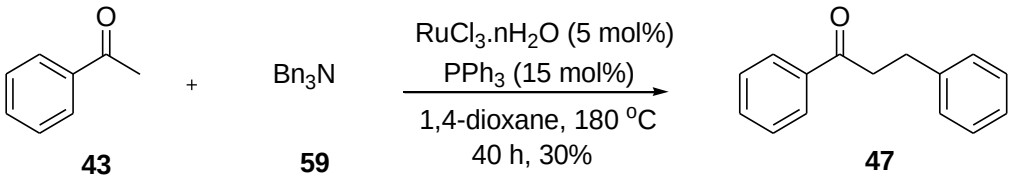


Scheme 11. Base-promoted α-alkylation of unactivated ketones

3.1.2.6 Direct α-alkylation *via* transfer hydrogenation

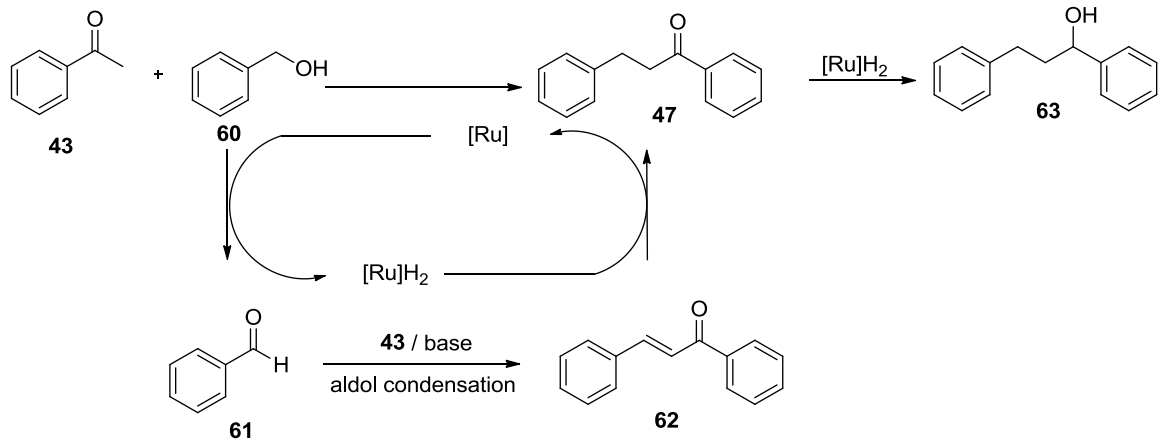
Primary alcohols have been employed in alkylation *via* transfer hydrogenation. This strategy essentially involves oxidation of primary alcohol into aldehyde under transition metal catalysis which undergoes aldol reaction with the ketone and subsequent hydrogenation under the influence of metal catalyst present in the reaction results eventually the product of α-alkylation.

Cho *et al.* reported the first alkyl group transfer from trialkylamines to the α-carbon of ketone in a ruthenium-catalysed reaction.[39] Acetopheneone **43** and tribenzylamine **59** were treated with catalytic amount of Ru catalyst and triphenylphosphine under vigorous reaction conditions to get the alkylated product **47** (Scheme 12).



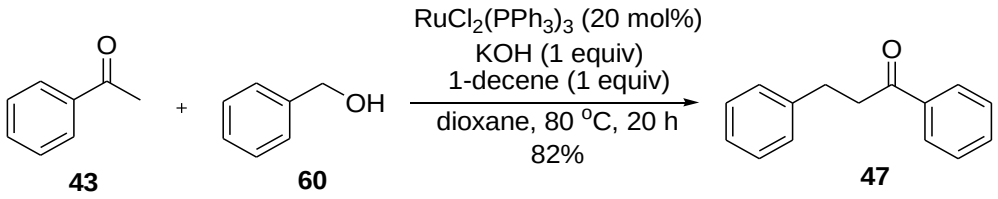
Scheme 12. α-Alkylation of acetophenone **43** catalysed by ruthenium catalyst

An unusual ruthenium-catalysed transfer hydrogenation reaction was reported by the same group to make secondary alcohols *via* α-alkylation of ketones followed by *in situ* reduction by dihydrido ruthenium species formed in the catalytic cycle (Scheme 13).[40] In mechanistic terms, Ru first oxidizes the alcohol **60** to aldehyde **61** and dihydrido ruthenium species was generated. This aldehyde **61** on condensation with ketone **43** in the presence of base forms chalcone **62**. This chalcone **62** is reduced by the dihydrido ruthenium species to get the α-alkylated product **47** which on further reduction with dihydrido ruthenium species give secondary alcohol **63**.



Scheme 13. Catalytic cycle for the α-alkylation of acetophenone **43** catalysed by ruthenium catalyst

The unwanted ketone reduction to alcohol can be prevented by introducing suitable hydrogen acceptor in the reaction. Regioselective α-alkylation of ketones was achieved by taking 1-decene in stoichiometric amount as hydrogen acceptor to avoid uncontrolled reduction to alcohols (Scheme 14).[41]



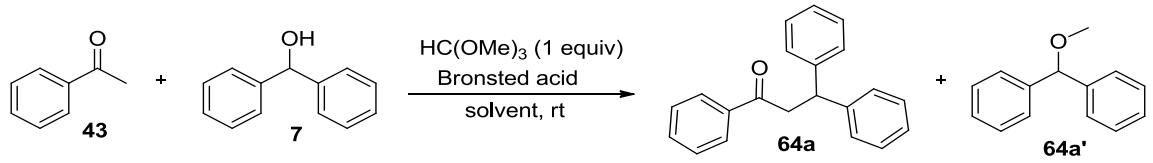
Scheme 14. α-Alkylation of acetophenone **43** catalysed by ruthenium catalyst and hydrogen acceptor

Several other catalysts have also been reported in literature such as $[Ru(DMSO)_4]Cl_2$,[42] $[Ir(Cl)(cod)]_2$,[43] and Pd/C/KOH,[44] Pd/AlO(OH),[45] and several other metal catalysts[46] are known for the α-alkylation of simple ketones *via* transfer hydrogenation.

3.2 Results and discussion

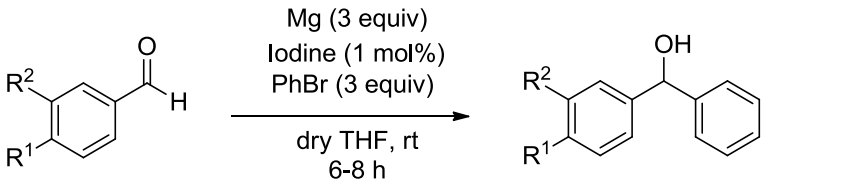
It is known that carbonyl compounds form acetals when treated with trimethyl orthoformate in the presence of acids.[47] Further the same acid can assist the elimination of alcohol in acetal to form enol ether.[47] The acid can activate alcohols to form electrophilic carbon. Hence we anticipated that treatment of a ketone with alcohol and trimethyl orthoformate in the presence of a Brønsted acid can result in direct alkylation of ketones. To explore this idea for direct alkylation *via in situ* generated acetals, acetophenone was reacted with benzhydrol in the presence of 1 equivalent of trimethyl orthoformate and different Brønsted acids separately at room temperature. Of the different Brønsted acids screened, strong Brønsted acid TfOH was found to be promising. Among the other Brønsted acids, while *p*-TSA, trichloroacetic acid and camphorsulfonic acid did not promote the reaction. Only methyl ether of benzhydrol was isolated in all the cases. In a separate experiment, dimethyl acetal derived from acetophenone was treated with benzhydrol and TfOH in CCl_4. This reaction resulted in 33% yield of the desired alkylated product along with 43% of acetophenone. These observations show that formation of acetal and its subsequent transformation into enol ether is the key in effecting smooth α-alkylation. The alkylation reaction was attempted at room temperature with catalytic amount of TfOH (20 mol%). Unfortunately, no alkylation product was observed and even at 60 °C and methyl ether **64a'** only formed exclusively.

Table 1. Optimization of acid reagent and solvent for the direct alkylation reaction



Entry[a]	Brønsted acid	Loading	Solvent	Time (h)	Yield[b] (%)	
					64a	**64a'**
1	*p*-TSA	1 equiv	CCl_4	12	-	85
2	CCl_3COOH	1 equiv	CCl_4	12	-	63
3	CSA	1 equiv	CCl_4	12	-	84
4	$HClO_4$	1 equiv	CCl_4	12	trace	80
5[c]	TfOH	1 equiv	CCl_4	16	9	-
6	TfOH	20 mol%	CCl_4	24	-	71
7[c,d]	TfOH	20 mol%	CCl_4	16	4	-
8	**TfOH**	**1 equiv**	**CCl_4**	**1**	**60**	**9**
9	TfOH	1 equiv	dioxane	12	0	91
10	TfOH	1 equiv	hexane	12	37	62
11[d]	TfOH	20 mol%	CCl_4	16	-	85

[a]Ketone **43** (1 equiv) and electrophile **7** (1.2 equiv) was used. [b]Isolated yields. [c]Without trimethyl orthoformate. [d]Reaction was heated to 60 °C.



65, $R^1 = CH_3$, $R^2 = H$
66, $R^1 = OCH_3$, $R^2 = H$
67, $R^1 = R^2 = -OCH_2O-$

68, $R^1 = CH_3$, $R^2 = H$, 92%
15, $R^1 = OCH_3$, $R^2 = H$, 74%
69, $R^1 = R^2 = -OCH_2O-$, 63%

Scheme 15. Synthesis of substituted benzhydrols from aldehydes by Grignard reaction

After finding the best reaction condition, we made differently substituted benzhydrols to employ them in the present α-alkylation methodology. These were made by trivial Grignard addition of aryl magnesium bromides on commercially available aryl aldehydes (Scheme 15). 4-Phenylbut-3-en-2-one was made by reacting benzaldehyde **61** in acetone

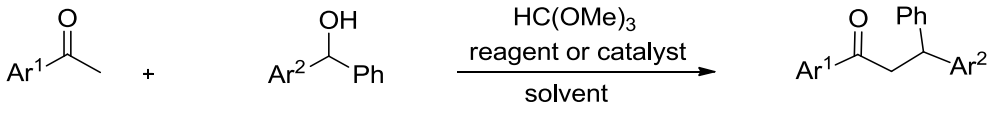
solvent in the presence of 16M NaOH aqueous solution at room temperature. Except 4-phenylbut-3-en-2-one, all the other ketone derivatives are commercially available.

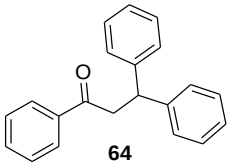
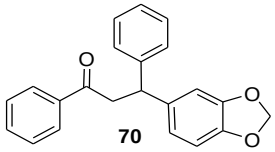
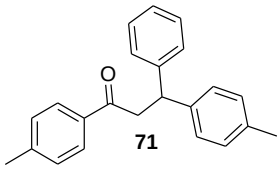
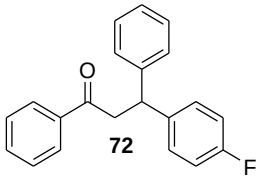
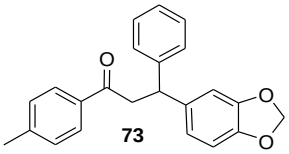
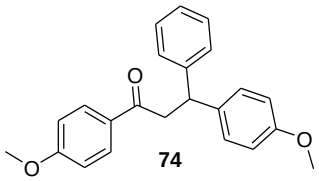
The substrate scope of the present α-alkylation was evaluated with a range of carbonyl compounds and diarylmethanols. All the reactions were carried out using 10 mol% of $AgSbF_6$ also (This catalyst was found by fellow co-worker for the alkylation of propargyl alcohols). Mayr's research group has made a seminal contribution to predict the reactivity of diversely substituted diarylmethanols with different nucleophiles under S_N1-type reaction conditions.[48] Based on several meticulous experiments they have established quantitative values for the nucleophilicity (N) and electrophilicity (E) of different nucleophiles and electrophiles respectively. It is anticipated that methyl vinyl ether is the species responsible for the product formation. According to Mayr's scale, the N value of closely related ethyl vinyl ether is 3.92.[48f, 49] This value is much less than that of reactive enamines (N >10) which reacts only with diarylmethanols having electron donating substituents.[33, 34e, 34f] These diarylmethanols result in stabilized carbocations (E<-4). [48f] In the present study we have reacted a wide range of electrophiles (E = +5.47 to -2.64) such as electron donating and electron withdrawing groups substituted diarylmethanols, xanthydrol, with ketones (nucleophiles) such as aryl methyl/aryl ethyl ketones, 4-phenylbut-3-en-2-one and cyclohexanone. To the best of our knowledge, none of the already reported protocols for direct α-alkylation of ketones has this range of substrate scope.

Table 2 presents the results of reaction of different ketones with diarylmethanol derivatives. Aryl ketones having electron donating groups such as Me, OMe and 3,4-methylenedioxy were tested. Alkylation of acetophenone with simple benzhydrol (E = 5.47) resulted the α-alkylated product in moderate yield only (60%). Some amount of corresponding methyl ether of benzhydrol also formed in this reaction. The yields of the alkylation products were better when halide functionality is present in the aryl ring of the ketone (**78-80**). Electron donating groups on one of the aryl rings of diarylmethanol also improved the yield of the alkylated product (**70**, **73**, **76**, **77**, **80**, **81** & **85**). On the other hand, electron withdrawing group such as fluoro as in (4-fluorophenyl)(phenyl)methanol (E = 5.20) resulted in moderate yield of the desired product **72**. In this case also some amount of corresponding methyl ether of the alcohol was obtained. Comparatively low yields of the

alkylated products in this case (45%) and in the reaction with simple benzhydrol (60%) is not surprising as they have high E value and do not form the benzylic carbocations that readily.

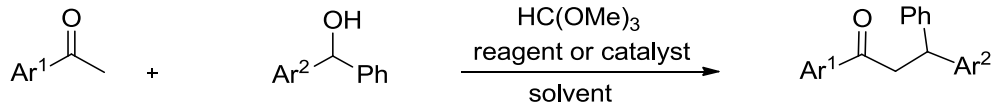
Table 2. Results of TfOH-mediated and $AgSbF_6$-catalysed α-alkylation of unactivated aryl methyl ketones

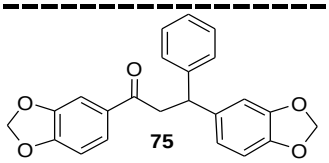
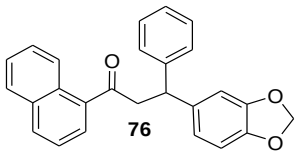
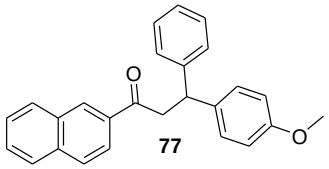
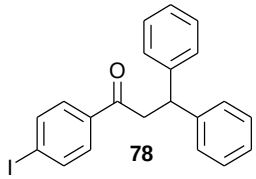
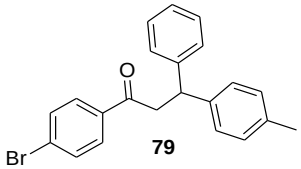


Entry	Product	TfOH[a] Time (h)	TfOH[a] Yield[c] (%)	$AgSbF_6$[b] Time (h)	$AgSbF_6$[b] Yield[c] (%)
1	 **64**	1	60	12	45
2	 **70**	1	87	5	79
3	 **71**	1	64	8	55[d]
4	 **72**	1	45	36	78
5	 **73**	1	74	4	68
6	 **74**	1	83	8	71[d]

[a]Trimethyl orthoformate (1 equiv) and triflic acid (1 equiv) in CCl_4 at room temperature. [b]Trimethyl orthoformate (2 equiv) and silver hexafluoroantimonate (10 mol%) in CH_2Cl_2 at 50 °C. [c]Isolated yields. [d]Trimethyl orthoformate (2 equiv) and AgOTf (10 mol%) in DCE at 80 °C.

Table 3. Results of TfOH-mediated and $AgSbF_6$-catalysed α-alkylation of unactivated aryl methyl ketones



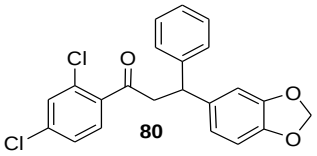
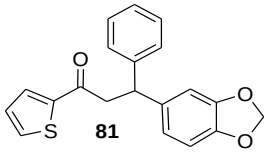
Entry	Product	**TfOH**[a]		**$AgSbF_6$**[b]	
		Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
7	 **75**	1	47	-	-
8	 **76**	1	91	5	78
9	 **77**	1	99	5	78
10	 **78**	1	90	6	95
11	 **79**	1	83	8	78[d]

[a]Trimethyl orthoformate (1 equiv) and triflic acid (1 equiv) in CCl_4 at room temperature. [b]Trimethyl orthoformate (2 equiv) and silver hexafluoroantimonate (10 mol%) in CH_2Cl_2 at 50 °C. [c]Isolated yields. [d]Trimethyl orthoformate (2 equiv) and AgOTf (10 mol%) in DCE at 80 °C.

However it is surprising that the α-alkylation did not work when (4-(dimethylamino)phenyl)(phenyl)methanol (having more –ve E value) which is expected to generate more stable benzylic carbocation was used at both room and reflux temperatures. Perhaps protonation of the amine nitrogen with strong TfOH might have occurred which makes it less reactive. However alcohol derived from benzoyl ferrocene (E = -2.64) underwent alkylation comfortably to yield **83** in 55% yield. Heteroaryl ketone such as 2-acetylthiophene also reacted nicely and yielded the corresponding α-alkylated product **81**.

This methodology can be applied to ketones other than aryl methyl ketones as well. Dialkyl ketones such as cyclohexanone also underwent α-alkylation. Only mono alkylated product **84** was obtained. Ethyl phenyl ketone resulted in a diastereomeric mixture of α-alkylated products **85**. α,β-Unsaturated ketone such as (*E*)-4-phenylbut-3-en-2-one could be employed to get the corresponding α-alkylated products (Table 7, **86** & **87**). It is worth mentioning that α,β-unsaturated carbonyl (in the form of aldehydes/ketones/enol acetates/silyl enol ethers) systems have not been studied so far in any of the reported alkylations involving diarylmethanols.

Table 4. Results of TfOH-mediated and $AgSbF_6$-catalysed α-alkylation of unactivated aryl methyl ketones

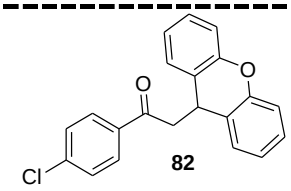
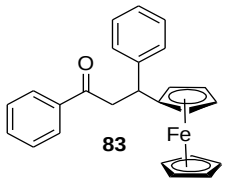
Entry	Product	**TfOH**[a]		**$AgSbF_6$**[b]	
		Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
12	 **80**	2	99	6	75
13	 **81**	1	92	6	68

[a]Trimethyl orthoformate (1 equiv) and triflic acid (1 equiv.) in CCl_4 at room temperature. [b]Trimethyl orthoformate (2 equiv) and silver hexafluoroantimonate (10 mol%) in CH_2Cl_2 at 50 °C. [c]Isolated yields.

We then studied the α-alkylation of ketones under silver hexafluoroantimonate ($AgSbF_6$)-catalysed reaction conditions. It was observed that, $AgSbF_6$-catalysed reactions require trimethyl orthoformate (2 equiv) to get good reaction outcome, where as in the case of TfOH-promoted reactions, 1 molar equivalent of trimethyl orthoformate is enough to promote the reaction efficiently. The reason might be the formation of methyl ether as reaction intermediate in the case of silver-catalysed reactions which require additional equivalent of trimethyl orthoformate. Unlike the reactions with TfOH, these reactions worked with catalytic (10 mol%) amount of silver hexafluoroantimonate efficiently but required heating condition to get the products in good yields. Most of the reactions require heating condition *i. e.*, CH_2Cl_2, 50 °C and for making compounds **71**, **74** and **79**, it requires DCE as solvent at 80 °C to get better yields. $AgSbF_6$-catalysed reactions require longer time

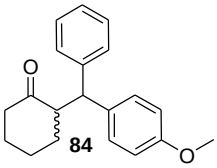
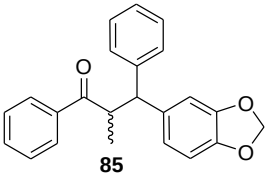
and furnished the products in low yields as compared to that of TfOH-promoted reactions, except in the reaction of 4-iodoacetophenone with benzhydrol to get the alkylation product **78**.

Table 5. Results of TfOH-mediated and $AgSbF_6$-catalysed α-alkylation of unactivated aryl methyl ketones

Entry	Product	**TfOH**[a]		**$AgSbF_6$**[b]	
		Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
14	 **82**	1	72	12	10
15	 **83**	1	55	-	-

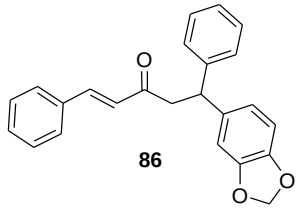
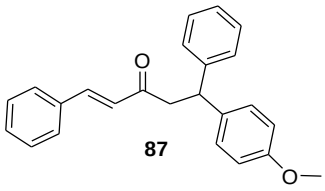
[a]Trimethyl orthoformate (1 equiv) and triflic acid (1 equiv) in CCl_4 at room temperature. [b]Trimethyl orthoformate (2 equiv) and silver hexafluoroantimonate (10 mol%) in CH_2Cl_2 at 50 °C. [c]Isolated yields.

Table 6. Results of TfOH-mediated and $AgSbF_6$-catalysed α-alkylation of unactivated ketones

Entry	Product	**TfOH**[a]			**$AgSbF_6$**[b]		
		Time (h)	Yield[c] (%)	dr[d]	Time (h)	Yield[c] (%)	dr[d]
1	 **84**	1	76	1:1	5	66	1.6:1
2	 **85**	1	80	1.5:1	5	40	3.5:1

[a]Trimethyl orthoformate (1 equiv) and triflic acid (1 equiv) in CCl_4 at room temperature. [b]Trimethyl orthoformate (2 equiv) and silver hexafluoroantimonate (10 mol%) in CH_2Cl_2 at 50 °C. [c]Isolated yields. [d]diastereomeric ratio was determined from ^{1}H-NMR spectrum.

Table 7. Synthesis of triarylpentenones by α-alkylation of unactivated ketones

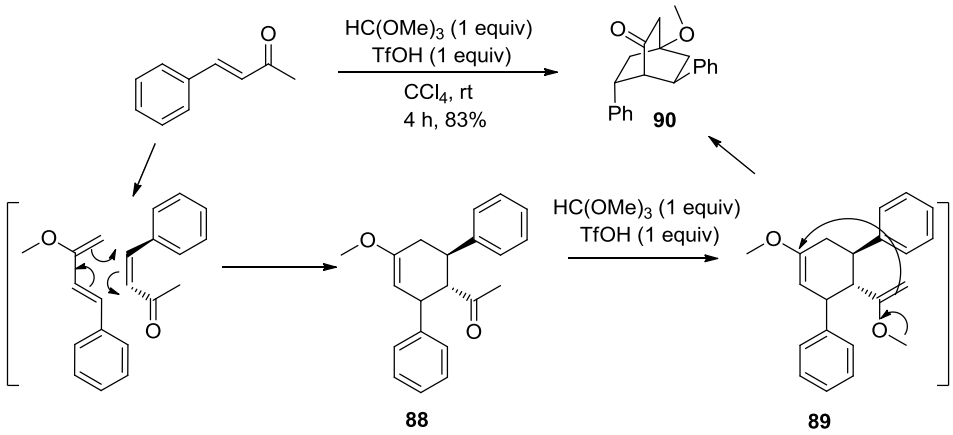
Entry	Product	**TfOH**[a]		**$AgSbF_6$**[b]	
		Time (h)	Yield[c] (%)	Time (h)	Yield[c] (%)
1	 **86**	3	80	12	0
2	 **87**	7	61	7	20

[a]Trimethyl orthoformate (1 equiv) and triflic acid (1 equiv) in CCl_4 at room temperature. [b]Trimethyl orthoformate (2 equiv) and silver hexafluoroantimonate (10 mol%) in CH_2Cl_2 at 50 °C. [c]Isolated yields.

Silver-catalysed reactions of unactivated ketone with xanthydrols failed to give the alkylated product (**82**). Cyclohexanone smoothly reacted with benzhydrol derivative **15** and furnished the diastereomeric mixture of alkylation product **84** in good yield. Propiophenone also furnished the alkylated product **85** in moderate yield under silver-catalysed conditions. It has to emphasized that in the case of silver-catalysed reactions, the diastereoselectivity improved as compared with TfOH-promoted reactions. 4-Phenylbut-3-en-2-one was also employed in silver-catalysed reaction. But, the reaction resulted in disappointing yields of the alkylation products (Table 7).

3.2.1 Triflic acid-promoted synthesis of bicyclo[2.2.2]octan-2-ones[50]

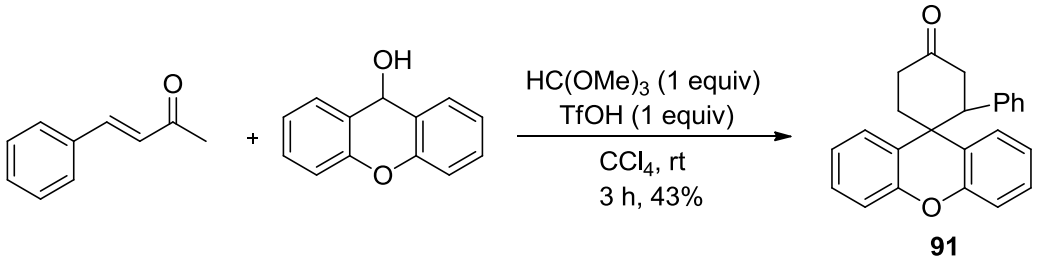
It was found that in the presence of trimethyl orthoformate under acid catalysis, these 4-phenylbut-3-en-2-one undergo intermolecular Diels-Alder reaction to give 4-methoxy bicyclo[2.2.2]octan-2-ones as shown in Scheme 16. We observed this product **90** in good yield (80%) while investigating the alkylation reaction with 4-phenylbut-3-en-2-one (Scheme 16).



Scheme 16. Triflic acid-mediated synthesis of 4-methoxy bicyclo[2.2.2]octan-2-one **90**

3.2.2 Triflic acid-mediated synthesis of spirocyclohexanones

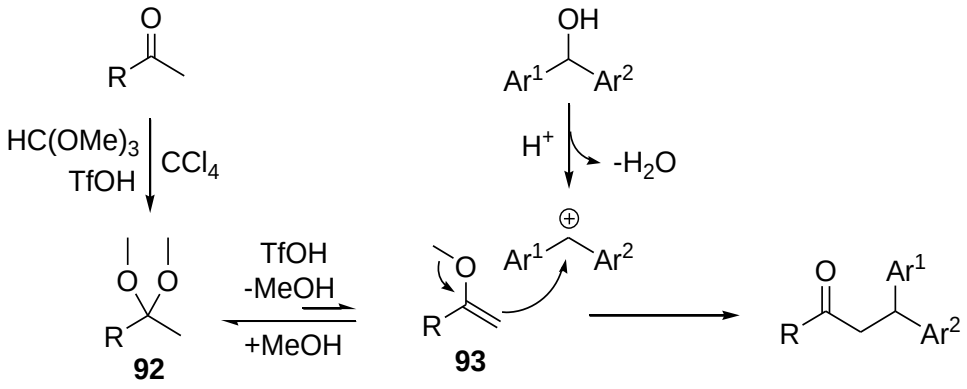
4-Phenylbut-3-en-2-one, when reacted with xanthydrol under optimized triflic acid reaction conditions, an interesting spirocyclohexanone derivative **91** was isolated in moderate yield (Scheme 17). Analysis of structure of the product revealed the incorporation of an additional carbon in the molecule, perhaps from trimethyl orthoformate. Attempts to improve the yield and understanding the mechanism of the reaction are underway in our laboratory.



Scheme 17. Triflic acid-mediated synthesis of spirocyclohexanone **91**

3.2.3 Mechanistic discussion

After scrutinisng the literature reports, it is believed that methyl ketone under optimized reaction conditions is converted into vinyl ether derivative **93**. This vinyl ether[47] derivative **93** in the presence of TfOH reacts with the suspended electrophiles generated from benzydrol to furnish the alkylated product as shown in Scheme 18.



Scheme 18. Mechanistic depiction of α-alkylation of unactivated ketone

3.3 Conclusions

A simple and one pot enolate formation from unactivated aryl and alkyl ketones and its alkylation reaction with benzhydrols have been developed under triflic acid-mediated and $AgSbF_6$-catalysed conditions. With triflic acid-mediated reactions, at ambient conditions, a wide variety of ketones were employed such as chloro, bromo, iodo, methyl and methoxy substituted acetophenones to get the alkylated products in good yield. Interestingly, aryl groups like naphthyl and heterocyclic thiophenyl methyl ketones also reacted smoothly under this acidic conditions to give the products in excellent yields. Comparatively vigorous reaction conditions were needed to get the alkylated products under $AgSbF_6$-catalysed conditions.

3.4 Experimental

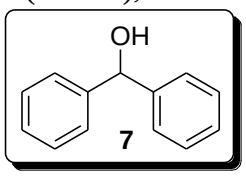
General Information

All reagents were obtained commercially and used without further purification unless otherwise mentioned. TfOH was purchased from Sigma-Aldrich chemical company and used without any further purification. Trimethyl orthoformate was distilled prior to use. HPLC grade CCl_4 procured from MERCK was used as solvent for alkylation reactions. Thin-layer chromatography was performed by using Merck silica gel F-254 coated aluminum plates and the visualization of spots were done using UV illumination and charring the TLC plates sprayed with Seebach solution. Column chromatography was performed on silica gel 100-200 mesh, using ethyl acetate and hexanes mixture as eluent. ^{1}H and ^{13}C NMR spectra of the

synthesized compounds were recorded in Bruker Avance 400 NMR machine using their solutions in $CDCl_3$. The ^1H NMR and ^{13}C NMR were referred respectively to TMS used as an internal standard and the central line of $CDCl_3$ peaks. IR spectra were recorded using JASCO FT/IR-5300 spectrometer. High resolution mass spectra (HRMS) were recorded using electro spray ionization in Bruker Maxis machine. Melting points were determined by using MR-VIS visual melting range apparatus and are uncorrected.

General procedure for the synthesis of benzhydrol

To a solution of benzophenone (3 g, 16.5 mmol) in dry methanol (50 mL), sodium borohydride (0.75 g, 19.7 mmol) was added portion wise at 0 °C. After around 3 h, the reaction mixture was quenched and methanol was evaporated. Ethyl acetate was added to the reaction mixture and it was washed with water, brine solution and concentrated. The residue was purified over silica gel column with ethyl acetate and hexanes (1:4) as eluents to get (2.3 g) of benzhydrol **7**.



Diphenylmethanol 7[51a]

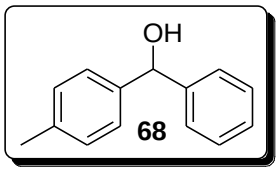
Yield: 76%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 8H), 7.27-7.23 (m, 2H), 5.82 (s, 1H), 2.27 (br s, 1H).

General procedure for the synthesis of substituted benzhydrols

To a rb flask equipped with a reflux condenser, magnesium turnings (3 equiv) and iodine (1 mol%) were added under nitrogen atmosphere. To this few drops of aryl bromide (neat) was added. After keeping the mixture for 5 min, THF (2-3 mL) was added with vigorous stirring. After disappearance of iodine colour with the evolution of heat, remaining aryl bromide (3 equiv) was added and the reaction mixture was stirred till the consumption of magnesium. To this grey colored reaction mixture, aryl aldehyde **65-67** (1 equiv) was added and the reaction mixture was stirred for 6-8 h. After complete consumption of aldehyde as indicated by TLC, aqueous NH_4Cl solution was added dropwise to quench the excess Grignard reagent. The reaction mixture was poured into water and extracted with ethyl acetate (2 times). The combined organic layers were washed with water, brine solution and concentrated under vacuum. The residue was purified by silica gel column chromatography

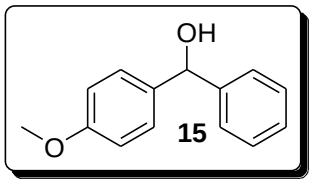
with EtOAc/ hexanes as eluent to furnish the substituted benzhydrols with moderate to good yields.

Phenyl(*p*-tolyl)methanol 68[51b]



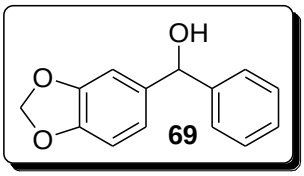
Yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 4H), 7.25 (d, *J* = 8.3 Hz, 3H), 7.13 (d, *J* = 2 Hz, 2H), 5.80 (s, 1H), 2.32 (s, 3H), 2.2 (br s, 1H).

(4-Methoxyphenyl)(phenyl)methanol 15[51b]



Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.30 (m, 4H), 7.28-7.23 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.76 (s, 1H), 3.77 (s, 3H), 2.21 (br s, 1H).

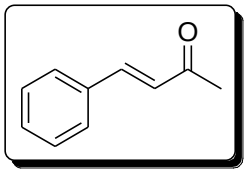
Benzo[d][1,3]dioxol-5-yl(phenyl)methanol 69[51c]



Yield: 63%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.20 (m, 4H), 7.27-7.23 (m, 1H), 6.84-6.81 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.91-5.90 (m, 2H), 5.73 (s, 1H), 2.27 (s, 1H).

General procedure for the synthesis of 4-phenylbut-3-en-2-one[51d]

To a stirred solution of benzaldehyde (1 g, 9.4 mmol) in dry acetone (3 mL), 16M sodium hydroxide solution (1.2 mL) was added dropwise. The reaction mixture was stirred at room temperature for overnight. After completion of the reaction, the reaction was diluted with ethyl acetate. The organic layer was washed with water several times and once with brine soluton. The ethyl acetate layer was concentrated and the residue was purified by column chromatography with ethyl acetate and hexane (1:10) as eluent to furnish (600 mg) 4-phenylbut-3-en-2-one. Yield: 44%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.49 (m, 3H), 7.41-7.39 (m, 3H), 6.72 (d, *J* = 16.3 Hz, 1H), 2.38 (s, 3H).



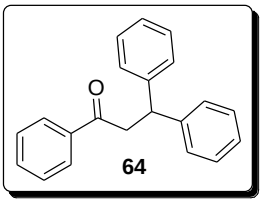
General procedure for α-alkylation of unactivated ketones

To a solution of unactivated ketone (1 equiv) and diarylmethanol (1.2 equiv) in CCl_4 (2 mL), trimethyl orthoformate (1 equiv) and triflic acid (1 equiv) were added. The reaction

mixture was stirred at room temperature. After complete consumption of the ketone as revealed by TLC, solvent was evaporated, and the crude product was directly loaded on a silica gel column (usual water workup in case of **83**) and eluted with ethyl acetate/hexanes to get the pure alkylated product.

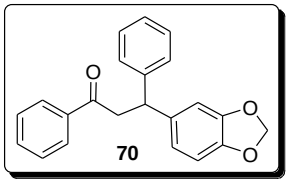
Characterization data of the alkylation products

1,3,3-triphenylpropan-1-one 64[52a]



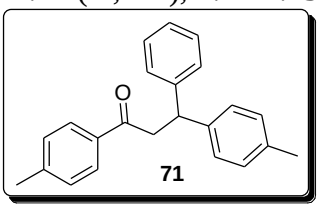
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.89 (m, 2H), 7.51-7.49 (m, 1H), 7.42-7.39 (m, 2H), 7.26-7.23 (m, 8H), 7.19-7.13 (m, 2H), 4.82 (t, *J* = 7.2 Hz, 1H), 3.72 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 144.1, 137.0, 133.0, 128.5, 128.4, 128.0, 127.8, 126.3, 45.9, 44.6.

3-(benzo[d][1,3]dioxol-5-yl)-1,3-diphenylpropan-1-one 70



Cream coloured solid; mp 96-98 °C; IR (KBr, cm^{-1}): 3413, 2882, 2783, 1671, 1594, 1490, 1446, 1238, 1035, 942, 745, 542; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.90 (m, 2H), 7.52-7.50 (m, 1H), 7.41 (t, *J* = 7.1 Hz, 2H), 7.28-7.21 (m, 4H), 7.17-7.16 (m, 1H), 6.74-6.72 (m, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.84 (s, 2H), 4.74 (t, *J* = 7.2 Hz, 1H), 3.67 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 147.7, 145.9, 144.2, 138.0, 136.9, 133.0, 128.5, 128.0, 127.6, 126.3, 120.6, 108.3, 108.1, 100.8, 45.5, 44.7; HRMS (ESI) m/z calcd for $C_{22}H_{18}O_3[M+H]^+$= 331.1334, found = 331.1334.

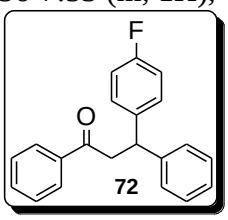
3-phenyl-1,3-di-*p*-tolylpropan-1-one 71[52b]



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.25-7.21 (m, 7H), 7.17-7.13 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 4.78 (t, *J* = 7.3 Hz, 1H), 3.68 (d, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 144.5, 143.8, 141.2, 141.2, 135.8, 134.6, 129.2, 128.5, 128.2, 127.8, 127.7, 126.2, 45.6, 44.6, 21.6, 21.0.

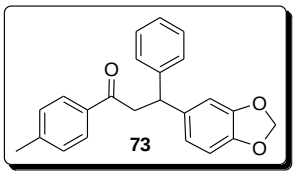
3-(4-fluorophenyl)-1,3-diphenylpropan-1-one 72[52c]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 8.0 Hz, 0.8 Hz, 2H), 7.56-7.53 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.29-7.16 (m, 7H), 6.94 (t, *J* = 8.8 Hz, 2H), 4.82 (t, *J* = 7.6 Hz, 1H), 3.71 (dd, *J* = 6.8 Hz, 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 161.4 (d, *J* = 242.9 Hz), 144.1, 139.9, 137.1, 133.3, 129.4, 129.3, 128.7, 128.2, 127.8, 126.6, 115.6 (d, *J* = 21.1 Hz), 45.3, 44.9; ^{19}F NMR (376.3 MHz, $CDCl_3$): -116.7 (s).



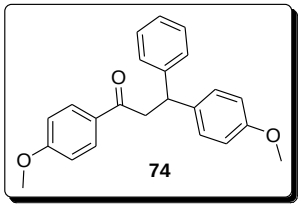
3-(benzo[d][1,3]dioxol-5-yl)-3-phenyl-1-*p*-tolylpropan-1-one 73

Cream coloured solid; mp 88-90 °C; IR (KBr, cm^{-1}): 3435, 2893, 1665, 1484, 1430, 1232, 1030, 931, 805; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.25-7.23 (m, 4H), 7.21-7.19 (m, 2H), 7.16-7.14 (m, 1H), 6.73-6.71 (m, 2H), 6.69-6.66 (m, 1H), 5.82 (s, 2H), 4.73 (t, *J* = 7.1 Hz, 1H), 3.63 (d, *J* = 7.1 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 147.6, 145.9, 144.3, 143.8, 138.1, 134.5, 129.2, 128.5, 128.1, 127.6, 126.3, 120.6, 108.3, 108.1, 100.8, 45.6, 44.5, 21.5; HRMS (ESI) m/z calcd for $C_{23}H_{20}O_3[M+H]^+$= 345.1491, found = 345.1490.



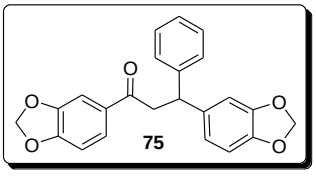
1,3-bis(4-methoxyphenyl)-3-phenylpropan-1-one 74[52d]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.7 Hz, 2H), 7.26-7.22 (m, 4H), 7.17-7.12 (m, 3H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 4.76 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.63 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 M Hz, $CDCl_3$): δ 196.6, 163.4, 157.9, 144.6, 136.4, 130.3, 130.1, 128.7, 128.4, 127.7, 126.2, 113.8, 113.6, 55.4, 55.1, 45.2, 44.5.



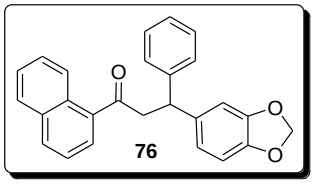
1,3-di(benzo[d][1,3]dioxol-5-yl)-3-phenylpropan-1-one 75

Yellow colored solid; mp 116-118 °C; IR (KBr, cm^{-1}): 3452, 3051, 1676, 1446, 1043, 931, 869, 734, 706; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 1H), 7.39-7.37 (m, 1H), 7.28-7.21 (m, 4H), 7.18-7.13 (m, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.73-6.66 (m, 3H), 6.00 (s, 2H), 5.86 (s, 2H),



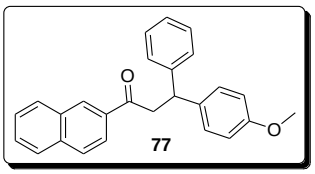
4.71 (t, *J* = 7.3 Hz, 1H), 3.58 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 151.7, 148.1, 147.7, 145.9, 144.2, 138.1, 131.8, 128.5, 127.6, 126.3, 124.2, 120.6, 108.3, 108.1, 107.9, 107.8, 101.8, 100.8, 45.7, 44.4; HRMS (ESI) m/z calcd for $C_{23}H_{18}O_5[M+Na]^+$= 397.1052, found = 397.1052.

3-(benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-1-yl)-3-phenylpropan-1-one 76



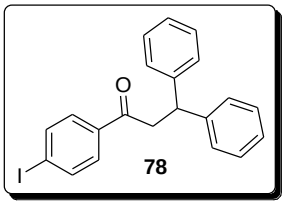
Gummy liquid; IR (KBr, cm^{-1}): 3447, 2924, 1682, 1487, 1440, 1240, 1039, 935, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.3 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.85-7.83 (m, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.51-7.44 (m, 3H), 7.29-7.24 (m, 4H), 7.21-7.15 (m, 1H), 6.75-6.72 (m, 2H), 6.68 (d, *J* = 7.4 Hz, 1H), 5.88 (s, 2H), 4.77 (t, *J* =7.6 Hz, 1H), 3.76 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 147.8, 146.0, 143.9, 137.8, 136.5, 133.9, 132.4, 129.9, 128.6, 128.3, 127.7, 126.9, 126.5, 126.4, 125.7, 124.3, 120.7, 108.5, 108.2, 100.9, 48.4, 46.3; HRMS (ESI) m/z calcd for $C_{26}H_{20}O_3[M+Na]^+$= 403.1310, found = 403.1310.

3-(4-methoxyphenyl)-1-(naphthalen-2-yl)-3-phenylpropan-1-one 77



Light yellow solid; mp 116-118 °C; IR (KBr, cm^{-1}): 3059, 2833, 1674, 1265, 1176, 1035, 812, 702, 557, 478; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.98 (m, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.60-7.51 (m, 2H), 7.30-7.24 (m, 4H), 7.21-7.14 (m, 3H), 6.81 (m, 2H), 4.84 (t, *J* = 7.4 Hz, 1H), 3.83 (d, *J* = 7.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 158.0, 144.5, 136.3, 135.5, 134.4, 132.5, 129.7, 129.5, 128.8, 128.5, 128.4, 127.7, 126.8, 126.3, 123.9, 113.9, 55.2, 45.3, 45.0; HRMS (ESI) m/z calcd for $C_{26}H_{22}O_2[M+Na]^+$= 389.1517, found = 389.1518.

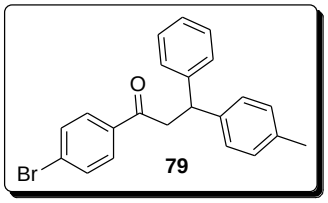
1-(4-Iodophenyl)-3-phenyl-3-*p*-tolylpropan-1-one 78



Light yellow solid; mp 120-122 °C; IR (KBr, cm^{-1}): 3024, 1682, 1579, 981, 748, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.28-7.23 (m, 8H), 7.19-7.15 (m, 2H), 4.79 (t, *J* = 7.2 Hz, 1H), 3.67 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 143.9, 137.9, 136.3, 129.4, 128.6, 127.8, 126.5, 101.0, 45.9,

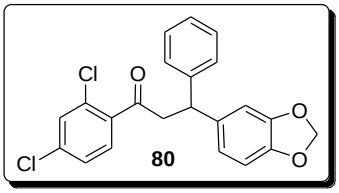
44.6; HRMS (ESI) m/z calcd for $C_{21}H_{17}IO[M+Na]^+$= 435.0222, found = 435.0222.

1-(4-bromophenyl)-3-phenyl-3-*p*-tolylpropan-1-one 79



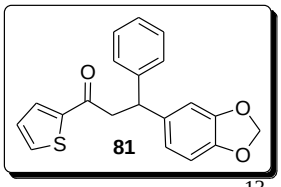
Light yellow colored solid; mp 128-130 °C; IR (KBr, cm^{-1}): 3022, 2916, 1680, 1583, 1259, 1205, 989, 817, 698, 557; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.26-7.15 (m, 5H), 7.13 (d *J* = 7.1 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.75 (t, *J* = 7.4 Hz, 1H), 3.67 (d, *J* = 7.4 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 144.1, 140.9, 136.0, 135.8, 131.9, 129.6, 129.3, 128.6, 128.2, 127.7, 127.6, 126.4, 45.6, 44.7, 21.0; HRMS (ESI) m/z calcd for $C_{22}H_{19}BrO[M+Na]^+$= 401.0517, found = 401.0517.

3-(benzo[d][1,3]dioxol-5-yl)-1-(2,4-dichlorophenyl)-3-phenylpropan-1-one 80



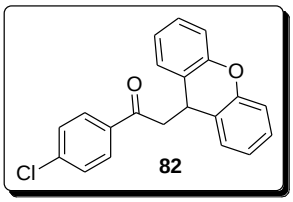
Light brown liquid; IR (neat, cm^{-1}): 3584, 2926, 1697, 1583, 1485, 1242, 933, 665; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 1.9 Hz, 1H), 7.25-7.22 (m, 2H), 7.20-7.16 (m, 4H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.68-6.67 (m, 3H), 5.87 (s, 2H), 4.60 (t, *J* = 7.8 Hz, 1H), 3.64 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 147.7, 146.1, 143.4, 137.7, 137.3, 137.2, 131.7, 130.1, 128.6, 127.6, 127.2, 126.5, 120.6, 108.3, 108.1, 100.9, 49.1, 46.2; HRMS (ESI) m/z calcd for $C_{22}H_{16}Cl_2O_3[M+Na]^+$= 421.0374, found = 421.0374.

3-(benzo[d][1,3]dioxol-5-yl)-3-phenyl-1-(thiophen-2-yl)propan-1-one 81



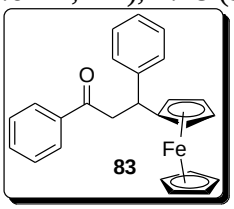
Cream coloured solid; mp 134-136 °C; IR (KBr, cm^{-1}): 3084, 2872, 1639, 1487, 1415, 1244, 1039, 939, 729, 543; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 3.5 Hz, 1H), 7.61 (d, *J* = 4.8 Hz, 1H), 7.29-7.24 (m, 4H), 7.19-7.15 (m, 1H), 7.10 (d, *J* = 4.3 Hz, 1H), 6.74 (d, *J* = 9.4 Hz, 2H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.89 (s, 2H), 4.73 (t, *J* = 7.6 Hz, 1H), 3.60 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 147.7, 146.0, 144.3, 143.9, 137.8, 133.7, 131.8, 128.6, 128.1, 127.6, 126.5, 120.7, 108.4, 108.2, 100.9, 45.8, 45.5; HRMS (ESI) m/z calcd for $C_{20}H_{16}O_3S[M+H]^+$= 337.0898, found = 337.0889.

1-(4-chlorophenyl)-2-(9H-xanthen-9-yl)ethanone 82



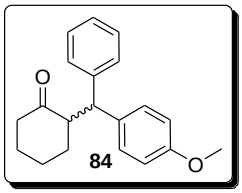
Yellow colored solid; mp 92-94 °C; IR (KBr, cm^{-1}): 3038, 1682, 1477, 1456, 1257, 829, 760; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.30-7.25 (m, 2H), 7.22-7.18 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.03-6.99 (m, 2H) 4.81 (t, *J* = 6.6 Hz, 1H), 3.29 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 152.4, 139.7, 135.4, 129.6, 128.8, 128.8, 128.0, 125.4, 123.6, 116.7, 49.6, 35.0; HRMS (ESI) m/z calcd for $C_{21}H_{15}ClO_2[M+Na]^+$= 357.0658, found = 357.0659.

3-Ferrocenyl-1,3-diphenylpropan-1-one 83



Yellow colored solid; mp 134-136 °C**;** IR (KBr, cm^{-1}): 3052, 1676, 1452, 1210, 986, 745; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.90 (m, 2H), 7.53-7.51 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.27-7.21(m, 4H), 7.16-7.14 (m, 1H), 4.54 (dd, *J* = 8.0 Hz, *J* = 5.6 Hz, 1H), 4.18 (s, 1H),4.11 (s, 1H),4.06 (s, 6H), 4.0 (s, 1H), 3.66-3.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 144.9, 137.4, 133.1, 128.7, 128.4, 128.2, 127.9, 126.5, 93.5, 68.8, 68.1, 67.8, 67.4, 67.1, 46.4, 41.0. HRMS (ESI) m/z calcd for $C_{25}H_{22}OFe$ $[M]^+$= 394.1020, found = 394.1019.

2-((4-methoxyphenyl)(phenyl)methyl)cyclohexanone 84

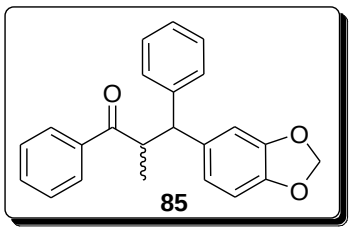


Mixture of diastereomers; Liquid; IR (neat, cm^{-1}): 2935, 1711, 1512, 1249, 1033, 700; ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.26-7.17 (m, 10H), 7.15-7.08 (m, 4H), 6.79-6.76 (m, 4H), 4.27 (d, *J* = 10.8 Hz, 2H), 3.71 (s, 3H), 3.70 (s, 3H), 3.29 (m, 2H), 2.43-2.29 (m, 4H), 2.03-1.96 (m, 2H), 1.84-1.70 (m, 6H), 1.67-1.58 (m, 2H), 1.44-1.34 (m, 2H); ^{13}C NMR(100 MHz, $CDCl_3$): δ 212.5, 212.4, 157.9, 157.7, 144.1, 143.2, 135.8, 135.0, 129.1, 128.5, 128.4, 128.3, 128.1, 127.4, 126.1, 125.9, 113.8, 113.7, 55.0, 55.0, 54.9, 50.0, 50.0, 42.3, 42.2, 33.3, 33.2, 29.1, 24.4, 24.2; HRMS (ESI) m/z calcd for $C_{20}H_{22}O_2[M+Na]^+$= 317.1517, found = 317.1526.

3-(benzo[d][1,3]dioxol-5-yl)-2-methyl-1,3-diphenylpropan-1-one 85

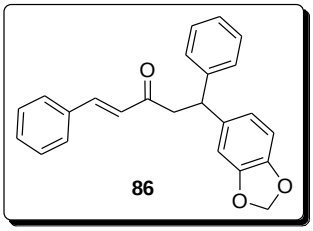
Mixture of diastereomers; White solid; mp 108-110 °C; IR (KBr, cm^{-1}): 2874, 1674, 1502, 1487, 1440, 1232, 1037, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (t, *J* = 8.5 Hz,

3.3H), 7.56-7.52 (m, 2H), 7.46-7.41 (m, 3.5 H), 7.34-7.29 (m, 2.9H), 7.21 (d, *J* = 7.1 Hz, 2.8H), 7.11 (t, *J* = 7.1 Hz, 2.2H), 7.04-7.00 (m, 1H), 6.83-6.81 (m, 2H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.73-6.69 (m, 1.3H), 6.55 (dd, *J* = 7.8 Hz, 1H), 5.90 (d, *J* = 7.3 Hz, 2H), 5.77 (d, *J* = 4.9 Hz, 1.3H), 4.38-4.29 (m, 3.3H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 1.9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 203.2, 147.8, 147.5, 146.1, 145.8, 143.6, 143.0, 137.6, 137.0, 136.7, 132.9, 128.6, 128.4, 128.3, 128.1, 128.1, 127.4, 126.5, 126.2, 121.6, 120.3, 108.5, 108.4, 108.2, 108.1, 100.9, 100.7, 53.9, 53.9, 44.9, 44.8, 18.0, 17.9; HRMS (ESI) m/z calcd for $C_{23}H_{20}O_3[M+Na]^+$= 367.1310, found = 367.1310.



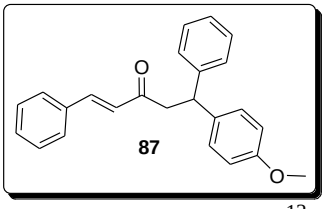
(*E*)-5-(benzo[d][1,3]dioxol-5-yl)-1,5-diphenylpent-1-en-3-one 86

Gummy solid; mp 106-108 °C; IR (KBr, cm^{-1}): 3022, 2920, 1651, 1487, 1234, 1176, 1037, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 3H), 7.37-7.36 (m, 3H), 7.29-7.21 (m, 4H), 7.18-7.15 (m, 1H), 6.74-6.67 (m, 4H), 5.89 (s, 2H), 4.65 (t, *J* = 7.4 Hz, 1H), 3.35 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 147.7, 145.9, 144.1, 142.8, 137.9, 134.3, 130.5, 128.9, 128.5, 128.2, 127.8, 126.4, 126.1, 120.8, 108.3, 108.1, 100.8, 46.9, 45.7; HRMS (ESI) m/z calcd for $C_{24}H_{20}O_3[M+Na]^+$= 379.1310, found = 379.1311.



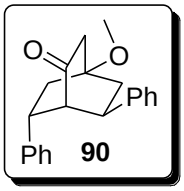
(*E*)-5-(4-methoxyphenyl)-1,5-diphenylpent-1-en-3-one 87

White solid; mp 124-126 °C; IR (KBr, cm^{-1}): 3026, 2930, 1635, 1512, 1251, 1180, 1032, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 16.2 Hz, 1H), 7.50-7.49 (m, 2H), 7.38-7.36 (m, 3H), 7.31-7.23 (m, 5H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.81 (m, 2H), 6.69 (d, *J* = 16.2 Hz, 1H), 4.67 (t, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 3.38 (d, *J* = 7.6 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 158.1, 144.4, 142.8, 136.2, 134.5, 130.5, 128.9, 128.8, 128.6, 128.3, 127.7, 126.3, 126.3, 113.9, 55.2, 47.2, 45.4; HRMS (ESI) m/z calcd for $C_{22}H_{22}O_2[M+H]^+$= 343.1698, found = 343.1700.



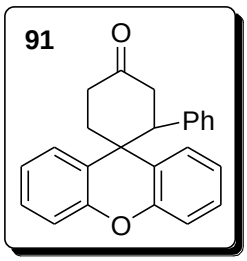
Experimental procedure for making 4-methoxybicyclo[2.2.2]octan-2-one 90[50]

To a solution of 4-phenylbut-3-en-2-one (50 mg, 0.34 mmol) in carbon tetra chloride (2 mL), trimethyl orthoformate (23 μL, 0.34 mmol) was added and the reaction mixture was stirred for 5 min. To this reaction mixture, triflic acid (30 μL, 0.34 mmol) was added slowly. The resultant dark reaction mixture was strirred for 4 h at room temperature. After completion of the reaction as indicated by TLC, the solvent was evaporated and the reaction mixture directly loaded onto the silica gel column and purified using ethylacetate and hexane as eluents to get the product **90** (44 mg) as light brown liquid. Yield: 83%; liquid; ^{1}H NMR (400 MHz, $CDCl_3$): 7.40-7.34 (m, 4H), 7.30-7.22 (m, 3H), 7.17-7.14 (m, 1H), 7.03 (d, *J* = 7.7 Hz, 2H), 3.41-3.35 (m, 2H), 3.34 (s, 3H), 2.69-2.64 (m, 2H), 2.51 (dd, *J* = 18.0, 2.5 Hz, 1H), 2.46-2.39 (m, 1H), 2.34-2.19 (m, 2H), 1.92-1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 143.7, 140.8, 128.7, 128.6, 127.5, 126.9, 126.6, 74.7, 54.5, 49.8, 47.2, 38.6, 37.9, 34.9, 33.7.



Spirocyclohexanone derivatives

Spirocyclohexanaone **91** was made by using the procedure mentioned for α-alkylation reaction, Yield: 43%; liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.0 Hz, 1H), 7.31-7.24 (m, 3H), 7.22-7.06 (m, 7H), 7.00 (m, 2H), 3.39 (d, *J* = 16.2 Hz, 1H), 3.04 (dt, *J* = 15.2, 2.1 Hz, 1H), 2.90-2.79 (m, 2H), 2.63-2.56 (m, 1H), 2.23 (dq, *J* = 13.4, 2.5 Hz, 1H), 1.90 (t, *J* = 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.3, 152.5, 152.1, 142.9, 130.0, 129.0, 128.6, 128.1, 128.0, 126.8, 126.8, 126.6, 123.8, 123.4, 123.2, 117.1, 48.5, 46.9, 46.6, 42.0, 38.1; HRMS (ESI) m/z calcd for $C_{24}H_{20}O_2$ $[M+H]^+$ = 341.1542, found = 341.1543.



3.5 References

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Chapter 3

3.6 Representative ^{1}H NMR and ^{13}C NMR spectra

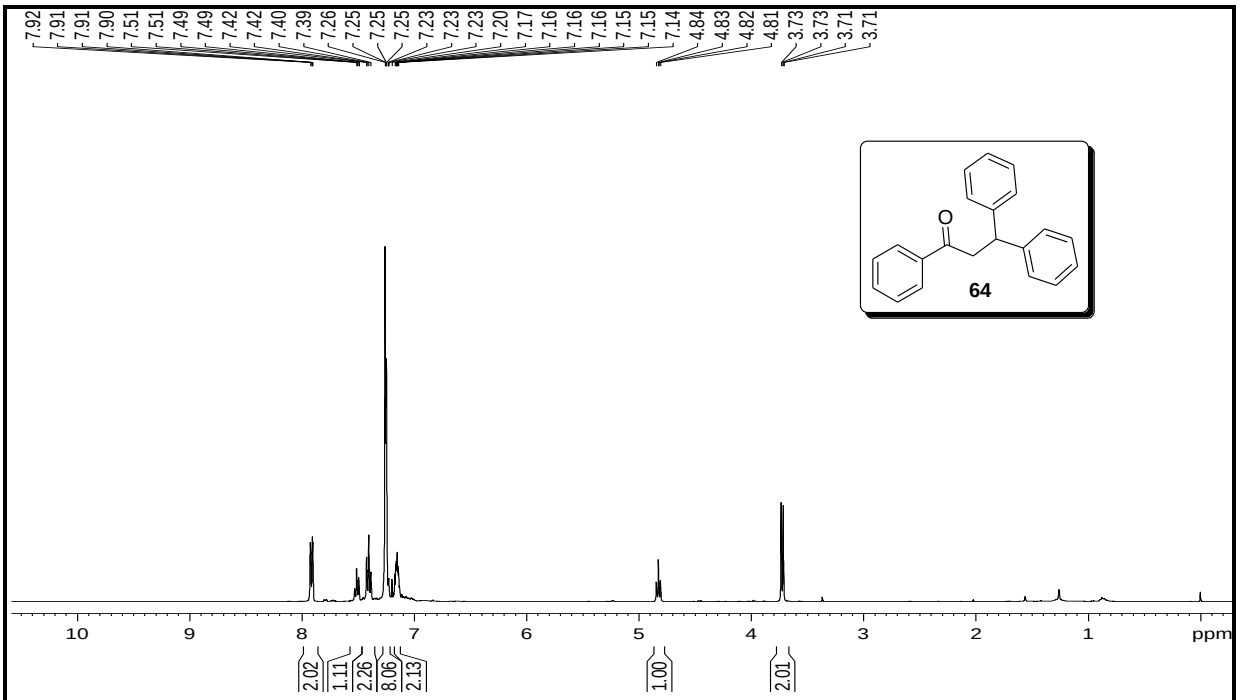


Figure 2. 400 MHz ^{1}H NMR spectrum of compound **64**

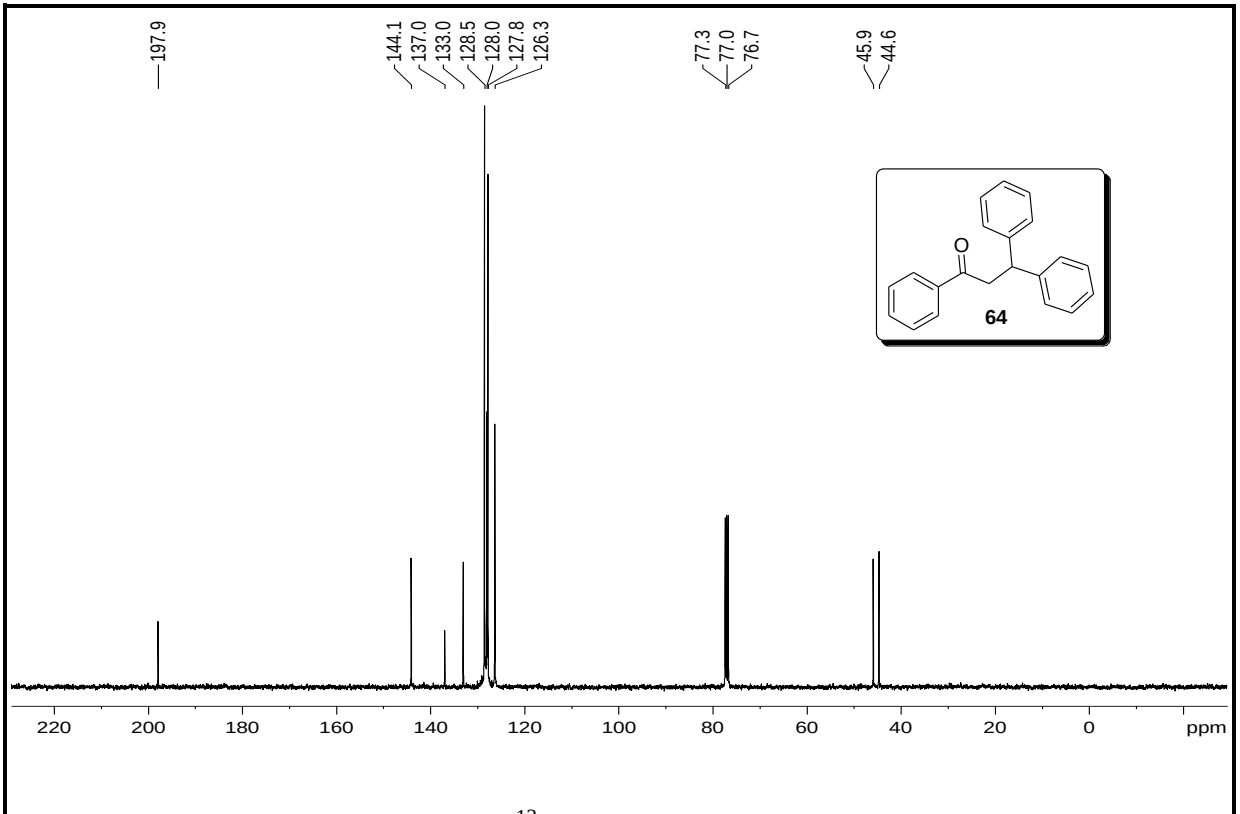


Figure 3. 100 MHz ^{13}C NMR spectrum of compound **64**

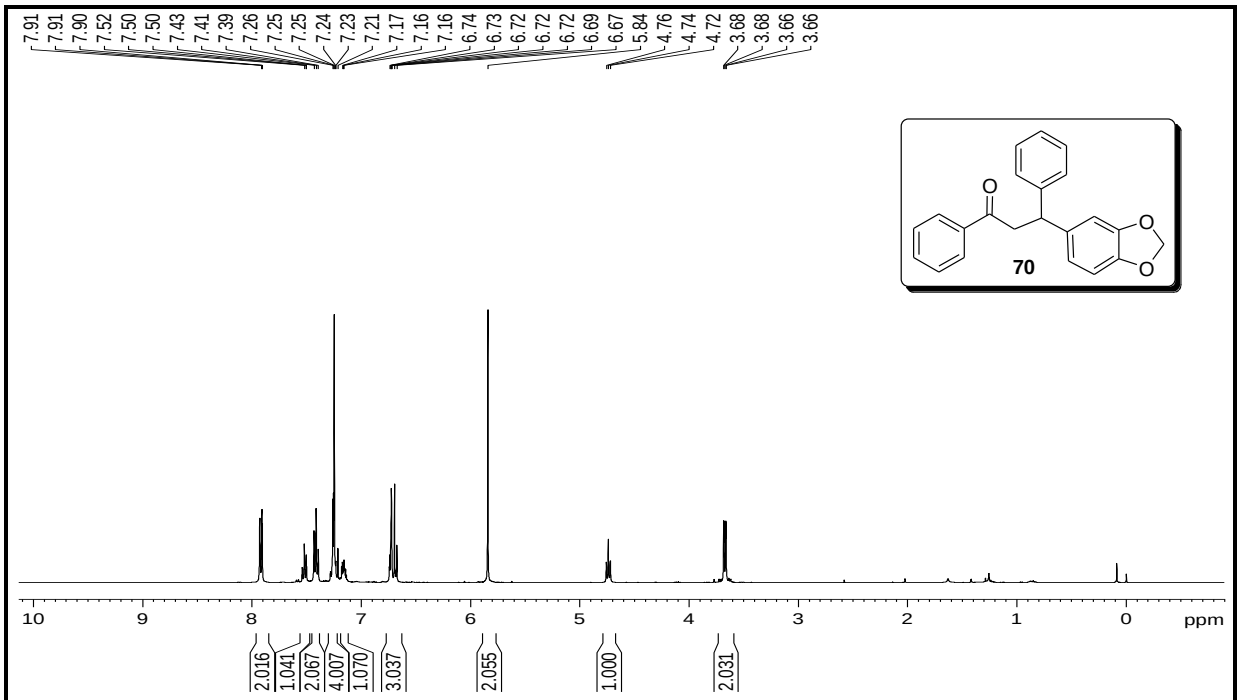


Figure 4. 400 MHz ^{1}H NMR spectrum of compound **70**

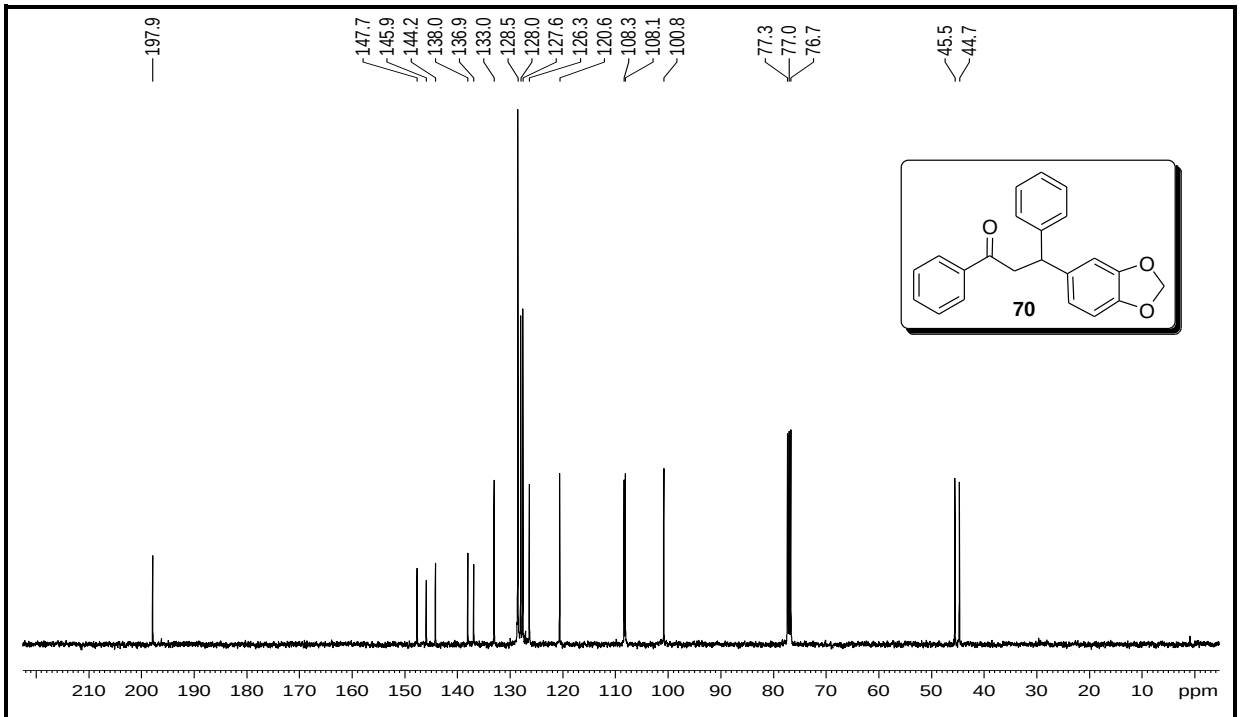


Figure 5. 100 MHz ^{13}C NMR spectrum of compound **70**

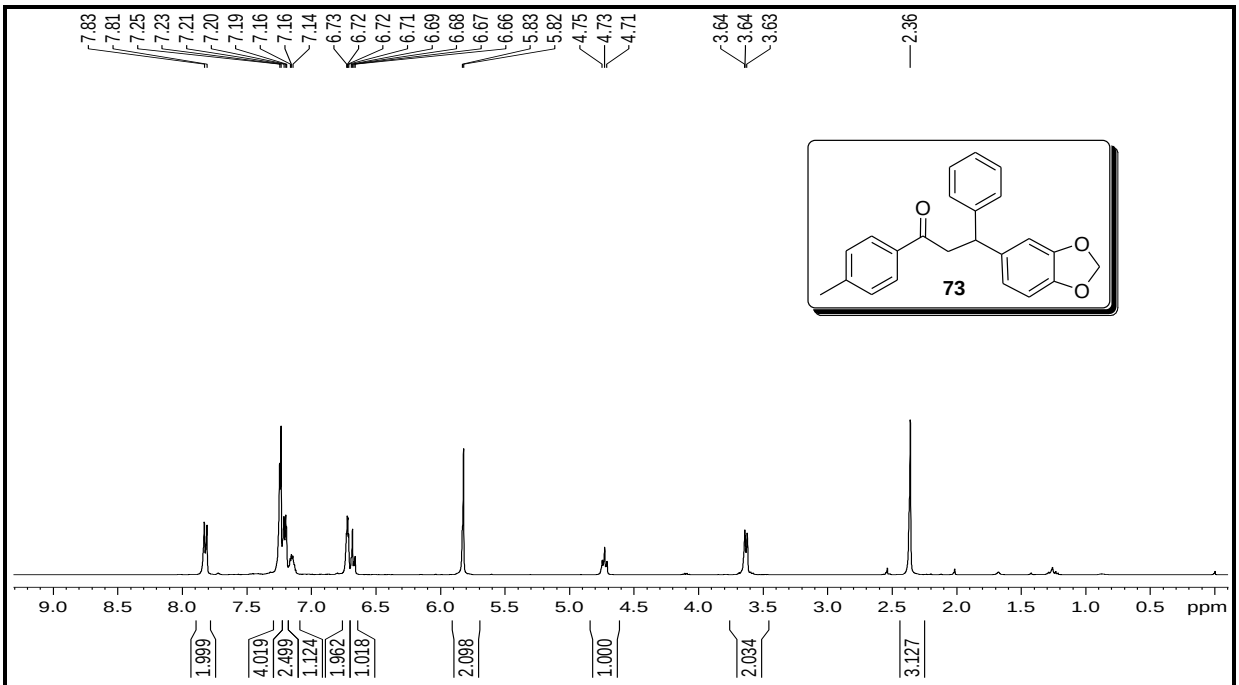


Figure 6. 400 MHz ^{1}H NMR spectrum of compound **73**

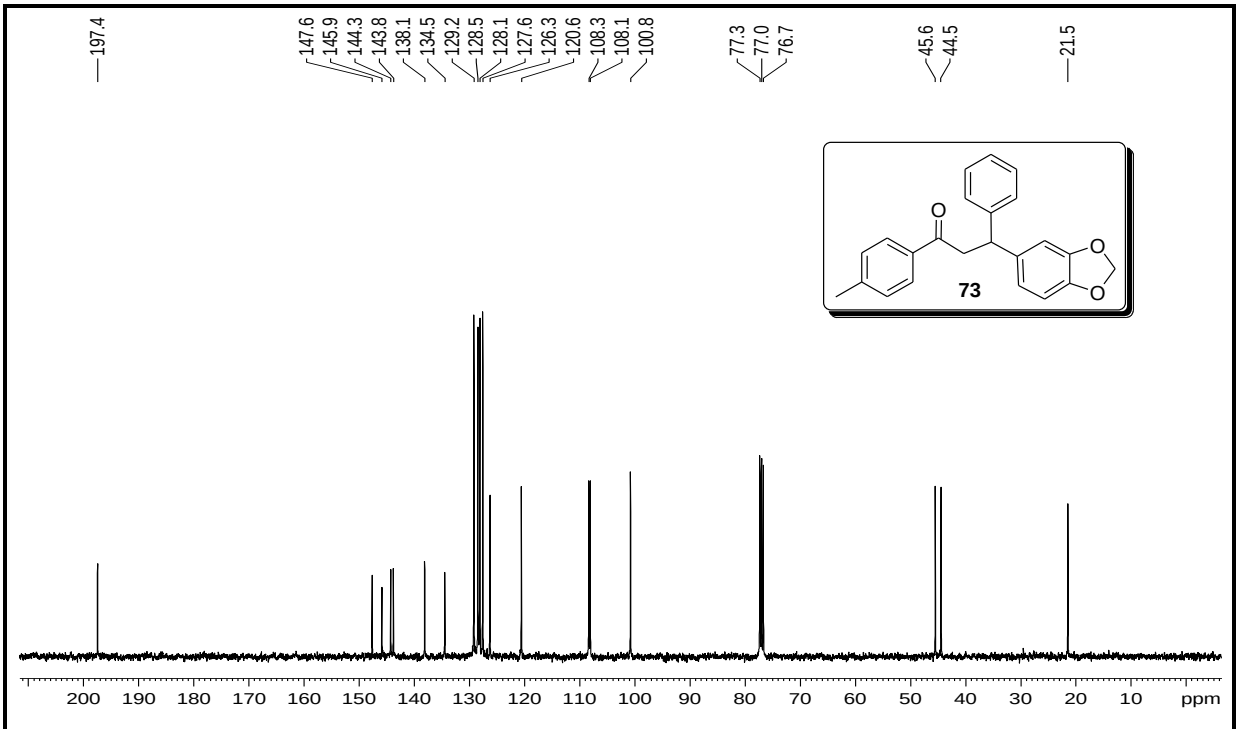


Figure 7. 100 MHz ^{13}C NMR spectrum of compound **73**

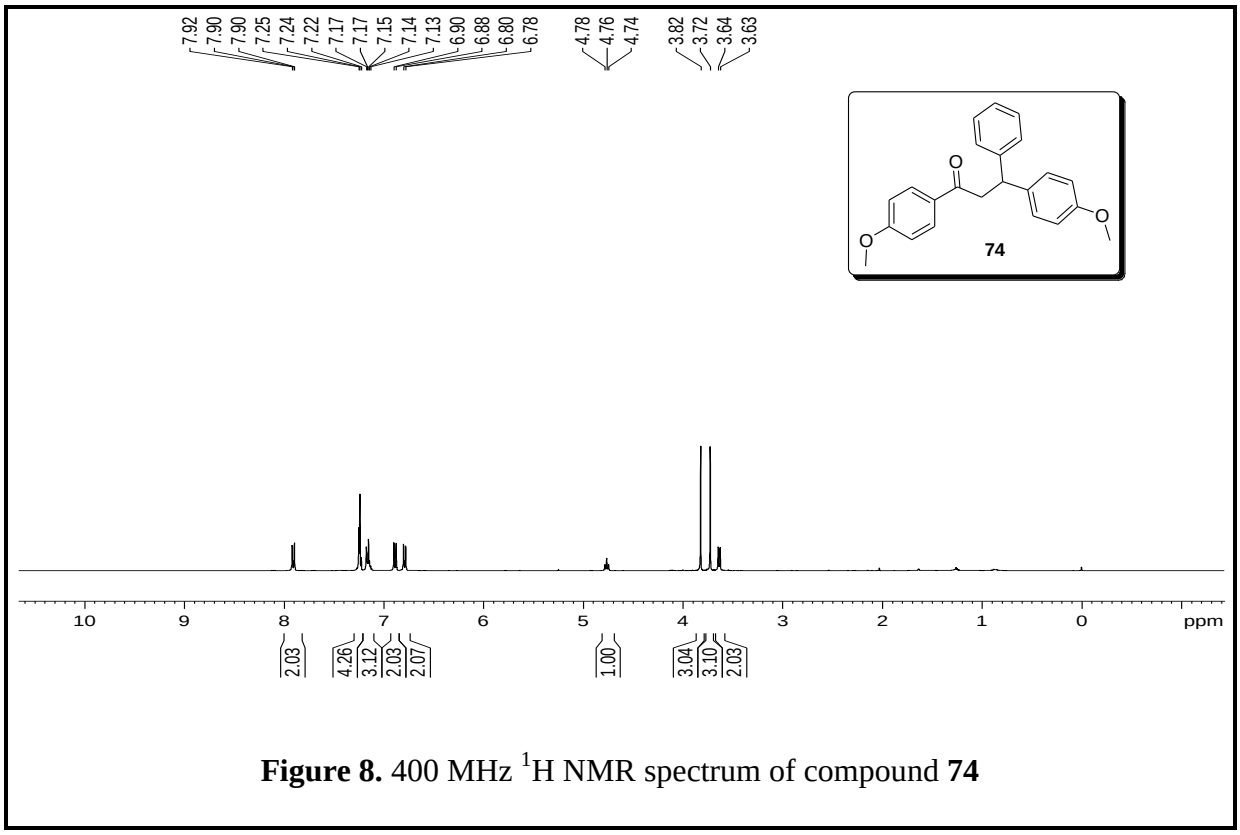


Figure 8. 400 MHz ^{1}H NMR spectrum of compound **74**

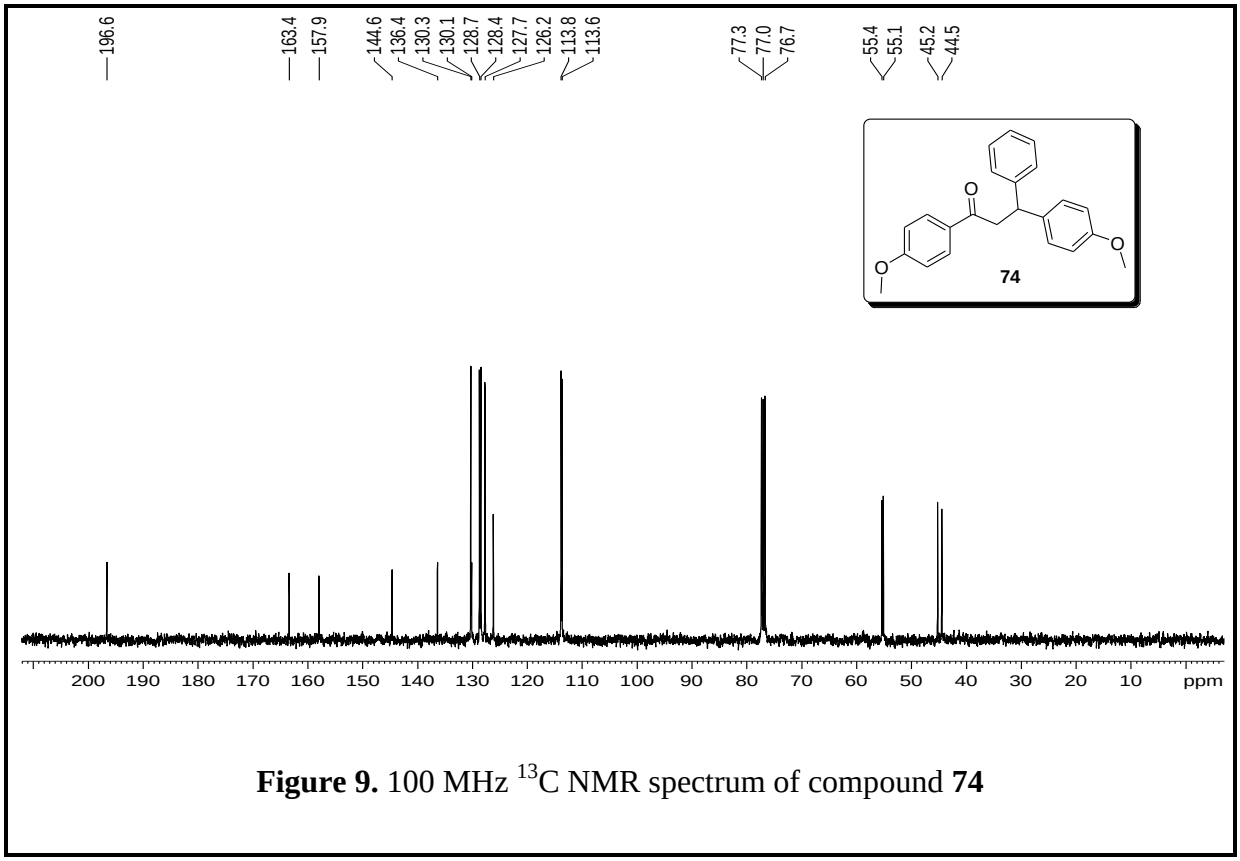


Figure 9. 100 MHz ^{13}C NMR spectrum of compound **74**

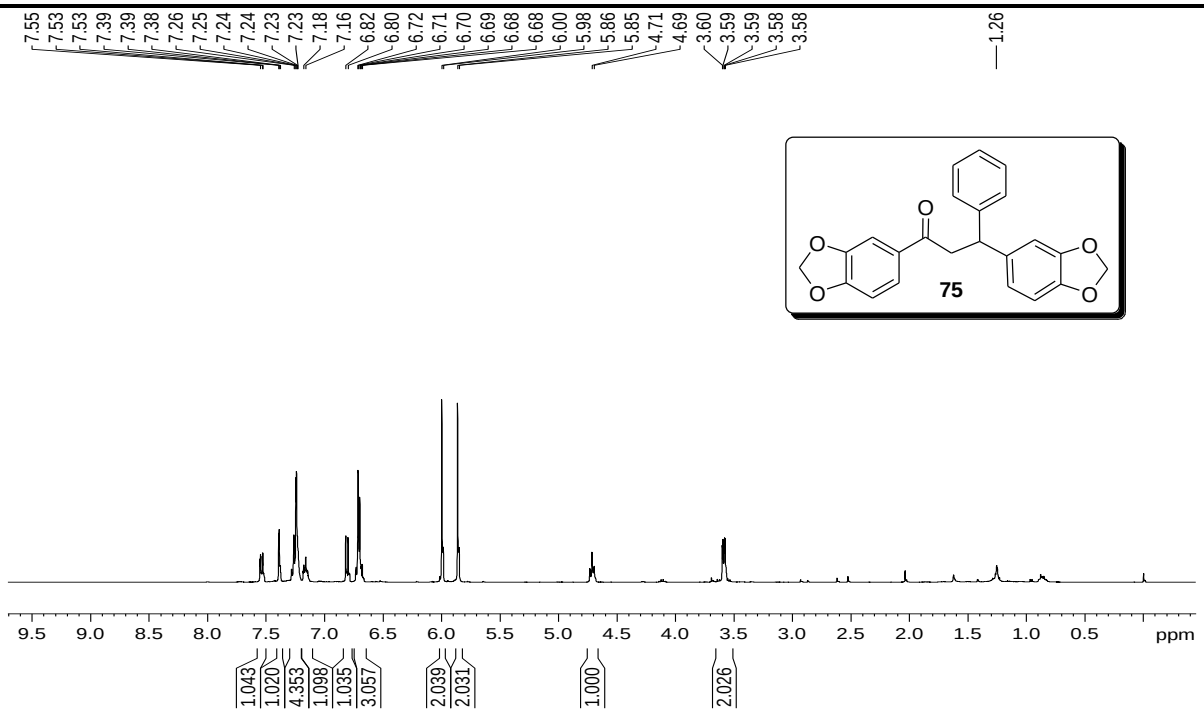


Figure 10. 400 MHz ^{1}H NMR spectrum of compound **75**

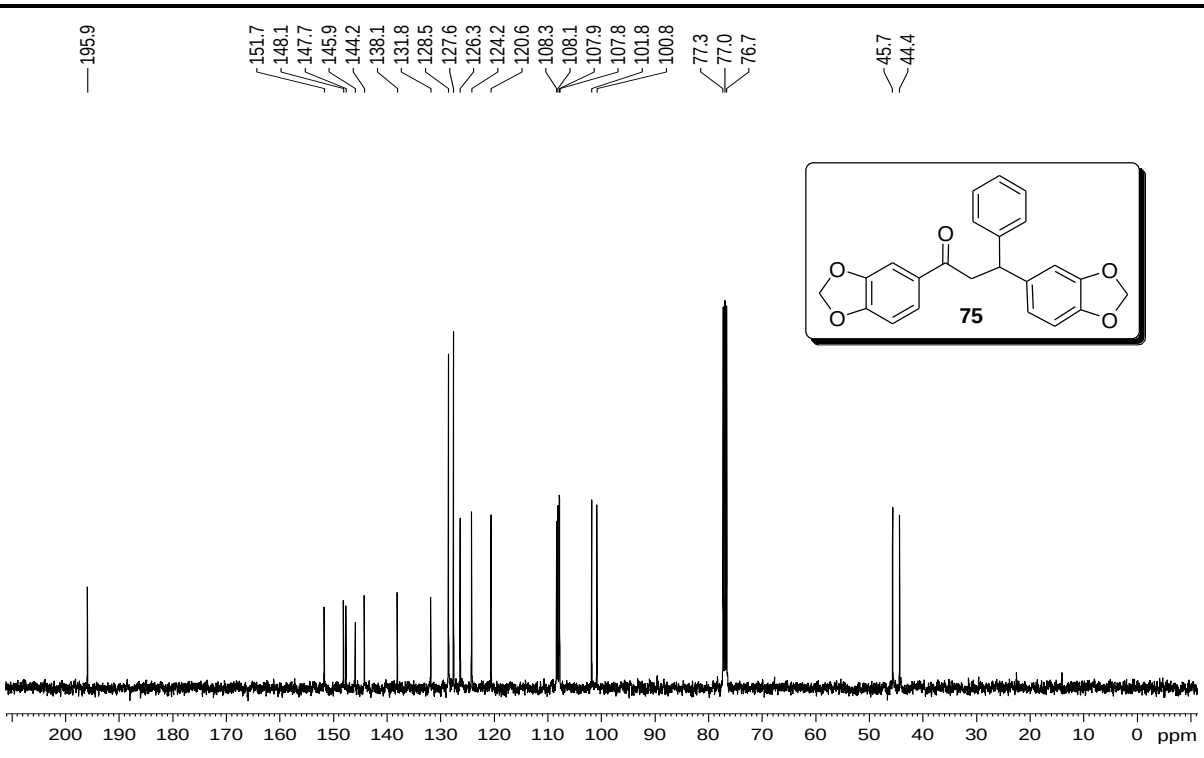


Figure 11. 100 MHz ^{13}C NMR spectrum of compound **75**

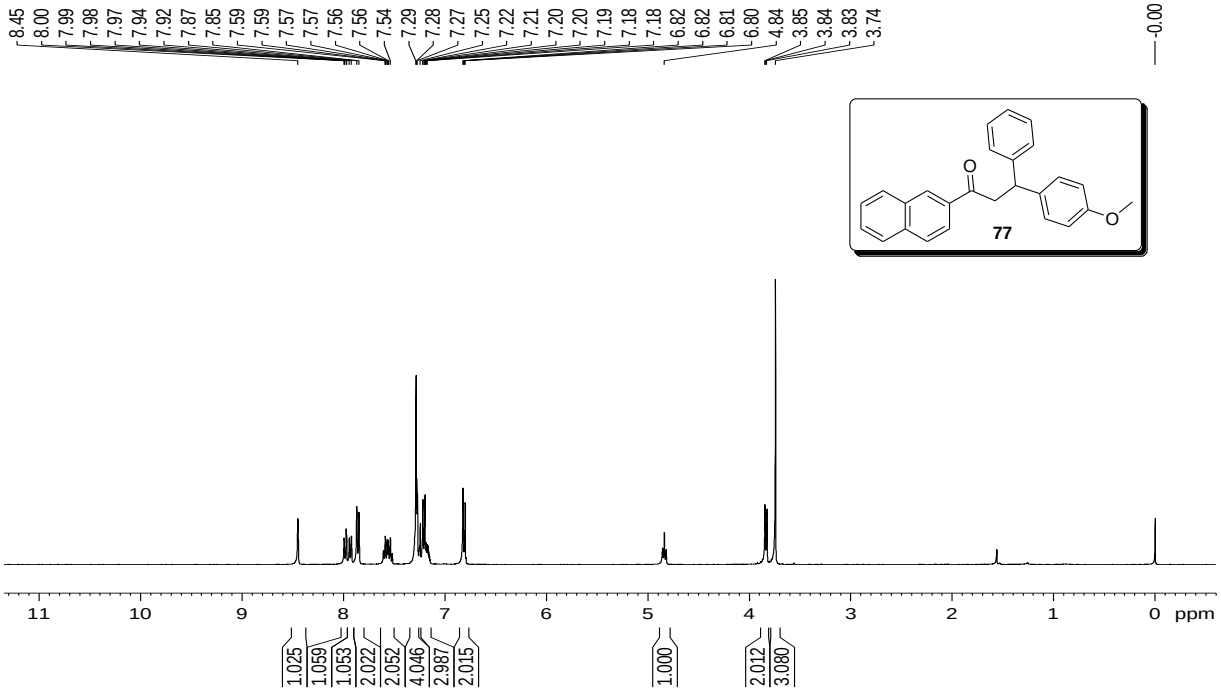


Figure 12. 400 MHz ^{1}H NMR spectrum of compound **77**

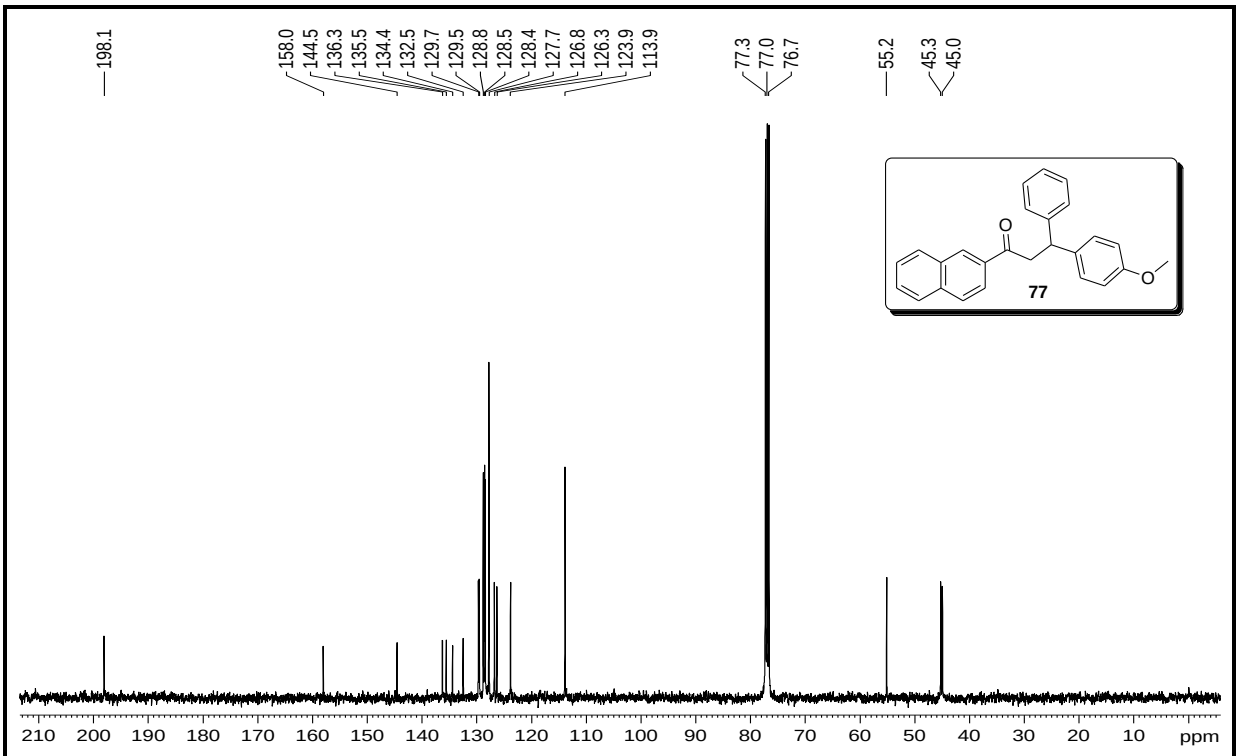


Figure 13. 100 MHz ^{13}C NMR spectrum of compound **77**

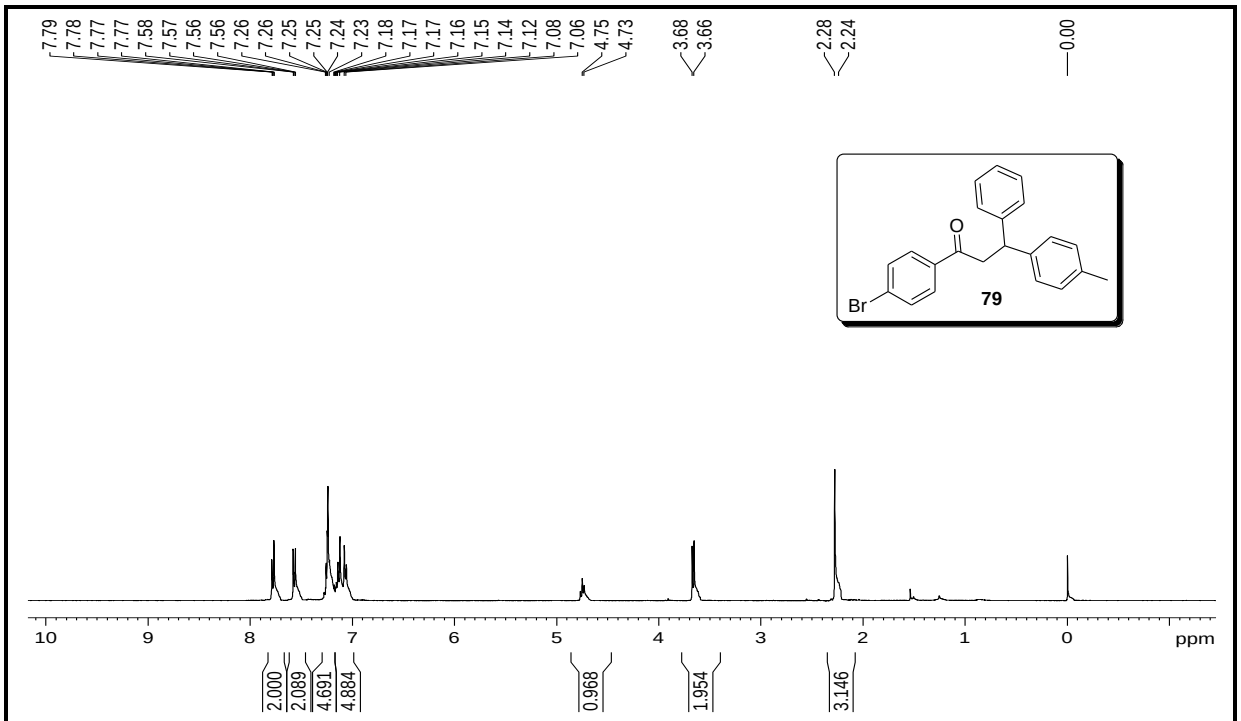


Figure 14. 400 MHz ^{1}H NMR spectrum of compound **79**

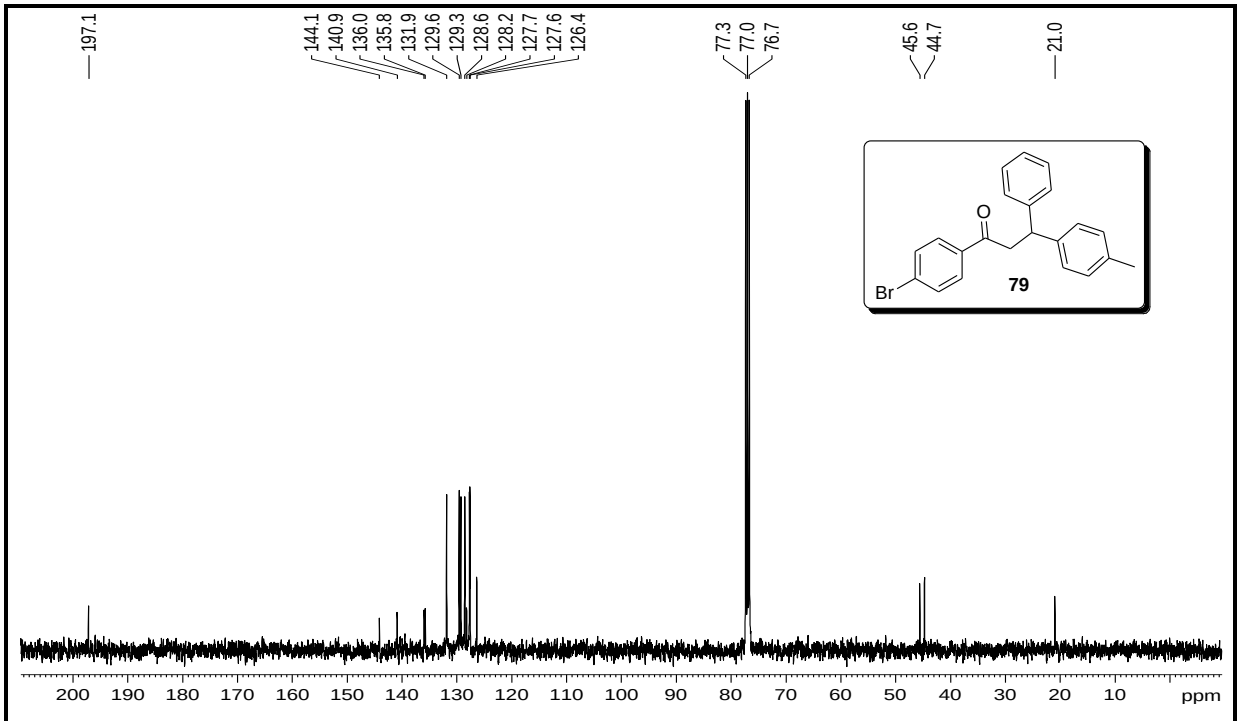


Figure 15. 100 MHz ^{13}C NMR spectrum of compound **79**

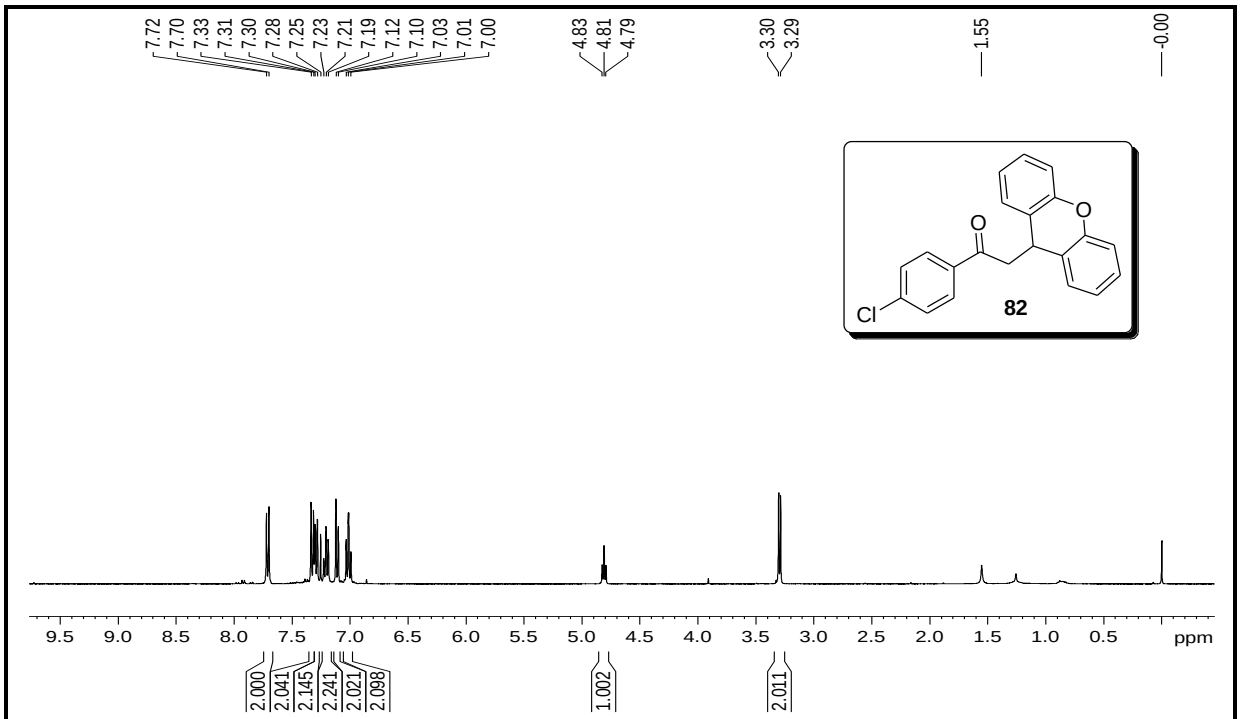


Figure 16. 400 MHz ^{1}H NMR spectrum of compound **82**

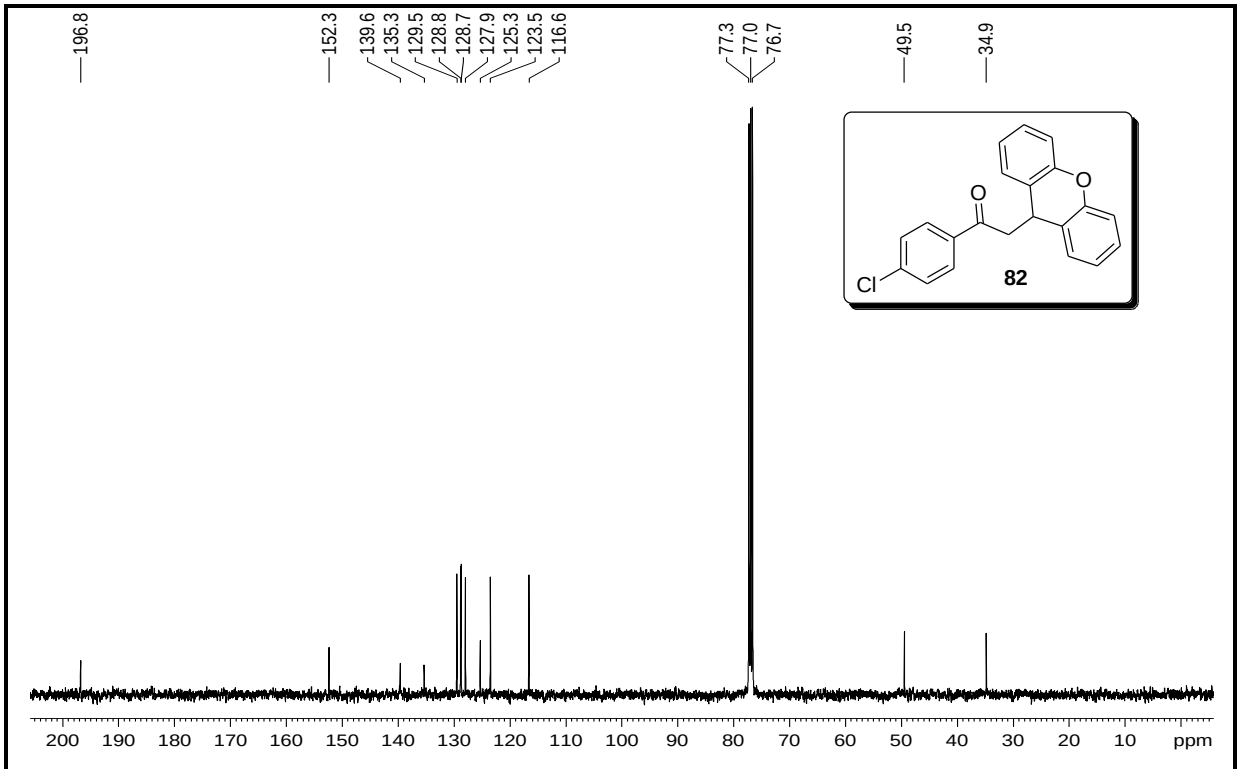


Figure 17. 100 MHz ^{13}C NMR spectrum of compound **82**

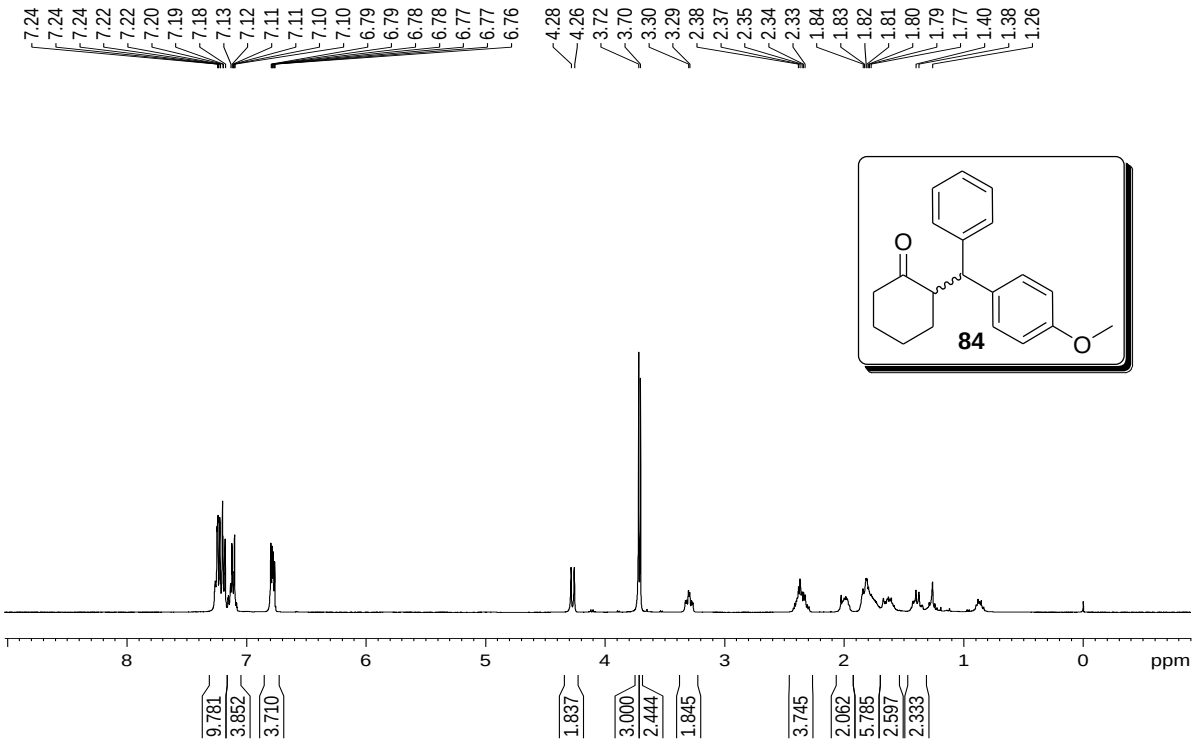


Figure 18. 400 MHz ^{1}H NMR spectrum of compound **84**

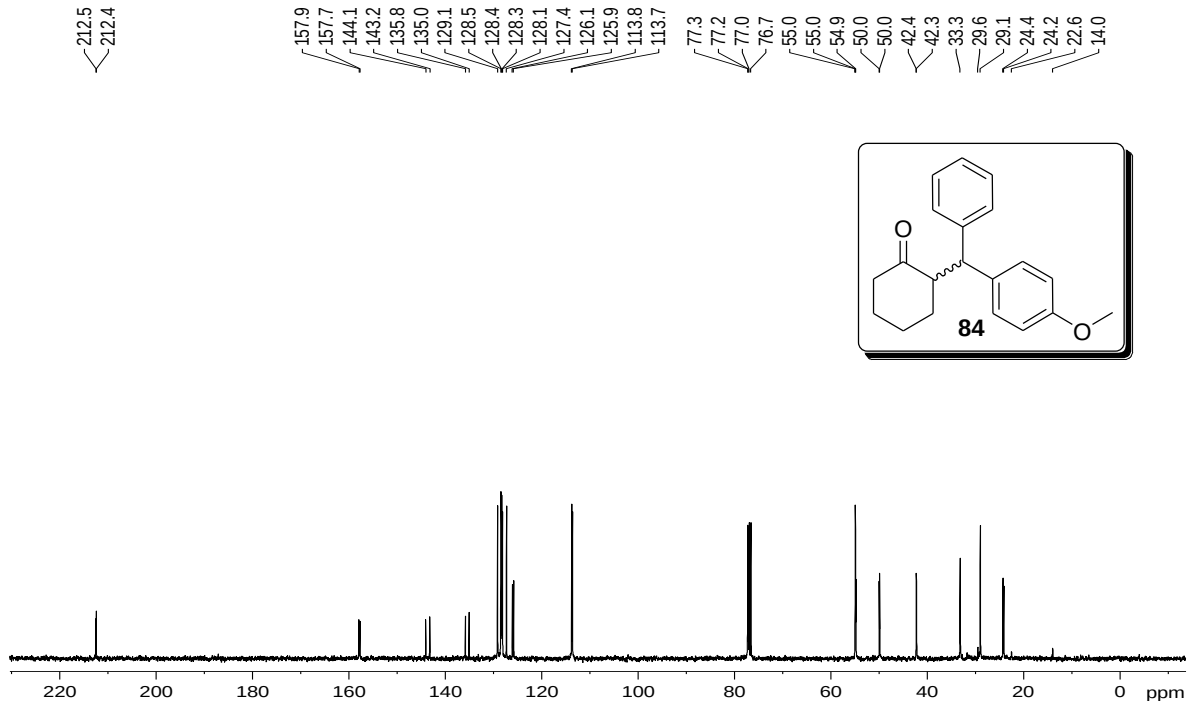


Figure 19. 100 MHz ^{13}C NMR spectrum of compound **84**

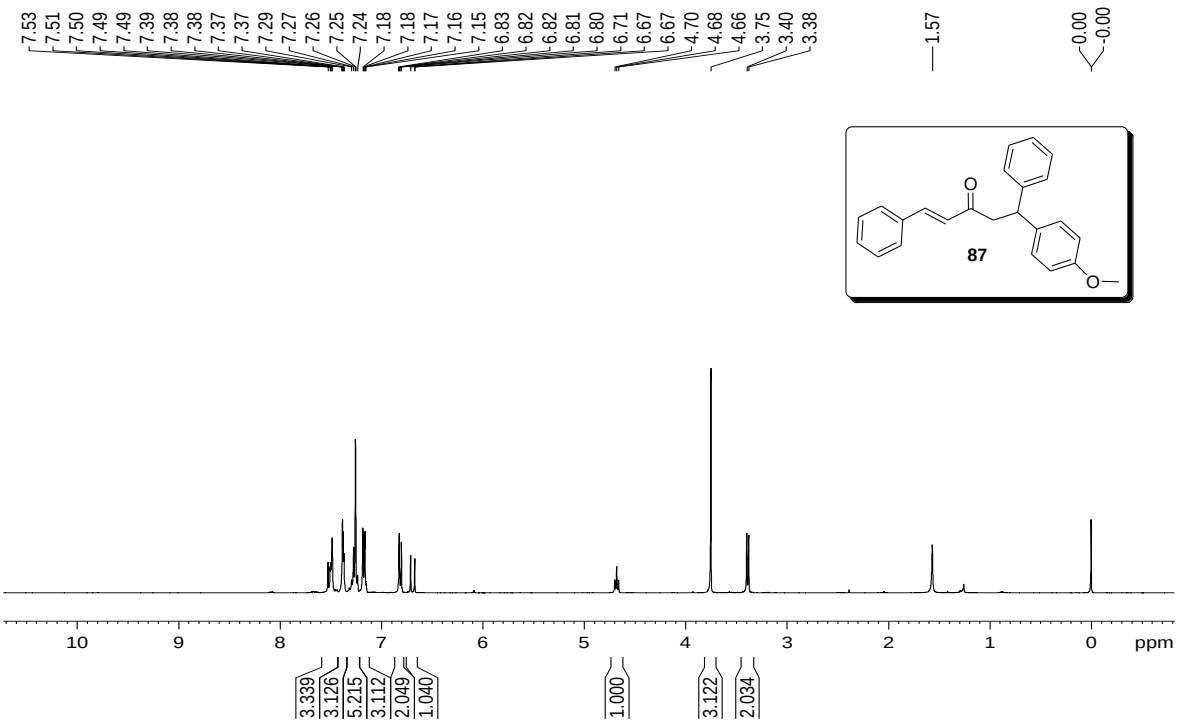


Figure 20. 400 MHz ^{1}H NMR spectrum of compound **87**

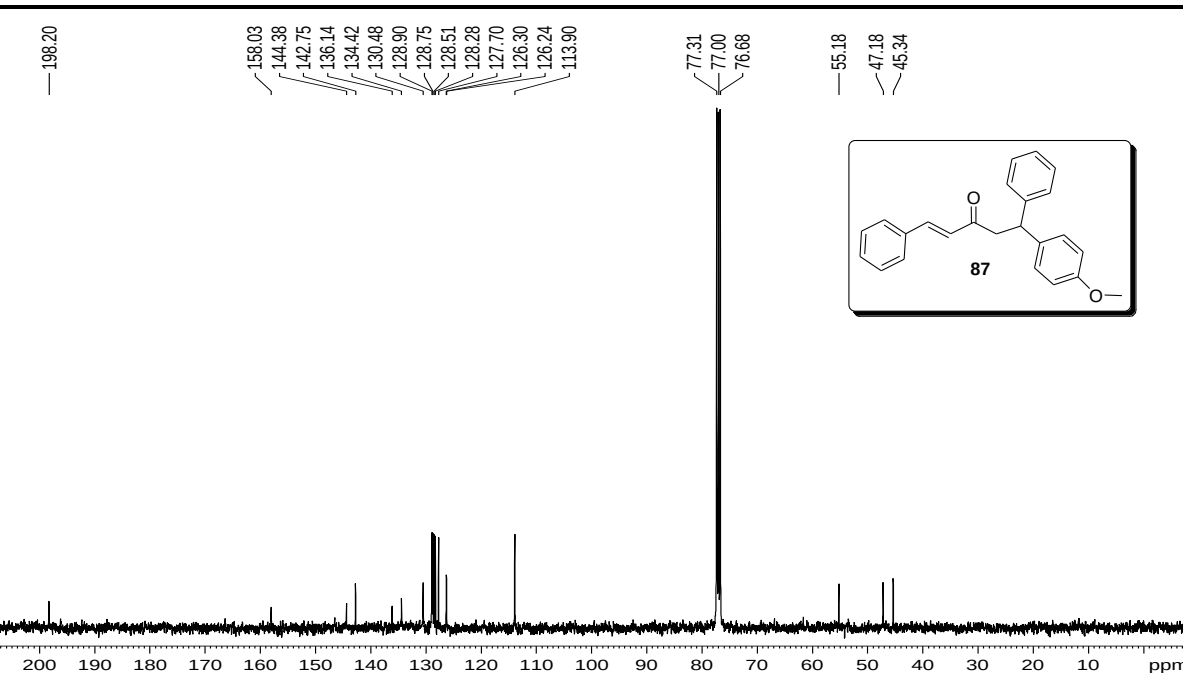


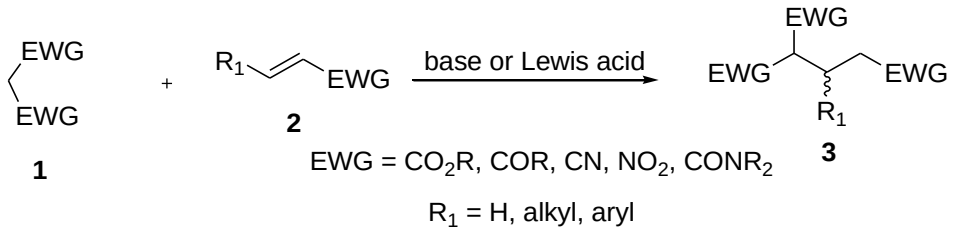
Figure 21. 100 MHz ^{13}C NMR spectrum of compound **87**

Chapter 4

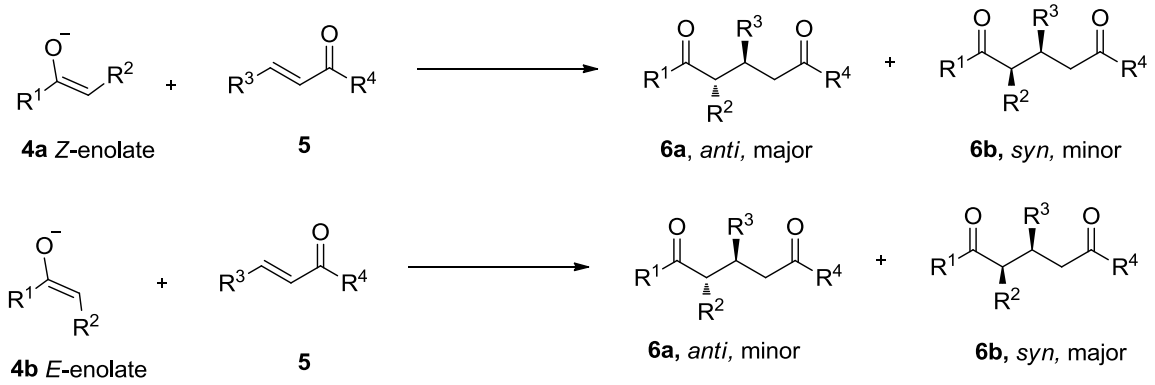
Triflic Acid-Promoted Synthesis of 1,5-Diketones from Unactivated Ketones

4.1 Introduction

After successfully generating enol ethers *via in situ* generated acetals and employing them in α-alkylation process, we turned our attention in extending its application further. In this lines, we considered Michael reaction. Michael reaction involves formation of C-C bond between enolates or stabilized carbanions and unsaturated systems in conjugation with activating groups like carbonyl, CN, NO_2 and so on. This reaction was reported by Michael in 1887.[1] Base-catalysed Michael reaction was well developed using inorganic bases like NaOH, KOH, sodium and potassium carbonates and mild bases like piperidine, *tert*-amines. Vast amount of progress has been achieved in this area such as asymmetric Michael reactions using organocatalysts and metal catalysts. As shown in schematic diagram for Michael reaction, base removes proton from the active methylene compound **1** to form stabilized carbanion (Scheme 1). This carbanion reacts with the suspended electron deficient entity **2** (Michael acceptor) to form products of prominent synthetic importance called Michael adduct **3** and the addition process is termed as 1,4-addition or conjugate addition.



Scheme 1. Schematic representation of Michael reaction



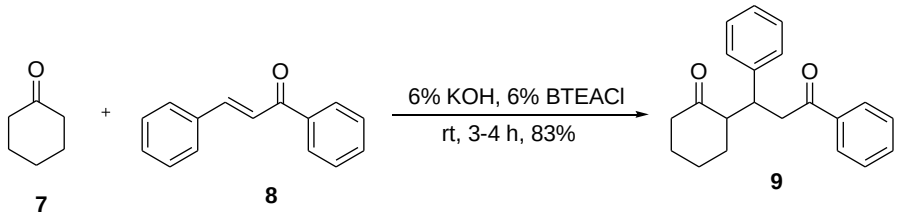
Scheme 2. Stereochemistry of Michael reaction

If substituents present on both enolate and Michael acceptor, then a mixture of *syn* and *anti* products will be formed. *Z*-Enolate **4a** results *anti* adduct **6a** and *E*-enolate **4b**

results *syn* adduct **6b** (Scheme 2). The formation of *syn* and *anti* adducts with *E*- and *Z*-enolates respectively can be explained by chelated transition state model.[2]

4.1.1 Base-catalysed Michael reaction

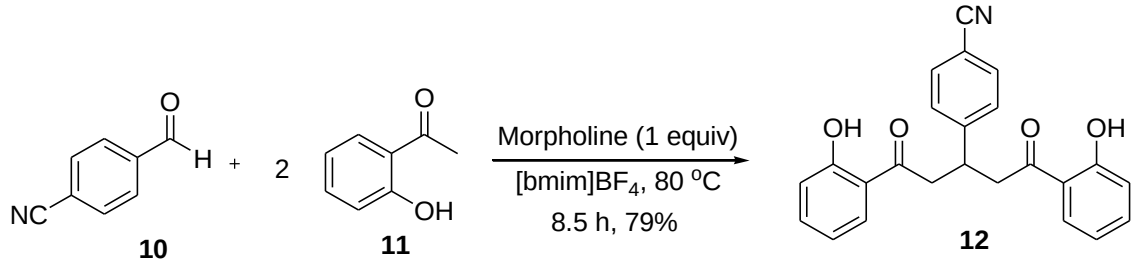
Several base-catalysed Michael reactions have been reported in the literature using NaOH,[3] KOH[4] and K_2CO_3.[5] The disadvantage of these reactions is that in most of the cases, stoichiometric amounts of bases were used. Ceylan *et al.* reported a potassium hydroxide-catalysed Michael reaction of cyclohexanone **7** and chalcone **8** under solvent free phase transfer conditions (Scheme 3).[4]



Scheme 3. Base-catalysed Michael reaction to synthesise 1,5-diketone **9**

4.1.2 Sequential aldol/Michael addition Reaction

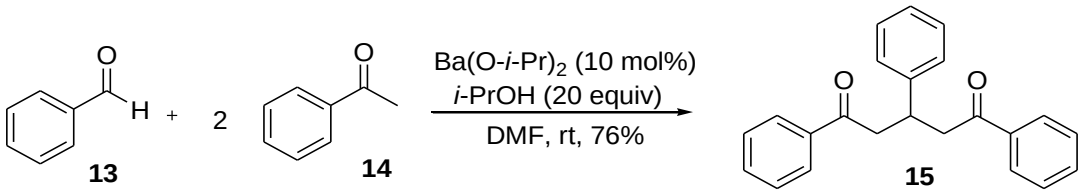
One pot aldol followed by Michael reaction catalysed by morpholine in ionic liquid to get 1,3,5-triarylpentanediones at high temperature has been reported.[6] 4-Cyanobenzaldehyde **10** was treated with two equivalents of 2-hydroxyacetophenone **11** in the presence of mild base morpholine in ionic liquid solvent [bmim]BF_4 at 80 $^{\circ}$C to get the diketone **12** in good yield. Here, one molecule of acetophenone **11** first reacts with aryl aldehyde **10** to form chalcone which on reaction with another molecule of acetophenone **11** forms the diketone.



Scheme 4. Morpholine-promoted synthesis of 1,5-diketone **12**

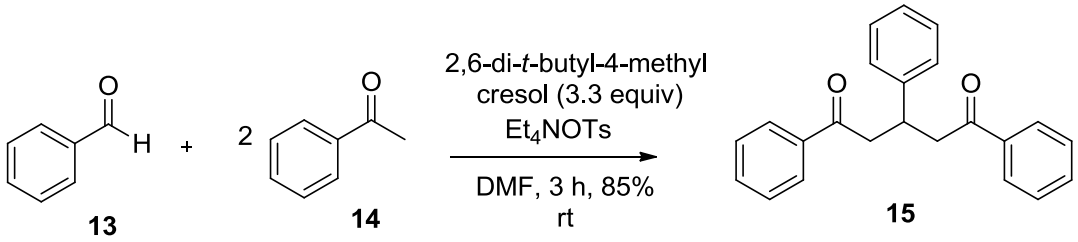
Yanagisawa *et al.* reported the barium isopropoxide-catalysed one pot 1,5-diketone synthesis by forming barium enolates.[7] This barium enolate, on aldol reaction, gives barium

alkoxide of aldol adduct followed by β-elimination leading to chalcone. Further conjugate addition of barium enolate of acetophenone to chalcone leads to barium enolate of Michael adduct. This on futher protonation gave 1,5-diketone **15**. It was observed that addition of isopropanol improved the reaction outcome by protonating the barium enolate of Michael adduct.



Scheme 5. Barium isopropoxide-catalysed Michael reaction to synthesise 1,5-diketone **15**

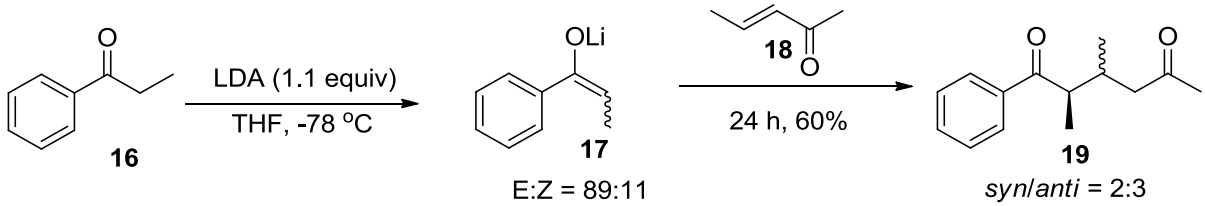
Fuchigami *et al.* reported a strategy for the synthesis of 1,5-diketones by cathodically generating the ammonium enolate of acetophenone by treating acetophenone **14** with tetraalkylammonium 2,6-di-*t*-butylphenoxide which promotes enolate formation.[8] The generated enolate reacts with the aldehyde **13** to give the alkoxide of aldol product which on elimination of ammonium salt leads to chalcone **8**. Michael reaction of the chalcone **8** with the ammonium enolate generated the 1,5-diketone **15** in good yield.



Scheme 6. Michael reaction involving ammonium enolate to prepare **15**

4.1.3 Lithium enolates as Michael donors

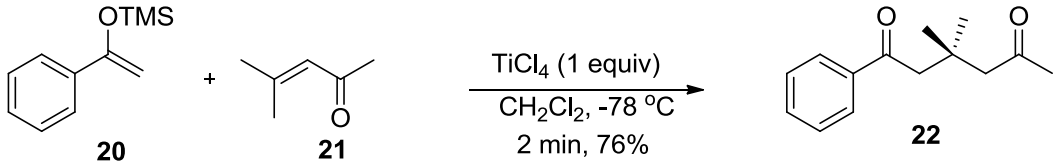
Heathcock and co-workers reported the Michael reaction of enones with lithium enolates as Michael donors to get the products stereoselectiviely.[9] Propiophenone **16** on treatment with LDA in THF solvent at -78 °C gave the *E*-enolate **17** selectively. This enolate **17** on reaction with the enone **18** furnished the diketone **19** with a *syn*/*anti* ratio of 2:3.



Scheme 7. Michael reaction involving lithium enolate **17**

4.1.4 Silyl enolates as Michael donors

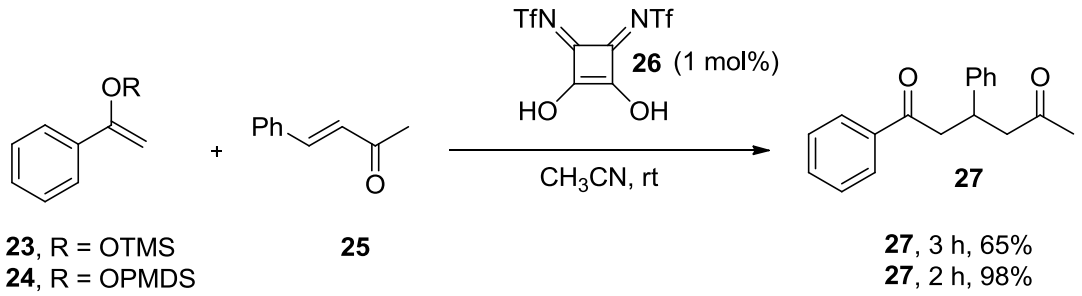
Mukaiyama-Michael reaction is the formation of C-C bond between silyl enolate (Michael donor) and α,β-unsaturated carbonyl compounds or their corresponding acetals to form Michael adducts. The first reaction was reported by Mukaiyama in 1974.[10] TMS enolate of acetophenone **20** and enone **21** were treated in the presence of titanium tetrachloride at -78 °C to get the diketone **22** in good yield.



Scheme 8. Michael reaction involving silyl enolate **20** to make 1,5-diketone **22**

A wide range of Lewis acid catalysts were reported for the Mukaiyama-Michael reaction such as trityl perchlorate,[11] LiOBn,[12] TMSOTf,[13] $SnCl_4$,[14] $BiCl_3$,[15] Me_2AlCl,[16] $Sn(OTf)_2$,[17] $Sc(OTf)_3$[18] and so on.

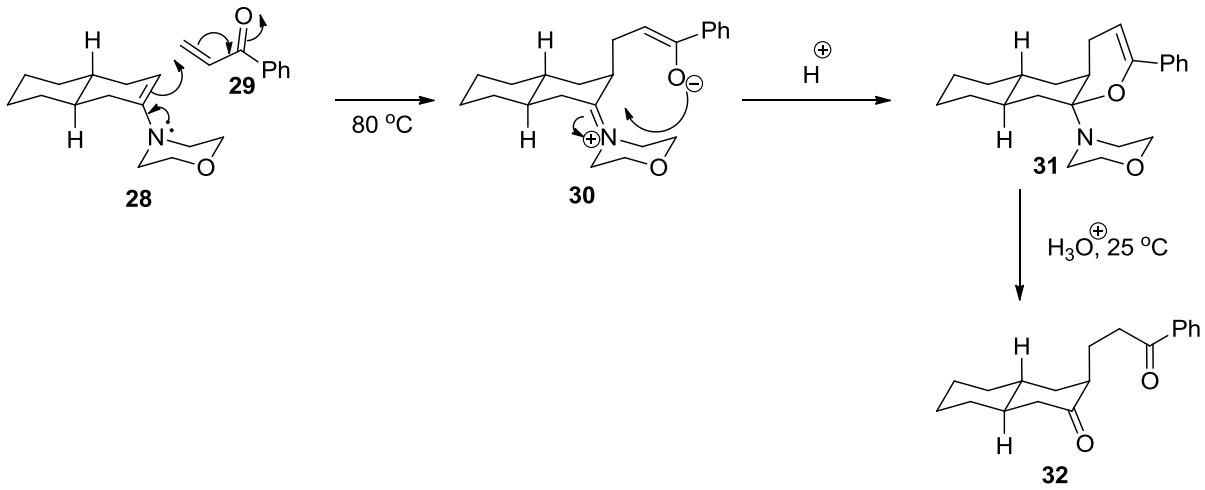
A new Brønsted acid bis-*N*-trifluoromethanesulfonyl squaramide **26** derived from squaric acid has been reported for catalyzing the Mukaiyama-Michael reaction.[19] Under this acidic reaction conditions trimethyl silyl enolates of ketone **23** was unstable due to protodesilylation and to overcome this, pentamethyldisilyl enolate **24** has been employed in this Mukaiyama-Michael reaction. Ketone silyl enolate **24** was treated with enone **25** in the presence of bis-*N*-trifluoromethanesulfonyl squaramide catalyst **26** at ambient conditions to furnish the diketone **27** with good yield. By using this new Brønsted acid catalyst Mukaiyama-aldol reaction also worked out and formed a variety of substituted aldol products.



Scheme 9. Squaramide-catalysed Michael reaction to make 1,5-diketone **27**

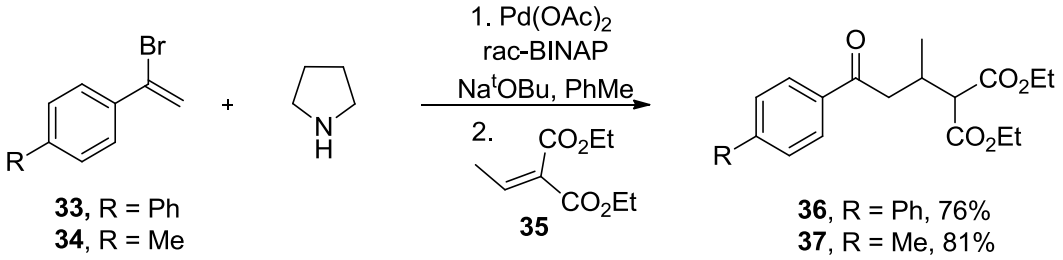
4.1.5 Enamines as Michael donors

Forchiassin and co-workers reported the reactions of enamines with *trans*-decalin-2-ones with β-nitrostyrene and phenyl vinyl ketone.[20] Enamine **28** reacts with phenyl methyl ketone **29** at heating conditions to give the Michael adduct and the iminium ion was attacked by the generated enolate oxygen to furnish the *N,O*-acetal **31** which on hydrolysis resulted the 1,5-diketone **32**.



Scheme 10. Michael reaction involving enamine to make 1,5-diketone **32**

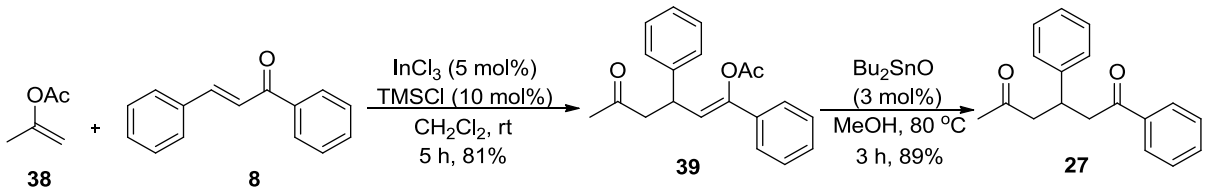
A one pot *cine*-substitution *via* palladium-catalysed C-N coupling and Michael reaction was reported to get the 1,5-dicarbonyl compounds in good yield.[21] Palladium-catalysed C-N coupling of vinyl bromide **33** with pyrrolidine leads to enamine. This enamine reacts with the suspended alkylidenemalonate **35** acceptor to form the keto diester **36**.



Scheme 11. One pot *cine*-substitution *via* palladium-catalysed C-N coupling and Michael reaction

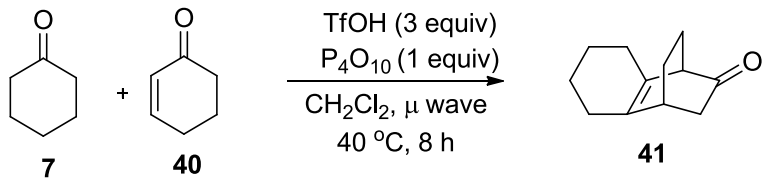
4.1.6 Enol acetates as Michael donors

Baba and co-workers reported the Michael reaction of enol acetates **38** with chalcones **8** in the presence of catalytic amounts of $InCl_3$ and TMSCl to furnish the enol acetate of Micheal adduct **39**.[22] A wide range of enol acetates derived from acetophenones, acetone, and cyclohexanones were employed in the reaction. These enolacetate derivative **39** has been further converted into corresponding diketone **27** by treating it with dibutyltin oxide under reflux conditions. It is believed that addition of TMSCl to $InCl_3$ enhances the Lewis acidity of silicon center of TMSCl and the silicon center activates the enone **8**, thus, playing a key role in catalyzing the Michael reaction.[23]



Scheme 12. Enol acetate **38** as Michael donor to make enol acetate of 1,5-diketone **39**

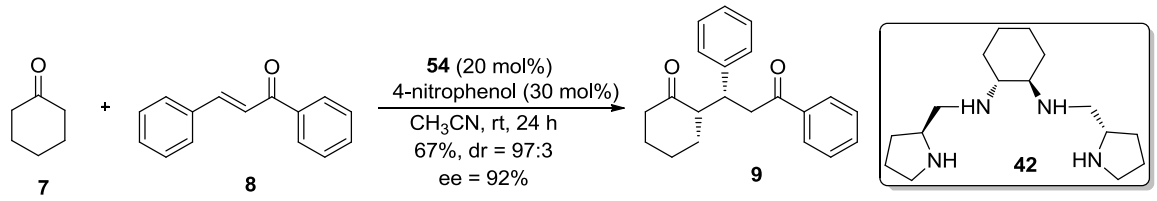
Jung *et al.* have reported the triflic acid-promoted Micheal reaction followed by aldol reaction of cyclohexanone **7** with cyclohexenone **40** (Robinson annulation) in the presence of a suitable dehydrating agent under microwave conditions to furnish the bicyclic compound **41**.[24]



Scheme 13. TfOH-promoted Michael reaction followed by aldol reaction

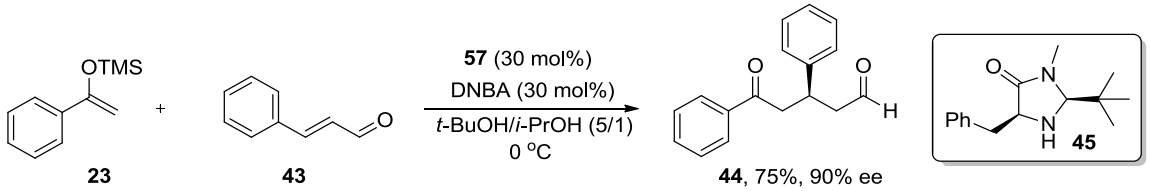
4.1.7 Organocatalytic activation

Ma *et al.* reported the Michael reaction of cyclohexanone **7** with chalcone **8** and nitro styrenes catalysed by C_2-symmetric pyrrolidine-based tetramine **42** in the presence of 4-nitrophenol additive at ambient conditions.[25] Diketone **9** formed in good yield and with excellent diastereo and enantioselectivities. The role of the phenolic additive was believed to increase the rate of enolization of the cyclohexanone **7**.



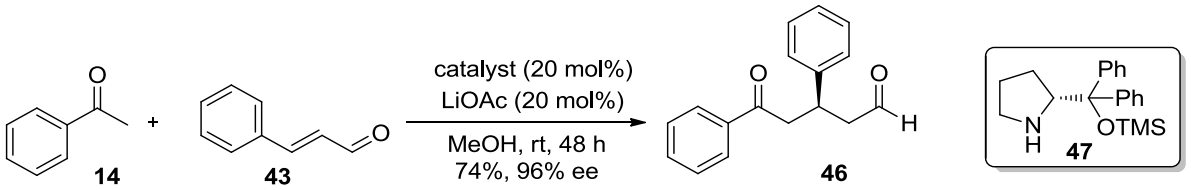
Scheme 14. C_2-Symmetric pyrrolidine based tetramine-catalysed Michael reaction

Wang *et al.* reported the catalytic asymmetric Michael reaction of silyl enolates with α,β-unsaturated aldehydes in the presence of chiral imidazolidinone catalyst **45** to furnish enantioenriched 1,5-dicarbonyl compounds.[26] An example of this reaction is shown in Scheme 15. Silyl enolate of acetophenone **23** was treated with cinnamaldehyde **43** in the presence of chiral MacMillan's catalyst **45** and an acid additive to get the 1,5-dicarbonyl compound **44** in good yield and with excellent enantioselectivity. Acid additive was added to facilitate the aldiminium ion formation which is a key intermediate in the reaction.



Scheme 15. Enantioselective Michael reaction of silyl enolates using MacMillan's catalyst

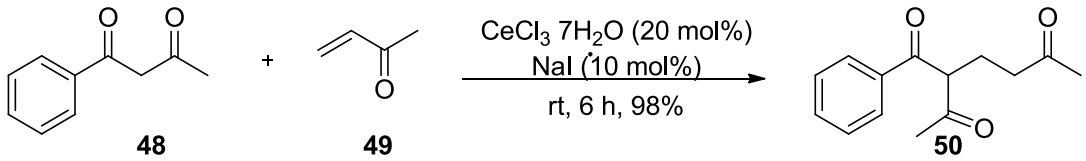
Later, Li *et al.* reported the silylated prolinol-catalysed Michael reaction of acetophenone **14** to α,β-unsaturated aldehyde **43** in the presence of a lithium salt to get the product in good yield.[27] In this method, unactivated ketones have been employed directly. Formation of aldol condensation products were also observed along with the desired product.



Scheme 16. Michael reaction of acetophenone with cinnamaldehyde

4.1.8 Michael reaction of 1,3-diketones

A number of Lewis acids have been reported for the direct Michael reaction of 1,3-dicarbonyl compounds with enones without prior activation of carbonyl compound. Ceric chloride hepta hydrate in the presence of NaI catalyses the Michael reaction of 1,3-diketone **48** with MVK **49** under solvent free condition to furnish the triketone **50** in excellent yield.[28] Other Lewis acids such as $FeCl_3 \cdot 6H_2O$[29] and ionic liquid-catalysed reactions[30] have been reported to effect the Michael reactions of 1,3-dicarbonyl compounds with α,β-unsaturated compounds.



Scheme 17. Direct Michael reaction of 1,3-diketones with enones

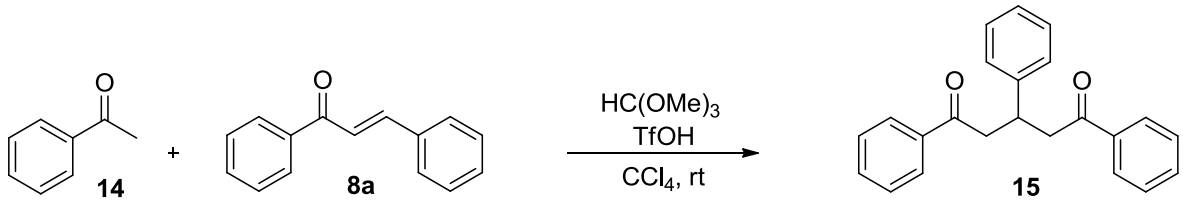
4.2 Results and discussion

After developing the triflic acid-promoted facile alkylation methodology *via in situ* generated acetal, we turned our attention to react the vinyl ether formed from the acetal with other electrophilic centers to make C-C bond. In this lines, chalcones were envisaged as the suitable electrophilic species to employ them in the triflic acid-promoted reaction of unactivated ketones to make unsymmetrical 1,5-diketones.

In order to check this, acetophenone was treated with chalcone **8a** in the presence of 1 equivalent of each trimethyl orthoformate and triflic acid at room temperature in CCl_4 (Table 1, entry 1). Carbon tetrachloride was chosen, as it was the best solvent for the alkylation reaction described in Chapter 3. This reaction resulted in the desired 1,5-diketone **15** in 40% yield. Encouraged by this result, we carried out few more reactions using 2, 3 and 5 equivalents of ketone with respect to the chalcones. Significant improvement in the yield of

the product was noticed as the amount of starting ketone is increased (entries 2-4). With 5 equivalents of acetophenone, the yield of 1,5-diketone obtained was quite good (77%). When the stoichiometry was reversed *i. e.*, with 1 equivalent of acetophenone and 5 equivalents of chalcone, the product was obtained in less yield (70%). It is interesting to note that the reaction carried out using 5 equivalents of acetophenone and 1 equivalent of chalcone in the absence of trimethyl orthoformate resulted in only 30% yield of the desired product (Table 1, entry 6). This result clearly demonstrates the formation of *in situ* vinyl ether is important for the effective Michael addition of the ketone.

Table 1. Results of optimization of substrates stoichiometry for the synthesis of 1,5-diketones



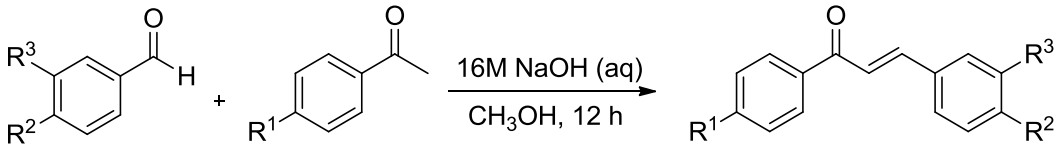
Entry	Ketone (equiv)	Chalcone (equiv)	**15** Yield (%)[a]
1	1.0	1.5	40
2	2.0	1.0	51
3	3.0	1.0	58
4	**5.0**	**1.0**	**77**
5	1.0	5.0	70
6[b]	5.0	1.0	30

[a]Isolated yields. [b]Without trimethyl orthoformate.

Then, other Brønsted acids were checked for their ability to promote the Michael reaction of acetophenone with chalcone in the presence of stoichiometric amount of trimethyl orthoformate (Table 2). Product formation was not observed in the reactions using *p*-TSA, trifluoroacetic acid and acetic acid (Table 2, entries 1-3). Interestingly, low yield (10%) of 1,5-diketone **15** was observed in the perchloric acid-mediated reaction (Table 2, entry 4). With methanesulfonic acid, the reaction was sluggish and the yield of 1,5-diketone improved

to 48% after 24 h, but it is significantly lesser than that of reaction involving TfOH. Hence the substrate scope of the reaction was evaluated with 5 equivalents of ketone with respect to chalcone and 1 equivalent of each triflic acid and trimethyl orthoformate in CCl_4 at room temperature.

Chalcones **8a-8e** were made by base-promoted aldol condensation of acetophenones **14a-14b** with aryl aldehydes **13a-13d**. This way methyl, methoxy, chloro and methylenedioxy chalcones were synthesized.



13a, R^2= R^3 = H,
13b, R^2= Cl, R^3 = H,
13c, R^2= OMe, R^3 = H,
13d, R^2= R^3 = -OCH_2O-
,

14a, R^1 = H,
14b, R^1 = Cl,

8a, R^1 =R^2= R^3 = H, 34%
8b, R^1 = H, R^2= Cl, R^3 = H, 38%
8c, R^1 = H, R^2= OMe, R^3 = H, 90%
8d, R^1 = Cl, R^2= OMe, R^3 = H, 51%
8e, R^1 = H, R^2= R^3 = -OCH_2O-, 64%

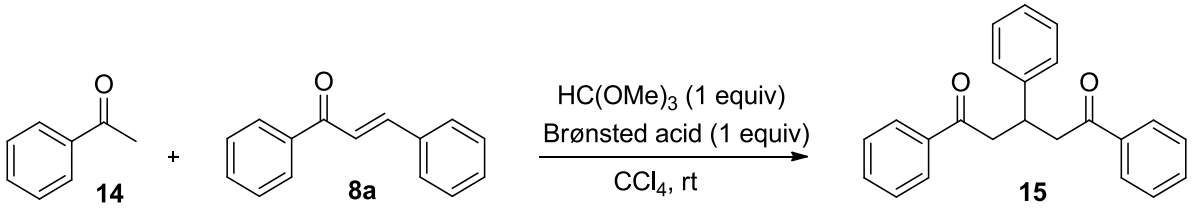
Scheme 18. Synthesis of chlcones **8a-8e** by aldol condensation

The synthesized chalcone derivatives were subjected to Michael addition reaction with different aryl methyl ketones using the condition described in entry 4 of table 1. The results are presented in table 3. These reactions result in unsymmetrical 1,5-diketones. Aryl methyl ketones and chalcones having electron donating groups on the aryl ring were employed. As such, there was no significant trend in the obtained yield of the product based on the electronic nature of the substituent on the aryl ring. Except few of cases, the yields were generally good. The general trend is when the chalcone having electron withdrawing aryl is at the β-carbon, the yields were generally good. Electron donating methylenedioxy in the aryl attached to the β-carbon of the chalcone resulted in poor yield of the product (**62** and **63**). Even heterocyclic ketone such as acetyl thiophene could be employed to get the corresponding Michael adduct.

Then we shifted our focus to check the stereochemical aspects of the present Michael reaction with propiophenone which will result in a mixture of diastereomeric mixture. Excess of propiophenone was treated with simple chalcone **8a** under the optimized conditions (Table

4). 2-Methyl-1,3,5-triphenylpentane-1,5-dione **64** was obtained in good yield with marginal diastereoselectivity (1.5:1). The diastereomeric ratio was determined by analyzing ^{1}H NMR spectrum of the mixture of products. Usually, the H-3 proton signal of the product appears at δ 3.00-3.05. In this case, signal overlap made the analysis a bit difficult. So, integration of methyl protons of the two isomers which are well separated and used to find the diastereomeric ratios. The reaction of chalcone derivative **8c** with propiophenone and cyclohexanone resulted in poor yield of the corresponding Michael adducts as a mixture of diastereomers. These results are not surprising, as electron donating groups in the aryl attached to β-carbon of the chalcone result in poor yield.

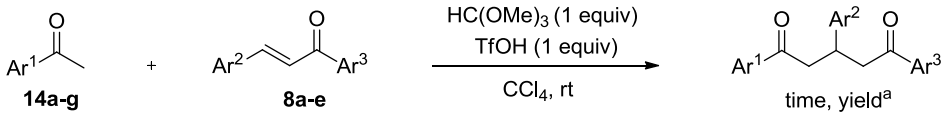
Table 2. Results of screening of Brønsted acids for the synthesis of 1,5-diketones

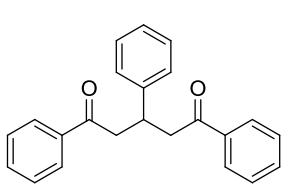


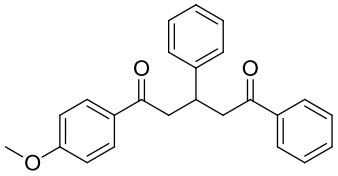
Entry	Brønsted acid (1 equiv)	Time (h)	**15** Yield[a,b] (%)
1	*p*-TSA	24	NR
2	trifluoroacetic acid	24	NR
3	acetic acid	12	NR
4	$HClO_4$	24	10
5	CH_3SO_3H	24	48
6	**TfOH**	**7**	**77**

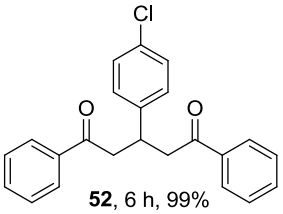
[a]Isolated yields. [b]Chalcone (1 equiv) and ketone (5 equiv) was used.

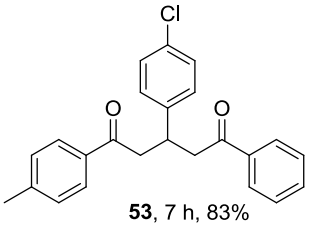
Table 3. Results of triflic acid-mediated synthesis of 1,5-diketones from unactivated ketones

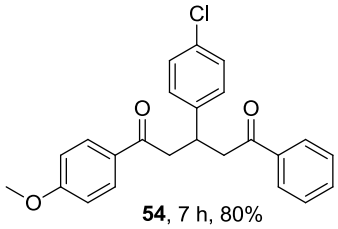


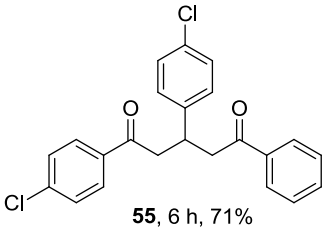

15, 5 h, 77%

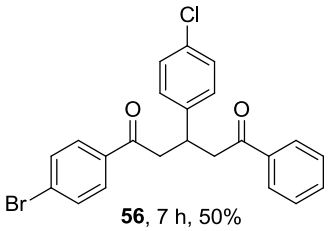

51, 8 h, 54%

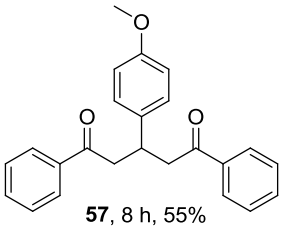

52, 6 h, 99%

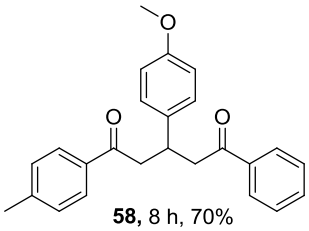

53, 7 h, 83%

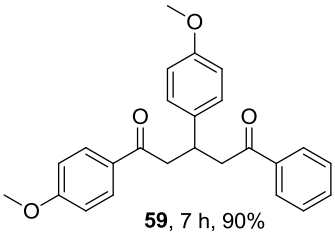

54, 7 h, 80%

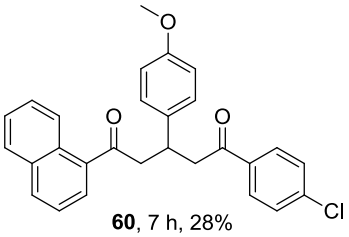

55, 6 h, 71%

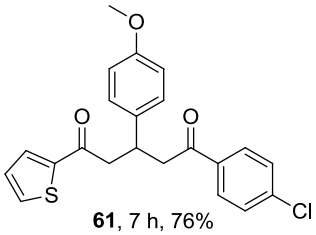

56, 7 h, 50%

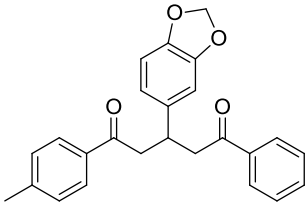

57, 8 h, 55%

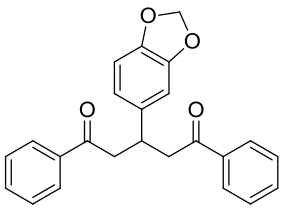

58, 8 h, 70%


59, 7 h, 90%


60, 7 h, 28%

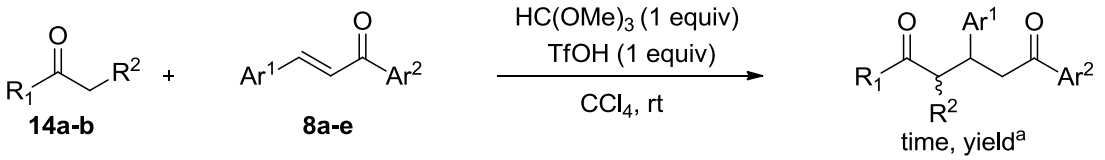

61, 7 h, 76%

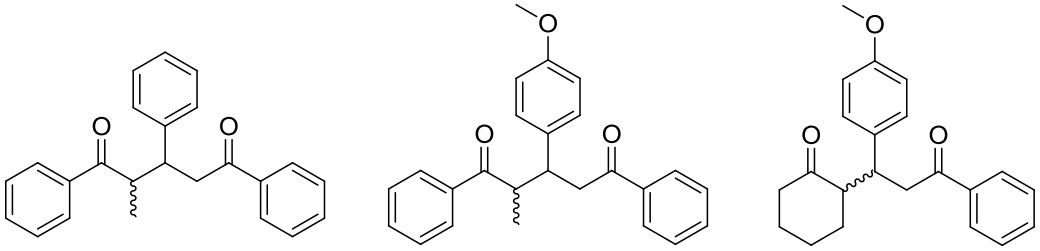

62, 8 h, 35%


63, 8 h, 29%

[a]Isolated yields.

Table 4. Results of triflic acid-mediated synthesis of 1,5-diketones from unactivated ketones

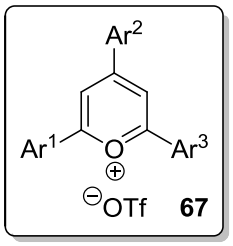




64, 7 h, 61%, dr = 1.5:1 **65**, 7 h, 35%, dr = 1.8:1 **66**, 7 h, 33%, dr = 2:1

[a]Isolated yields

Pyrylium salts were formed as the side product in few reactions along with the desired 1,5-diketone.[31] They can easily be separated as they get precipitated in the reaction. When the reaction was performed using cyclohexenone as acceptor and acetophenone as Michael donor, no product was observed.



4.3 Conclusions

Triflic acid-mediated Michael reaction of simple unactivated ketones like acetophenones and cyclohexanones as Michael donors has been developed. A range of chalcones with electron donating and accepting groups were employed in the reaction as Michael acceptors. The *in situ* generated vinyl ether using trimethyl orthoformate was utilised in the efficient Michael reaction of unactivated ketones. This reaction has so far been applied to chalcones only. Reaction with other α,β-unsaturated systems have to be optimized.

4.4 Experimental

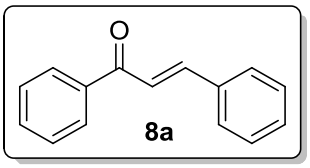
General information

Refer Chapter 3 for general information.

General Procedure for synthesis of chalcones

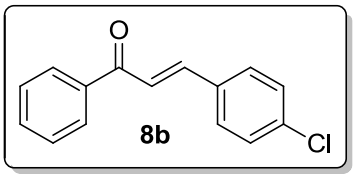
To a solution of aryl aldehyde **13a-13d** (1 equiv) in methanol, acetophenone **14a-14b** (1 equiv) was added at room temperature under nitrogen atmosphere. To this reaction mixture aqueous NaOH solution (16M) was added dropwisely. After completion of the reaction, the reaction mixture was cooled and filtered by Buchner filteration to get crude chalcone. This crude chalcone was washed first with water several times to remove sodium hydroxide and then with 5% cold MeOH in water to remove unreacted starting materials. After several washings, the solid chalcone was dried under vaccum to remove traces of solvents to get pure chalcone.

(*E*)-chalcone 8a[32]



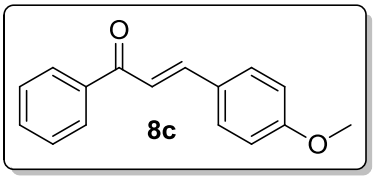
Yield: 34%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.0 Hz, 2H), 7.82 (d, *J* = 16.0 Hz, 1H), 7.66-7.64 (m, 2H), 7.61-7.19 (m, 4H), 7.43-7.42 (m, 3H).

(*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one 8b[32]



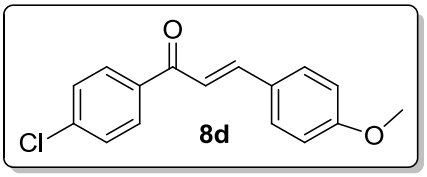
Yield: 38%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 15.5 Hz, 1H), 7.62-7.57 (m, 3H), 7.53-7.49 (m, 3H), 7.39 (d, *J* = 8.4 Hz, 2H).

(*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one 8c[32]



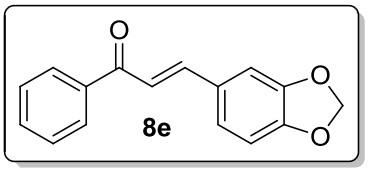
Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-8.00 (m, 2H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.62-7.56 (m, 3H), 7.52-7.48 (m, 2H), 7.42 (d, *J* = 15.8 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 2H), 3.86 (s, 3H).

(*E*)-1-(4-chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one 8d[33]



Yield: 51%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 15.5 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 15.5 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H) 3.85 (s, 3H).

(*E*)-3-(benzo[d][1,3]dioxol-5-yl)-1-phenylprop-2-en-1-one 2e[34]

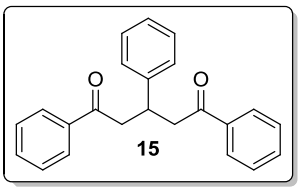


Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.34 Hz, 2H), 7.75 (d, *J* = 15.7 Hz, 1H), 7.60-7.56 (m, 1H), 7.52-7.48 (m, 2H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.18-7.12 (m, 2H), 6.85 d, *J* = 7.8 Hz, 1H), 6.04 (s, 2H).

General procedure for the synthesis of 1,5-diketones by Michael reaction

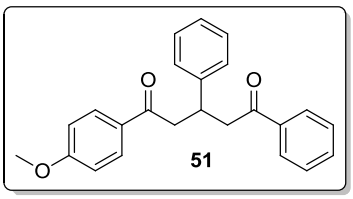
To a solution of chalcone (50 mg, 1 equiv) in carbon tetrachloride (2 mL), acetophenone (5 equiv) was added. To this reaction mixture trimethyl orthoformate (1 equiv) was added. After 5 min, triflic acid (1 equiv) was added to the reaction mixture. The reaction mixture was stirred for 5-8 h at room temperature. After completion of the reaction, the reaction mixture was concentrated under vaccum and directly loaded on to the column and purified using ethylacetate and hexane as eluents to get 1,5-diketone.

1,3,5-triphenylpentane-1,5-dione 15[35]



Yield: 77%; IR (KBr, cm^{-1}): 3068, 3030, 2882, 1683, 1268, 1206, 977, 701, 688; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.0 Hz, 4H), 7.56-7.52 (m, 2H), 7.45-7.41 (m, 4H), 7.28-7.25 (m, 4H), 7.20-7.15 (m, 1H), 4.06 (p, *J* = 7.0 Hz, 1H), 3.49 (dd, *J* = 16.6, 6.9 Hz, 2H), 3.35 (dd, *J* = 16.6, 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 143.8, 136.8, 133.1, 128.6, 128.1, 127.4, 126.7, 44.9, 37.1; HRMS (ESI) m/z calcd for $C_{23}H_{20}O_2$ $[M+H]^+$ = 329.1542, found = 329.1534.

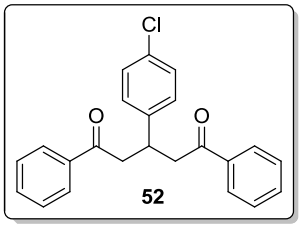
3-(4-methoxyphenyl)-1,5-diphenylpentane-1,5-dione 51[36]



Yield: 54%; IR (KBr, cm^{-1}): 3057, 3024, 2936, 1682, 1600, 1265, 1167, 756, 695; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.91 (m, 4H), 7.55-7.51 (m, 1H), 7.44-7.41 (m, 2H), 7.29-7.24 (m, 4H), 7.19-7.14 (m, 1H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.05 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.52-3.39 (m, 2H), 3.36-3.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 197.1, 163.4, 143.9, 136.8, 133.0, 130.4, 129.9, 128.5, 128.1,

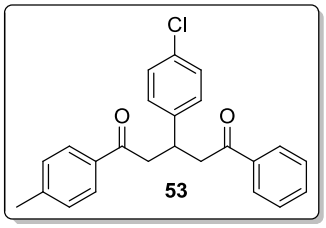
127.4, 126.6, 113.7, 55.4, 44.9, 44.6, 37.3; HRMS (ESI) m/z calcd for $C_{24}H_{22}O_3$ $[M+H]^+$ = 359.1647, found = 359.1645.

3-(4-chlorophenyl)-1,5-diphenylpentane-1,5-dione 52[37]



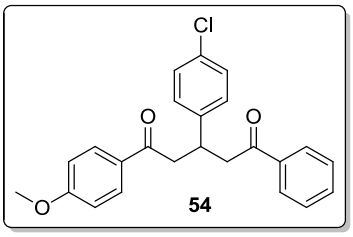
Yield: 99%; IR (KBr, cm^{-1}): 3051, 2964, 2936, 1687, 1599, 1254, 1167, 827, 690; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.6 Hz, 4H), 7.57-7.53 (m, 2H), 7.46-7.43 (m, 4H), 7.25-7.23 (m, 4H), 4.06 (q, *J* = 7.0 Hz, 1H), 3.48 (dd, *J* = 16.9, 6.9 Hz, 2H), 3.32 (dd, *J* = 16.7, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 142.3, 136.7, 133.2, 132.3, 128.9, 128.7, 128.6, 128.1, 44.7, 36.4; HRMS (ESI) m/z calcd for $C_{23}H_{19}ClO_2$ $[M+H]^+$ = 363.1152, found = 363.1151.

3-(4-chlorophenyl)-1-phenyl-5-p-tolylpentane-1,5-dione 53[38]



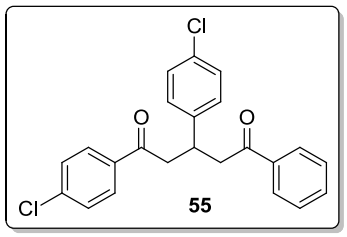
Yield: 83%; IR (KBr, cm^{-1}): 3051, 2920, 1682, 1605, 1495, 1265, 1178, 816, 690; ^1H NMR (400 MHz, $CDCl_3$) : 7.92 (d, *J* = 7.8 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.55-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.24-7.22 (m, 6H), 4.04 (q, *J* = 7.1 Hz, 1H), 3.50-3.40 (m, 2H), 3.33-3.25 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 197.8, 144.0, 142.3, 136.7, 134.2, 133.1, 132.1, 129.3, 128.8, 128.6, 128.1, 44.6, 36.5, 21.6; HRMS (ESI) m/z calcd for $C_{24}H_{21}ClO_2$ $[M+H]^+$ = 377.1308, found = 377.1307.

3-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-phenylpentane-1,5-dione 54



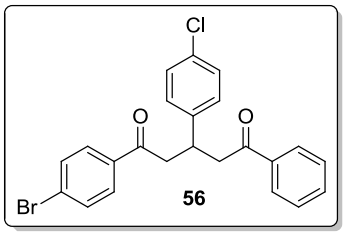
Yield: 80%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94-7.91 (m, 4H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.25-7.22 (m, 4H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.03 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.48 (dd, *J* = 16.8, 6.6 Hz, 1H), 3.41 (dd, *J* = 16.7, 6.7 Hz, 1H), 3.30 (dd, *J* = 16.7, 7.4 Hz, 1H), 3.25 (dd, *J* = 16.4, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 196.7, 163.5, 142.4, 136.7, 133.1, 132.2, 130.4, 129.8, 128.8, 128.6, 128.6, 128.0, 113.7, 55.4, 44.7, 44.4, 36.6; HRMS (ESI) m/z calcd for $C_{24}H_{21}ClO_3$ $[M+Na]^+$ = 393.1257, found = 393.1260.

1,3-bis(4-chlorophenyl)-5-phenylpentane-1,5-dione 55



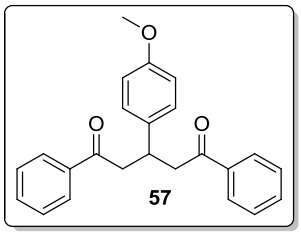
Yield: 71%; IR (KBr, cm^{-1}): 3063, 2920, 1682, 1600, 1210, 1084, 810, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.7 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.57-7.53 (m, 1H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.25-7.19 (m, 4H), 4.03 (q, *J* = 7.0 Hz, 1H), 3.46 (dd, *J* = 16.7, 6.8 Hz, 1H), 3.31 (d, *J* = 17.3, 7.0 Hz, 2H), 3.26 (d, *J* = 14.4, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 197.1, 143.3, 142.1, 136.6, 135.0, 133.3, 129.5, 129.2, 128.9, 128.7, 128.5, 128.1, 122.4, 44.7, 44.6, 36.4; HRMS (ESI) m/z calcd for $C_{23}H_{18}Cl_2O_2$ $[M+H]^+$ = 397.0762, found = 397.0761.

1-(4-bromophenyl)-3-(4-chlorophenyl)-5-phenylpentane-1,5-dione 56



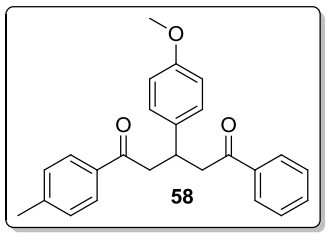
Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.59-7.54 (m, 3H), 7.46-7.42 (m, 2H), 7.25-7.19 (m, 4H), 4.02 (q, *J* = 6.9 Hz, 1H), 3.46 (dd, *J* = 16.8, 6.7 Hz, 2H), 3.34-3.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 197.2, 142.0, 136.6, 135.4, 133.3, 132.4, 131.9, 129.6, 128.8, 128.7, 128.6, 128.4, 128.0, 44.7, 44.6, 36.4; HRMS (ESI) m/z calcd for $C_{23}H_{18}BrClO_2$ $[M+Na]^+$ = 441.0257, found = 441.0256.

3-(4-methoxyphenyl)-1,5-diphenylpentane-1,5-dione 57[39]



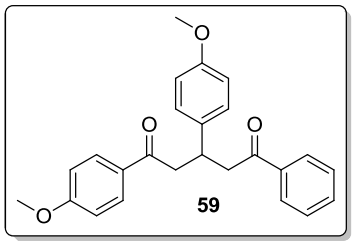
Yield: 55%; IR (KBr, cm^{-1}): 2887, 1665, 1512, 1238, 756; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.2 Hz, 4H), 7.55-7.52 (m, 2H), 7.45-7.41 (m, 4H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.02 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.46 (dd, *J* = 16.6, 6.8 Hz, 2H), 3.30 (dd, *J* = 16.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 158.2, 136.9, 135.7, 133.0, 128.5, 128.4, 128.1, 113.9, 55.1, 45.1, 36.4; HRMS (ESI) m/z calcd for $C_{24}H_{22}O_3$ $[M+K]^+$ = 397.1206, found = 397.1198.

3-(4-methoxyphenyl)-1-phenyl-5-p-tolylpentane-1,5-dione 58



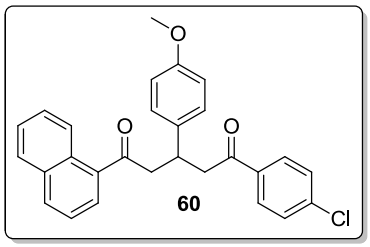
Yield: 70%; IR (KBr, cm^{-1}): 3002, 2926, 1676, 1610, 1506, 1243, 1183, 756; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.55-7.51 (m, 1H), 7.45-7.41 (m, 2H), 7.25-7.17 (m, 4H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.49-3.39 (m, 2H), 3.32-3.24 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 198.3, 158.1, 143.8, 136.9, 135.8, 134.4, 133.0, 129.2, 128.5, 128.4, 128.2, 128.1, 113.9, 55.1, 45.0, 36.5, 29.7, 21.6; HRMS (ESI) m/z calcd for $C_{25}H_{24}O_3$ $[M+Na]^+$ = 395.1623, found = 395.1622.

1,3-bis(4-methoxyphenyl)-5-phenylpentane-1,5-dione 59



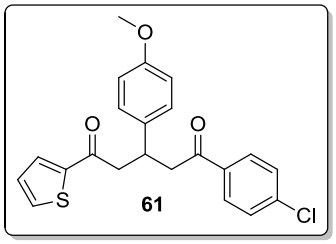
Yield: 90%; IR (KBr, cm^{-1}): 2931, 2838, 1676, 1600, 1506, 1249, 1178, 1030, 832; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.92 (m, 4H), 7.55-7.51 (m, 1H), 7.44-7.41 (m, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.47 (dd, *J* = 16.4, 6.7 Hz, 1H), 3.40 (dd, *J* = 16.0, 7.0 Hz, 1H), 3.29 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.24 (dd, *J* = 16.3, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 197.3, 163.4, 158.1, 136.9, 135.8, 133.0, 130.4, 129.9, 128.5, 128.3, 128.1, 113.9, 113.7, 55.4, 55.1, 45.1, 44.8, 36.7; HRMS (ESI) m/z calcd for $C_{25}H_{24}O_4$ $[M+Na]^+$ = 411.1572, found = 411.1573.

1-(4-chlorophenyl)-3-(4-methoxyphenyl)-5-(naphthalen-1-yl)pentane-1,5-dione 60



Yield: 28%; IR (KBr, cm^{-1}): 2958, 2925, 1687, 1512, 1249, 1090, 772; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30-8.28 (m, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.88-7.79 (m, 4H), 7.52-7.45 (m, 3H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.02 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.57 (dd, *J* = 16.7, 6.4 Hz, 1H), 3.45 (dd, *J* = 16.2, 6.9 Hz, 1H), 3.40-3.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.0, 197.5, 158.3, 139.5, 135.2, 133.9, 132.5, 129.6, 128.9, 128.5, 128.3, 127.7, 127.4, 126.4, 125.7, 124.3, 114.0, 55.2, 48.5, 45.1, 37.0; HRMS (ESI) m/z calcd for $C_{28}H_{23}ClO_3$ $[M+Na]^+$ = 465.1233, found = 465.1235.

1-(4-chlorophenyl)-3-(4-methoxyphenyl)-5-(thiophen-2-yl)pentane-1,5-dione 61



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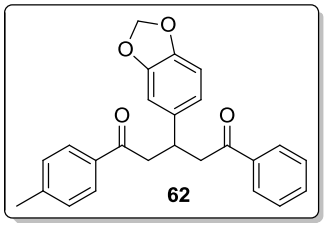
Yield: 76%; IR (KBr, cm^{-1}): 2936, 2838, 1676, 1517, 1419, 1243, 1035, 843, 717; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 3.7 Hz, 1H), 7.61 (m, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.12-7.10 (m, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.97 (q, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.47 (dd, *J* = 16.5, 6.6 Hz, 1H), 3.36 (dd, *J* = 16.0, 7.3 Hz, 1H), 3.29-3.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 191.5, 158.3, 144.3, 139.5, 135.2, 133.8, 132.1, 129.6, 128.9, 128.3, 128.1, 114.0, 55.2, 45.8, 44.8, 36.9; HRMS (ESI) m/z calcd for $C_{22}H_{19}ClO_3S$ $[M+Na]^+$ = 421.0641, found = 421.0642.

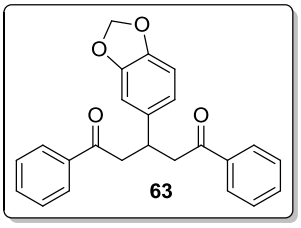
3-(benzo[d][1,3]dioxol-5-yl)-1-phenyl-5-p-tolylpentane-1,5-dione 62



62

Yield: 35%; IR (KBr, cm^{-1}): 2920, 1682, 1490, 1249, 1035, 805; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.56-7.52 (m, 1H), 7.46-7.42 (m, 2H), 7.25-7.23 (m, 2H), 6.77 (br s, 1H), 6.72-6.67 (m, 2H), 5.88 (m, 2H), 3.98 (q, d = 6.9 Hz, 1H), 3.47-3.37 (m, 2H), 3.30-3.23 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 198.2, 147.6, 146.1, 143.9, 137.7, 136.8, 134.3, 133.0, 129.3, 128.6, 128.2, 128.1, 120.4, 108.3, 107.8, 100.8, 45.1, 45.0, 37.1, 21.6; HRMS (ESI) m/z calcd for $C_{25}H_{22}O_4$ $[M+H]^+$ = 387.1596, found = 387.1596.

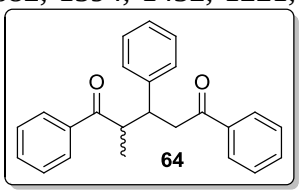
3-(benzo[d][1,3]dioxol-5-yl)-1,5-diphenylpentane-1,5-dione 63



63

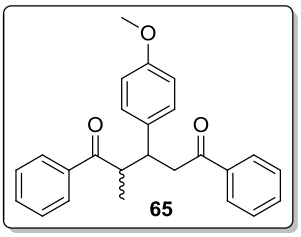
Yield: 29%; IR (KBr, cm^{-1}): 2882, 1682, 1490, 1249, 1035, 750, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.4 Hz, 4H), 7.57-7.53 (m, 2H), 7.46-7.43 (m, 4H), 6.77 (br s, 1H), 6.73-6.68 (m, 2H), 5.89 (s, 2H), 3.99 (q, *J* = 7.0 Hz, 1H), 3.44 (dd, *J* = 16.6, 6.9 Hz, 2H), 3.29 (dd, *J* = 16.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 147.8, 146.2, 137.7, 136.9, 133.2, 128.7, 128.2, 120.6, 108.4, 107.9, 101.0, 45.2, 37.1; HRMS (ESI) m/z calcd for $C_{24}H_{20}O_4$ $[M+H]^+$ = 373.1440, found = 373.1439.

2-methyl-1,3,5-triphenylpentane-1,5-dione 64[39]



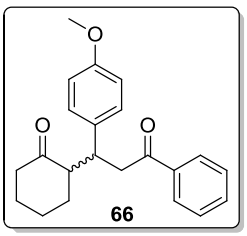
Yield: 61%; dr = 1.5:1; IR (KBr, cm^{-1}): 3063, 2964, 2920, 1682, 1594, 1452, 1221, 942, 712, 684; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.87-7.83 (m, 3.5H), 7.58-7.57 (m, 1H), 7.51-7.47 (m, 3H), 7.42-7.37 (m, 3H), 7.27-7.23 (m, 3H), 7.19-7.17 (m, 3H), 3.95-3.94 (m, 1.5H), 3.84-3.83 (m, 1H), 3.47-3.35 (m, 1.7H), 3.24 (dd, *J* = 16.0, 9.4 Hz, 1H), 1.27 (d, *J* = 6.0 Hz, 1.9H), 1.00 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 203.2, 198.5, 198.4, 142.8, 141.4, 137.0, 136.9, 136.8, 136.7, 133.2, 132.9, 132.8, 128.7, 128.6, 128.4, 128.1, 127.9, 126.8, 126.5, 45.9, 45.6, 44.3, 43.4, 42.7, 39.8, 16.6, 14.1; HRMS (ESI) m/z calcd for $C_{24}H_{22}O_2$ $[M+Na]^+$ = 365.1517, found = 365.1518.

3-(4-methoxyphenyl)-2-methyl-1,5-diphenylpentane-1,5-dione 65



Yield: 35%; dr = 1.8:1; IR (KBr, cm^{-1}): 2958, 2931, 1676, 1512, 1249, 1178, 706; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.86-7.83 (m, 3.5H), 7.59-7.57 (m, 1H), 7.52-7.48 (m, 4H), 7.42-7.38 (m, 3H), 7.15 (d, *J* = 8.6 Hz, 0.9H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 0.8H), 3.93-3.85 (m, 1.7H), 3.83-3.78 (m, 1H), 3.75 (s, 3H), 3.70 (s, 1.2H), 3.41-3.34 (m, 2H), 3.18 (dd, *J* = 15.7, 9.3 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 1.7H), 1.00 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 198.7, 158.3, 136.9, 136.8, 133.3, 133.2, 132.8, 129.2, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 113.8, 55.1, 46.1, 45.9, 43.6, 42.1, 40.1, 16.5, 14.2; HRMS (ESI) m/z calcd for $C_{25}H_{24}O_3$ $[M+Na]^+$ = 395.1623, found = 395.1622.

2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)cyclohexanone 66[40]



Yield: 33%; dr = 2:1; IR (KBr, cm^{-1}): 3473, 2942, 2920, 1704, 1676, 1616, 1243, 1024, 728, 695; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.1 Hz, 1H), 7.91 (d, *J* = 7.23 Hz, 2H), 7.52-7.48 (m, 1.7H), 7.44-7.38 (m, 3.2H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.89-3.83 (m, 0.5H), 3.74 (m, 3H), 3.69-3.67 (m, 1H), 3.48-3.47 (m, 1H), 3.44 (d, *J* = 4.0 Hz, 0.5H), 3.34 (dd, *J* = 16.2, 9.4 Hz, 0.5H), 3.17 (d, *J* = 16.0, 9.6 Hz, 1H), 2.70-2.64 (m, 1H), 2.53-2.47 (m, 1H), 2.41-2.34 (m, 1H), 2.29-2.21 (m, 0.5H), 2.07-

1.88 (m, 3H), 1.80-1.72 (m, 2H), 1.70-1.64 (m, 3H), 1.60-1.50 (m, 3H), 1.34-1.24 (m, 2H), 0.94-0.86 (m, 1.7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.9, 212.3, 199.0, 158.2, 137.0, 133.9, 132.8, 129.5, 129.3, 128.5, 128.2, 113.8, 113.7, 56.0, 55.2, 44.4, 42.4, 40.6, 40.4, 32.4, 29.7, 28.6, 27.6, 24.1; HRMS (ESI) m/z calcd for $C_{22}H_{24}O_3$ $[M+Na]^+$ = 359.1623, found = 359.1623.

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Chapter 4

4.6 Representative ^{1}H NMR and ^{13}C NMR spectra

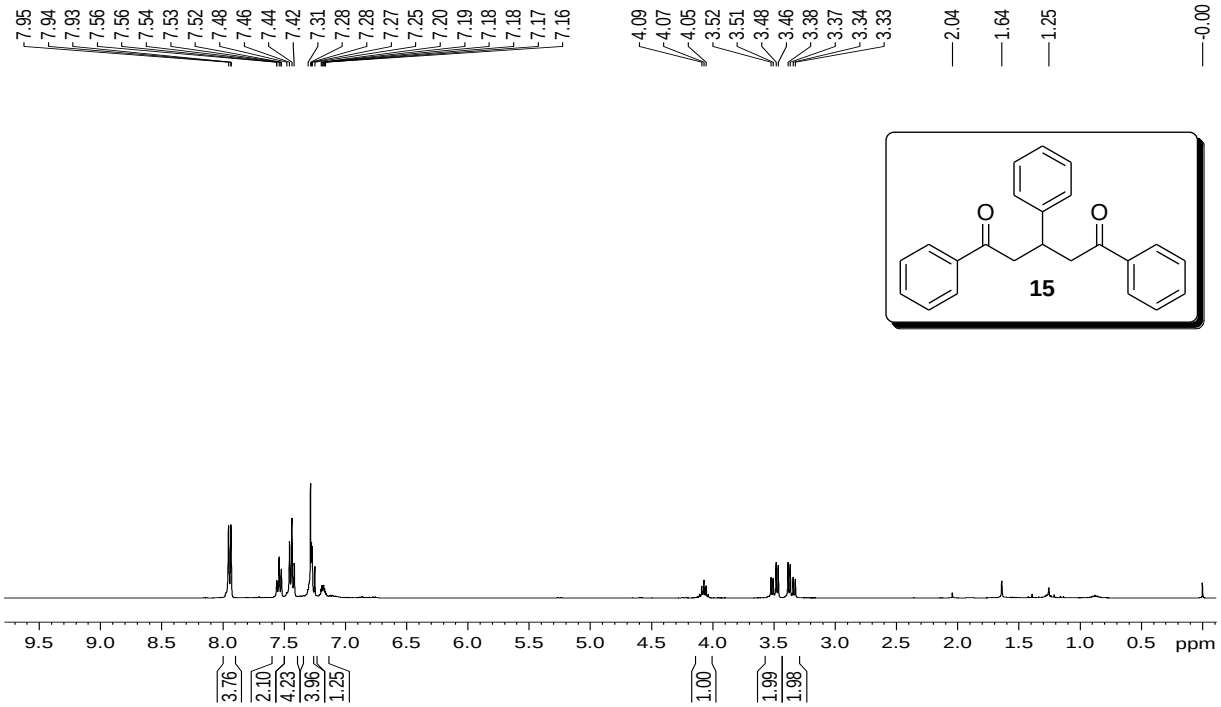

Figure 1. ^{1}H NMR Spectrum of compound **15**

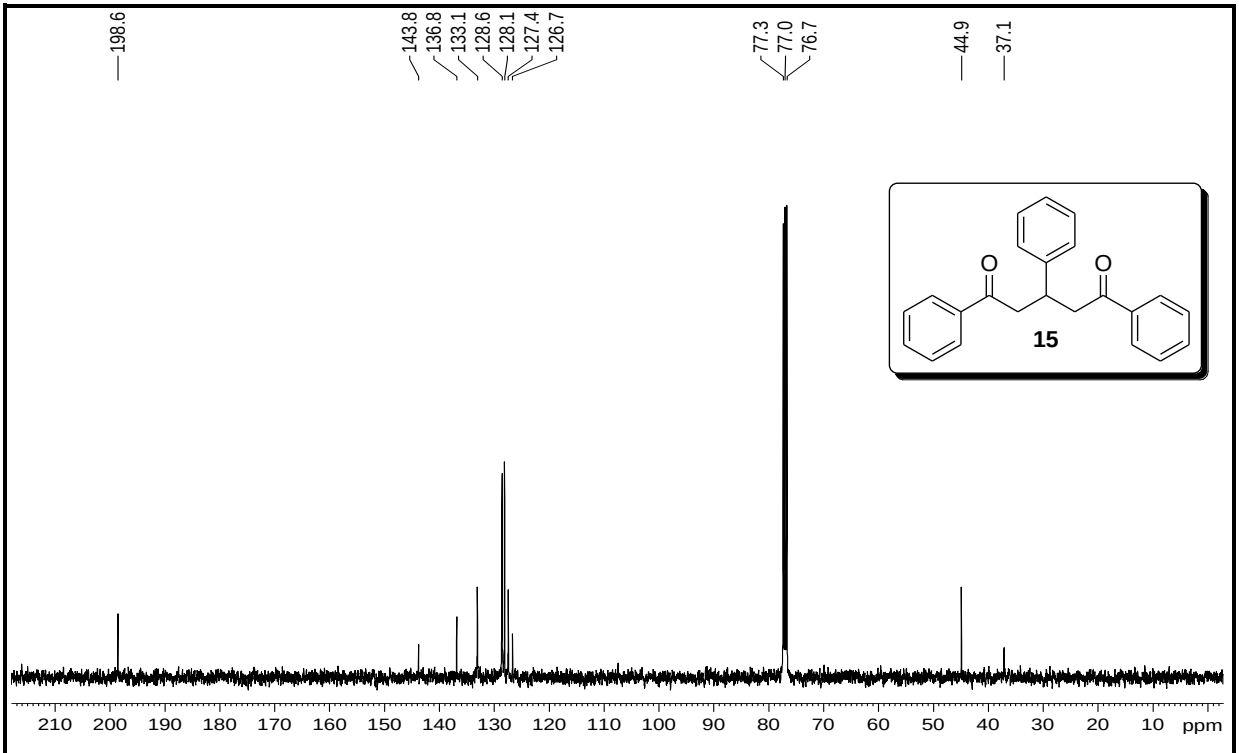

Figure 2.^{13}C NMR Spectrum of compound **15**

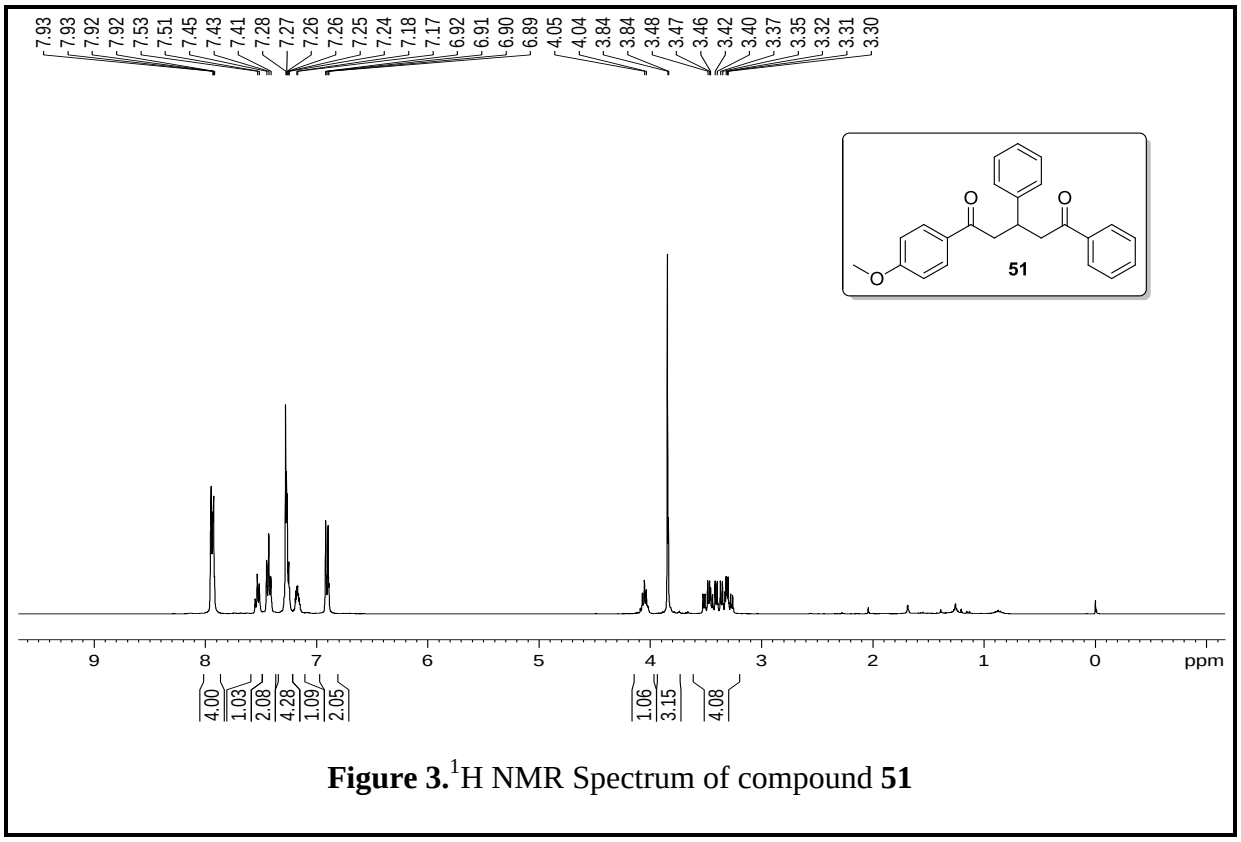

Figure 3.[1]H NMR Spectrum of compound **51**

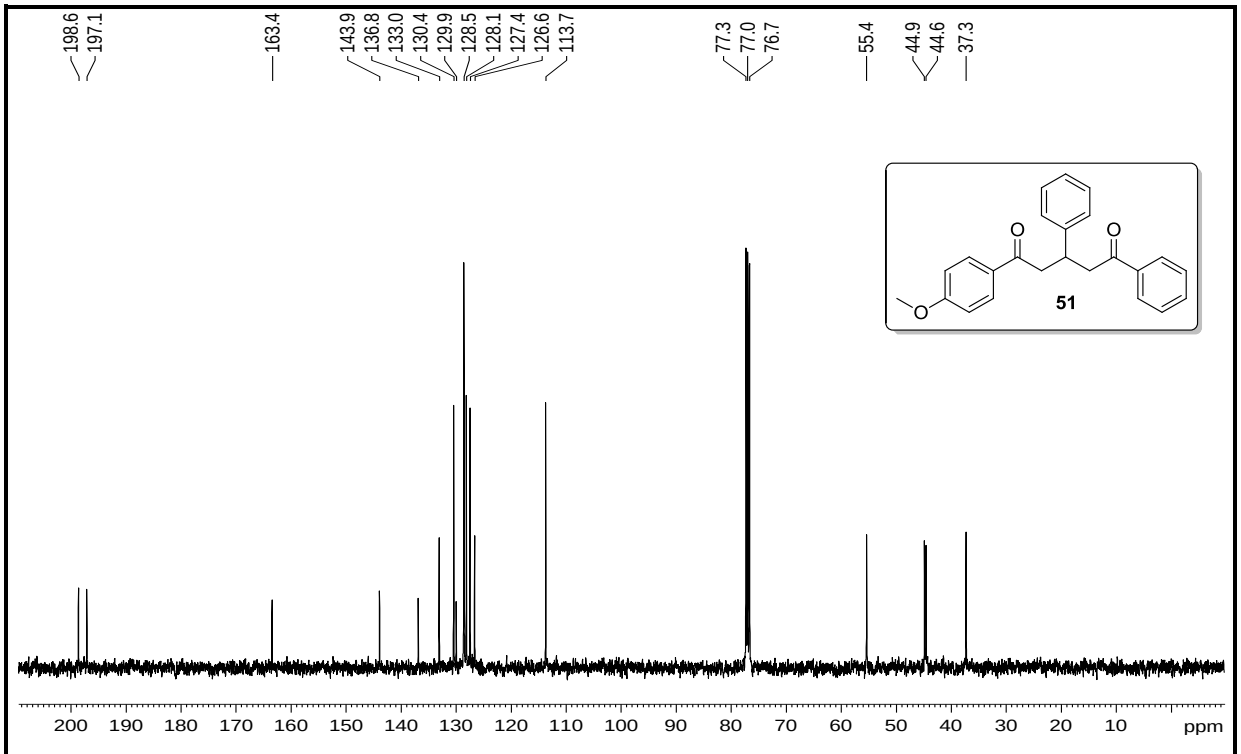

Figure 4.[13]C NMR Spectrum of compound **51**

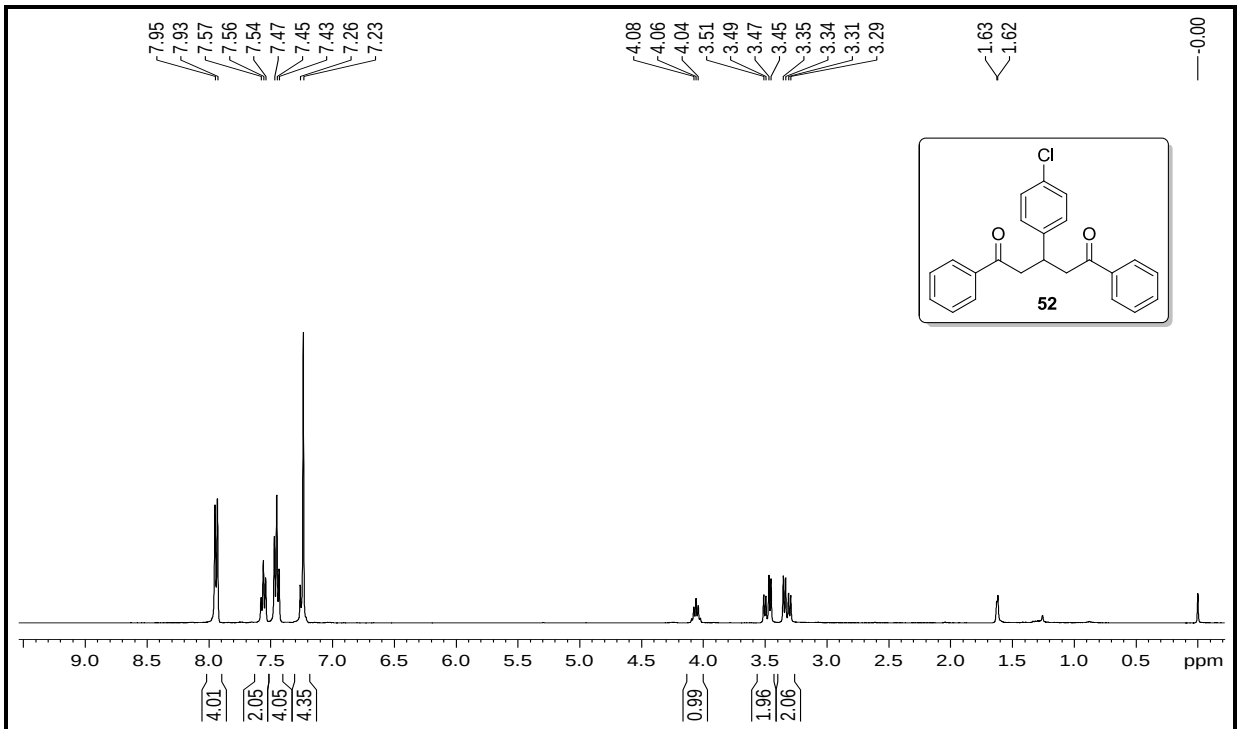

Figure 5. ^{1}H NMR Spectrum of compound **52**

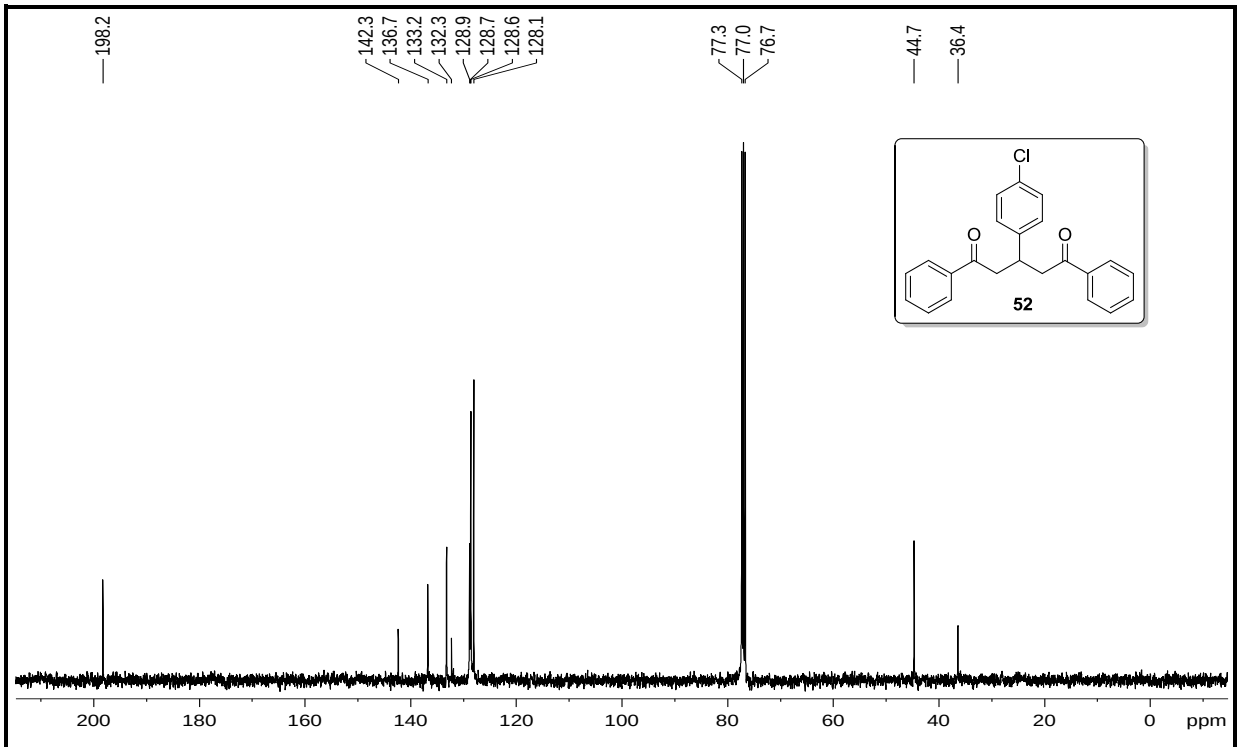

Figure 6. ^{13}C NMR Spectrum of compound **52**

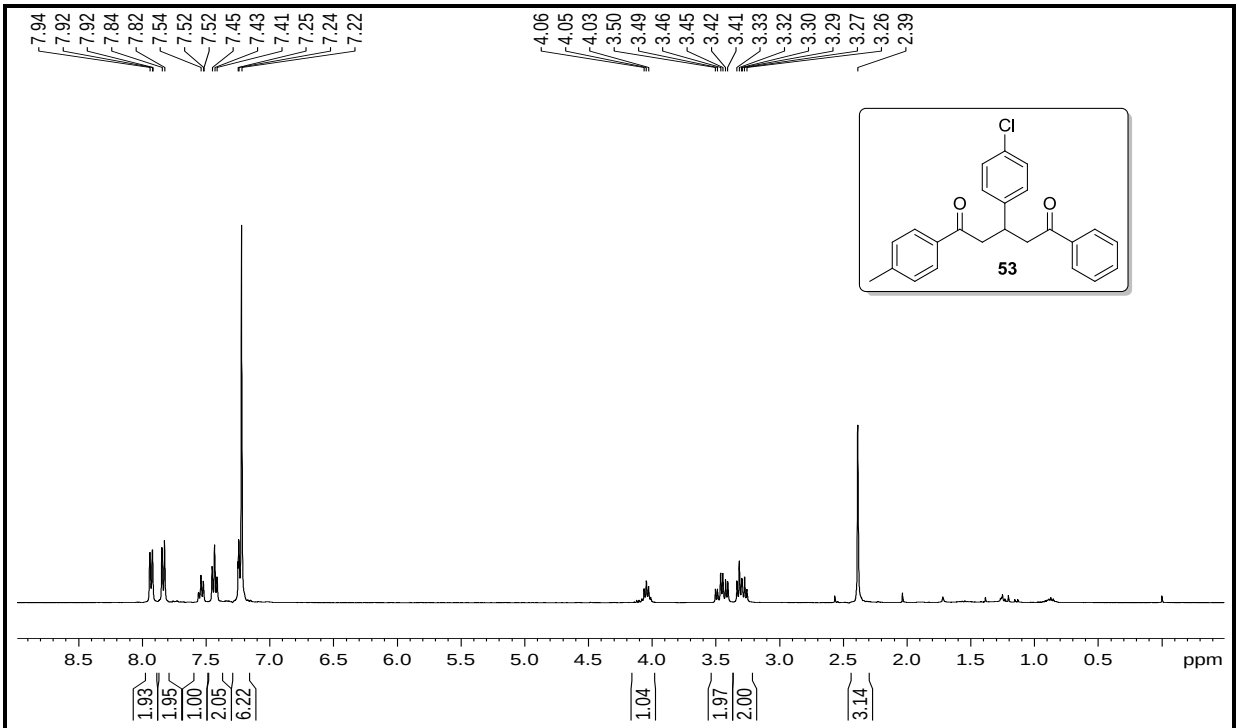

Figure 7.[1]H NMR Spectrum of compound **53**

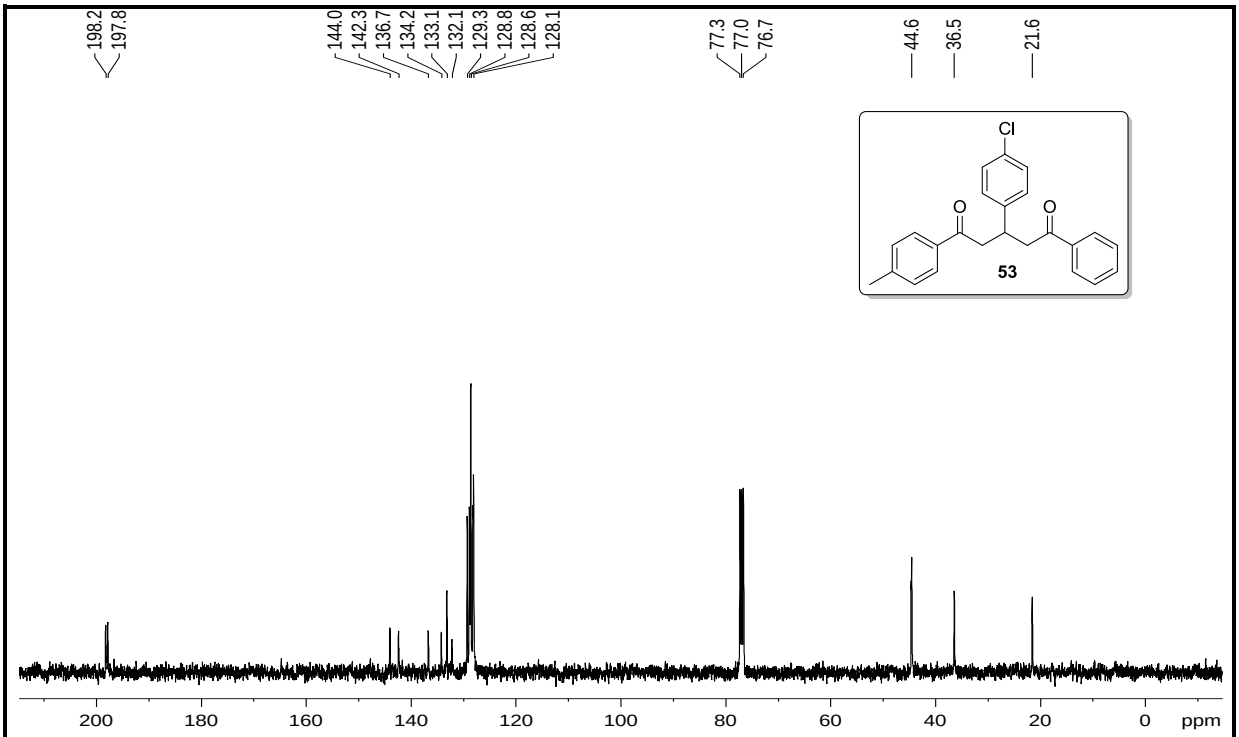

Figure 8.[13]C NMR Spectrum of compound **53**

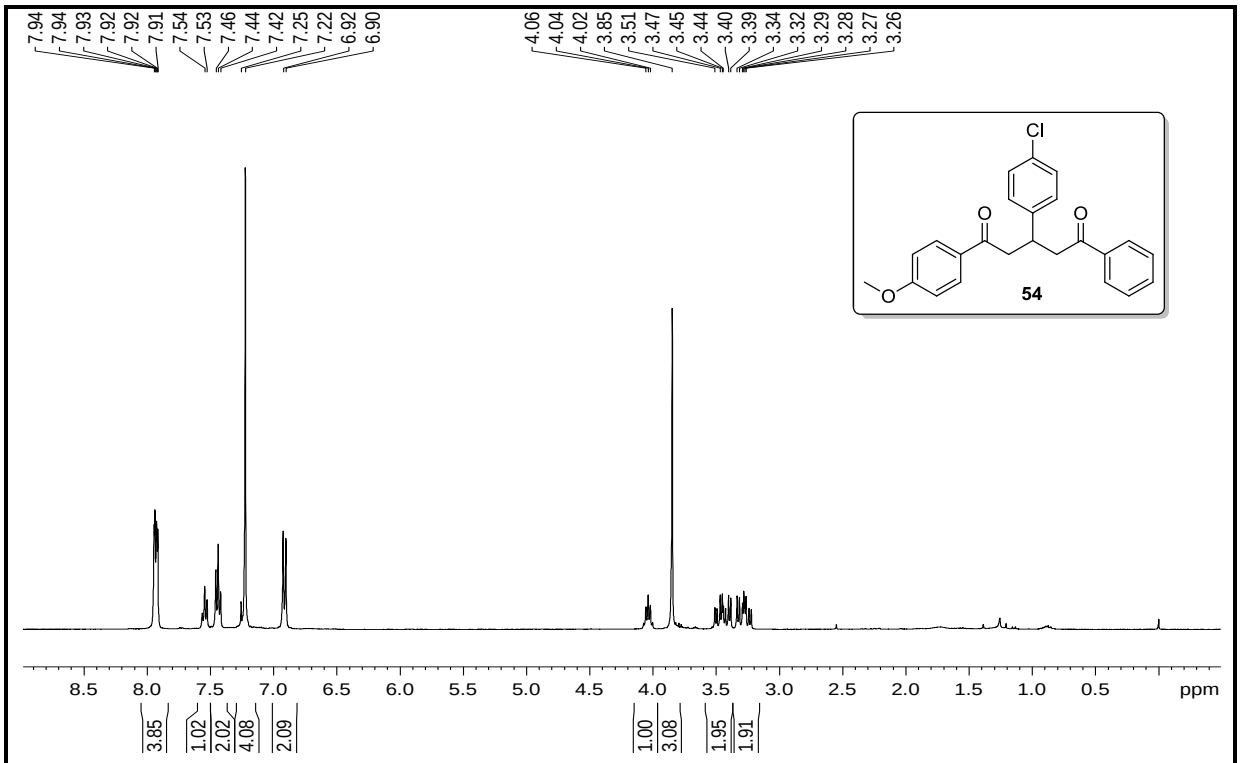

Figure 9.[1]H NMR Spectrum of compound **54**

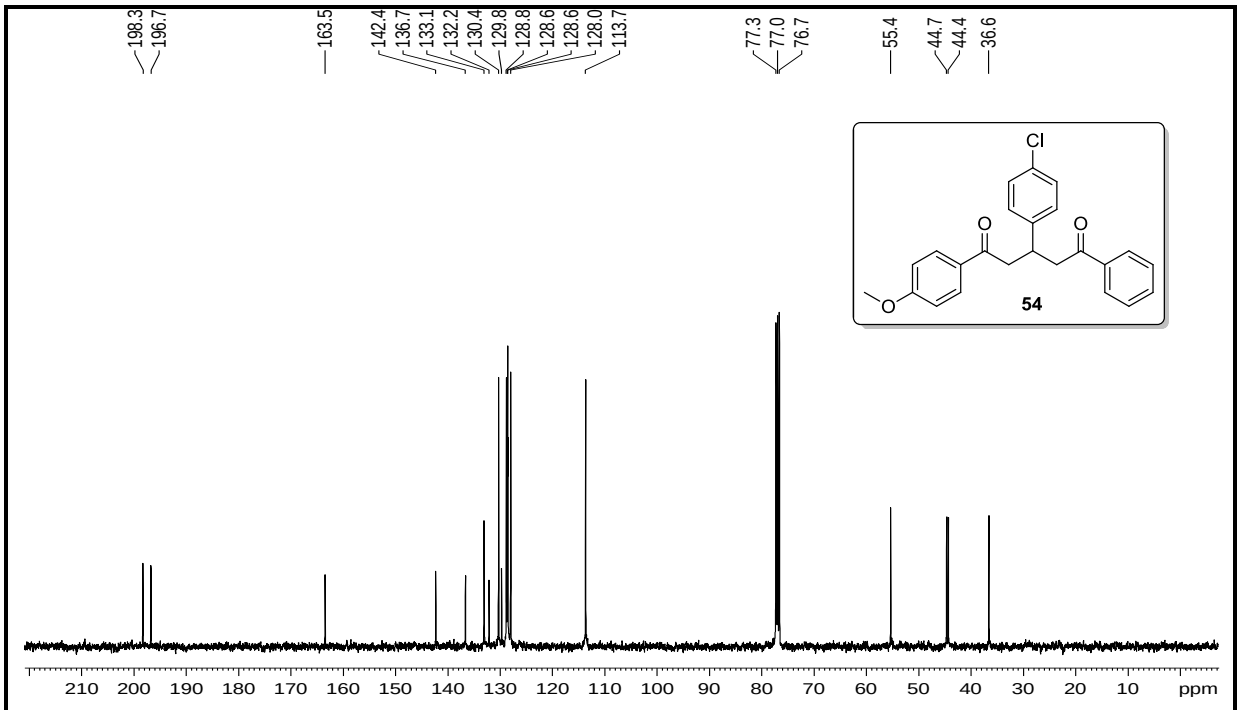

Figure 10. [13]C NMR Spectrum of compound **54**

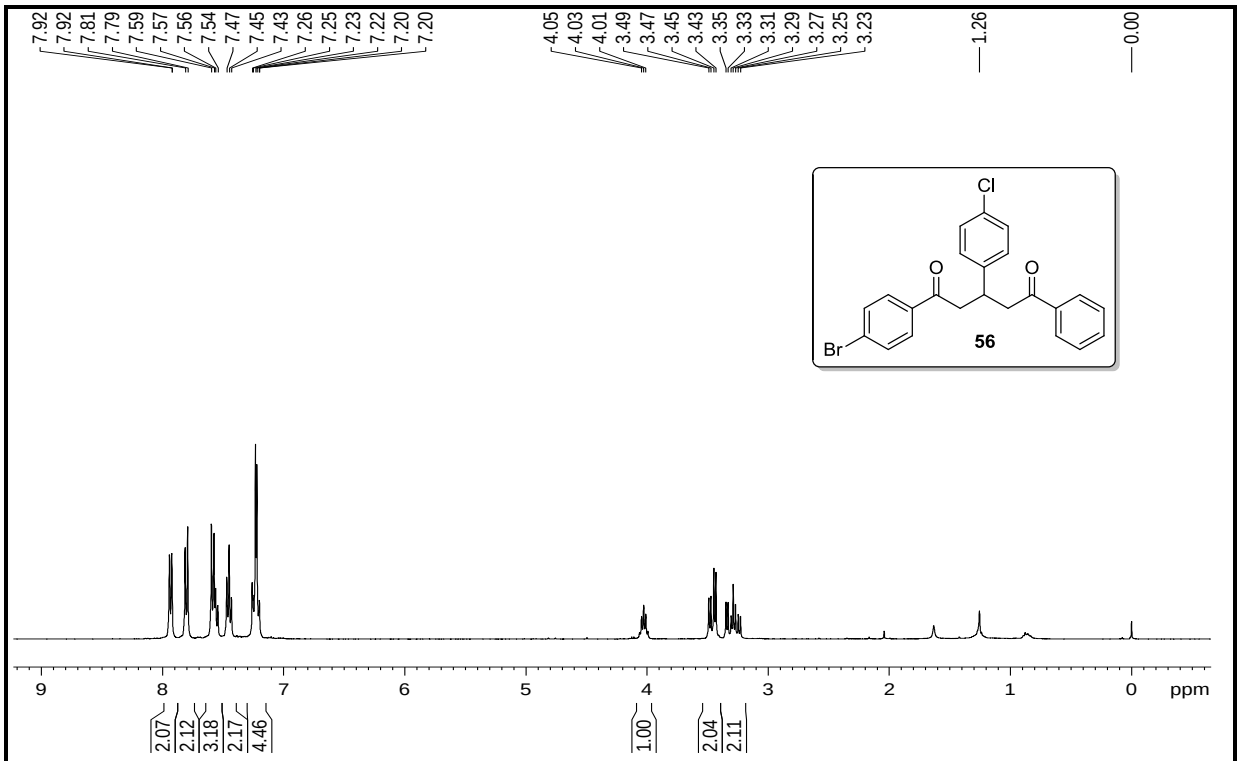

Figure 11. ^{1}H NMR Spectrum of compound **56**

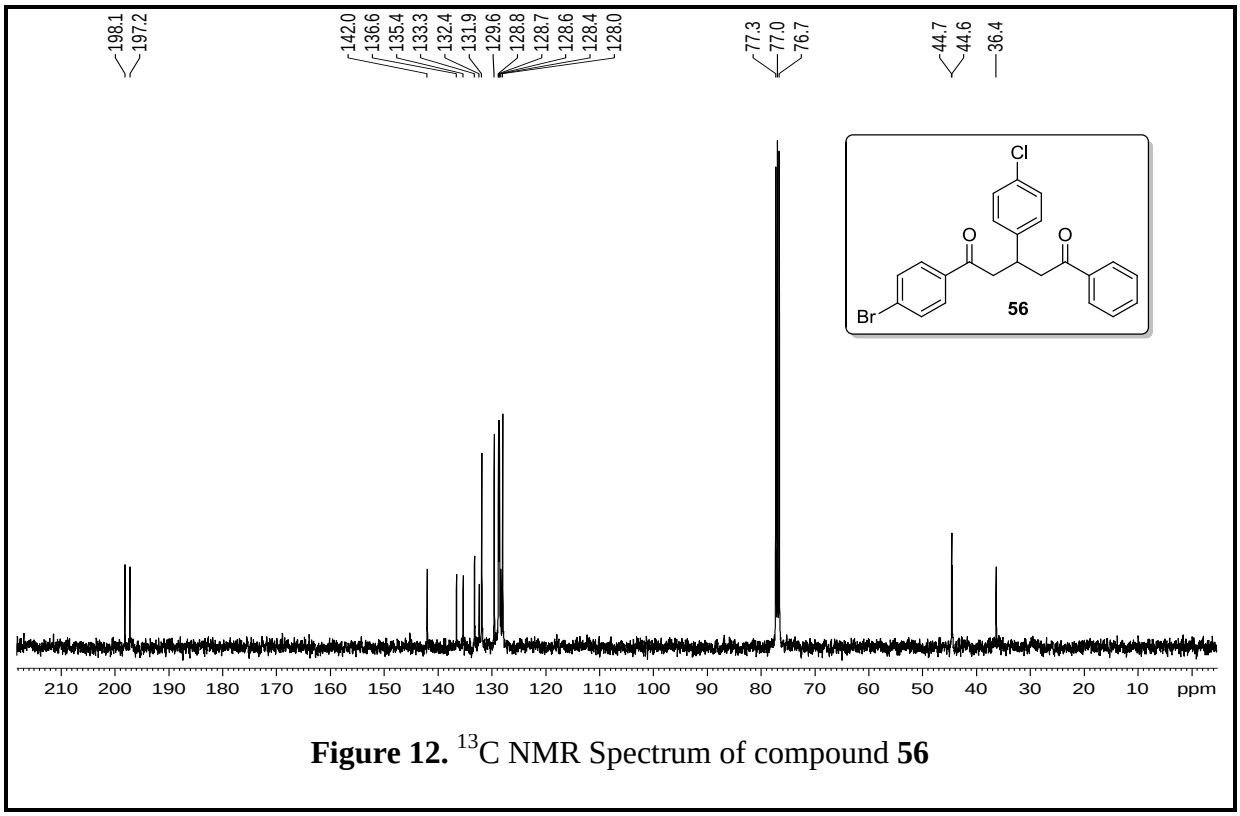

Figure 12. ^{13}C NMR Spectrum of compound **56**

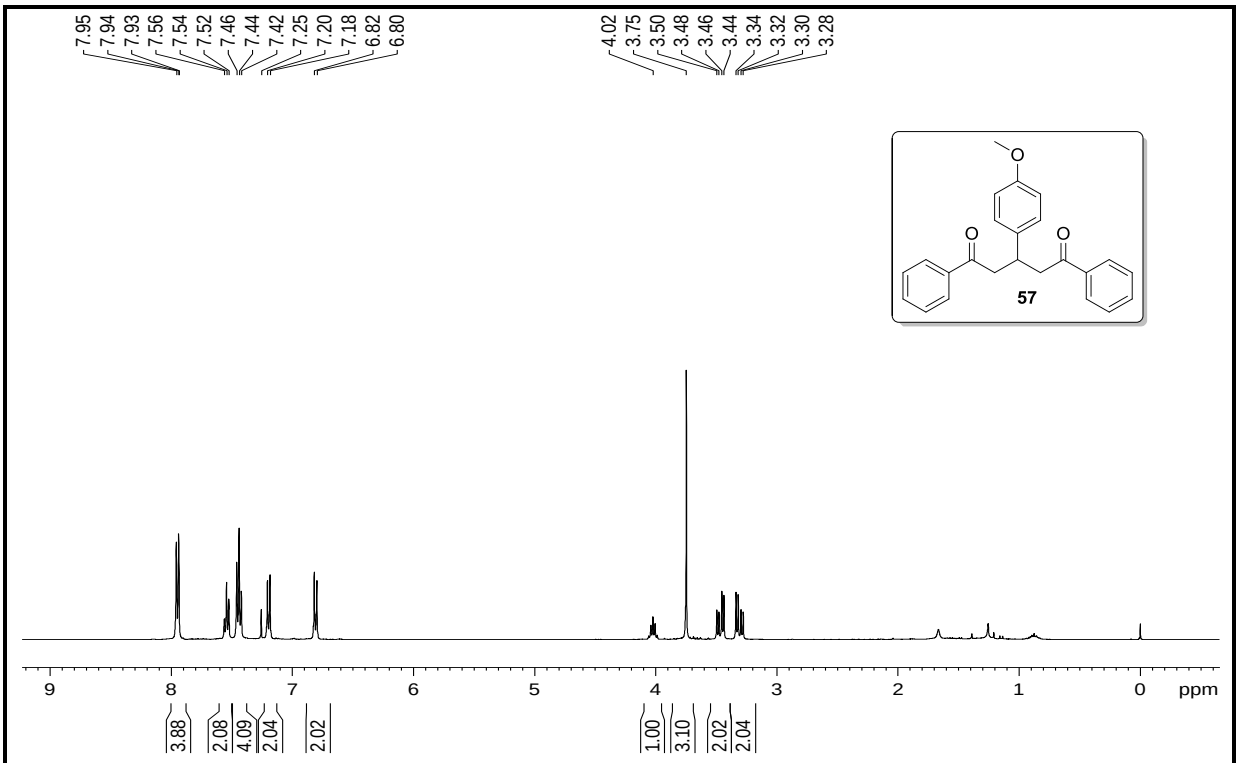

Figure 13. ^{1}H NMR Spectrum of compound **57**

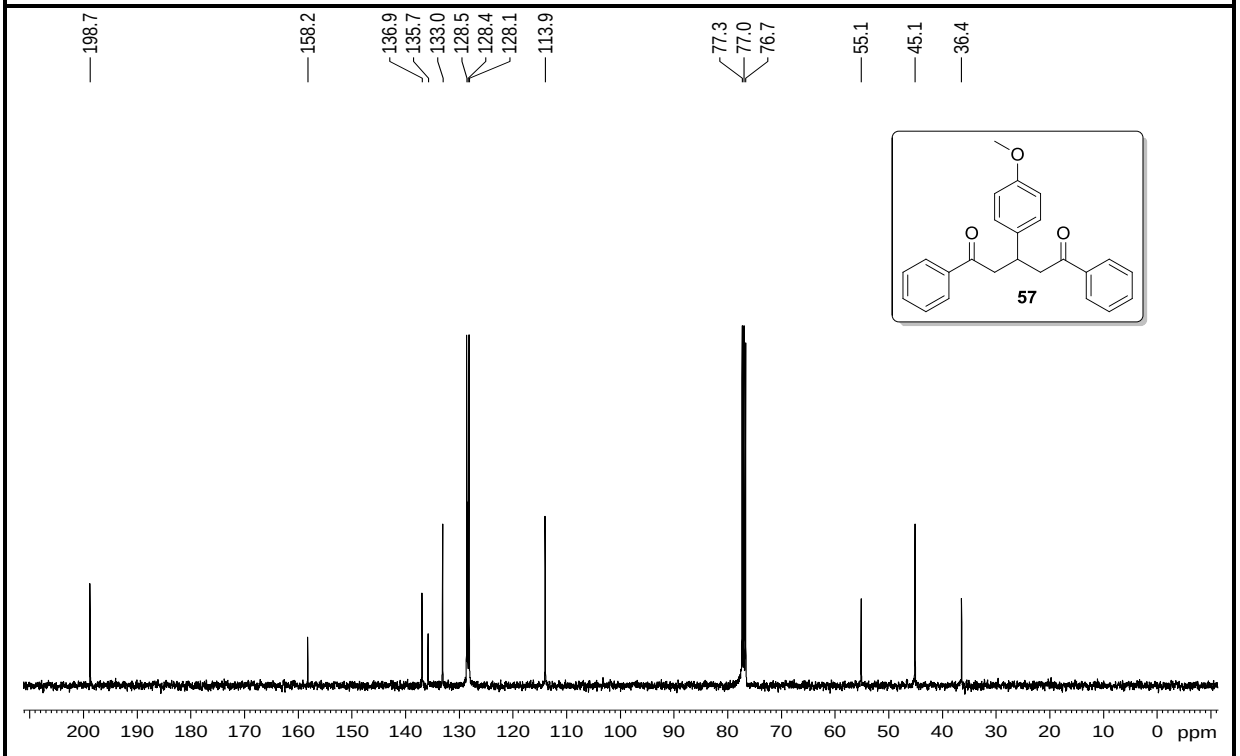

Figure 14. ^{13}C NMR Spectrum of compound **57**

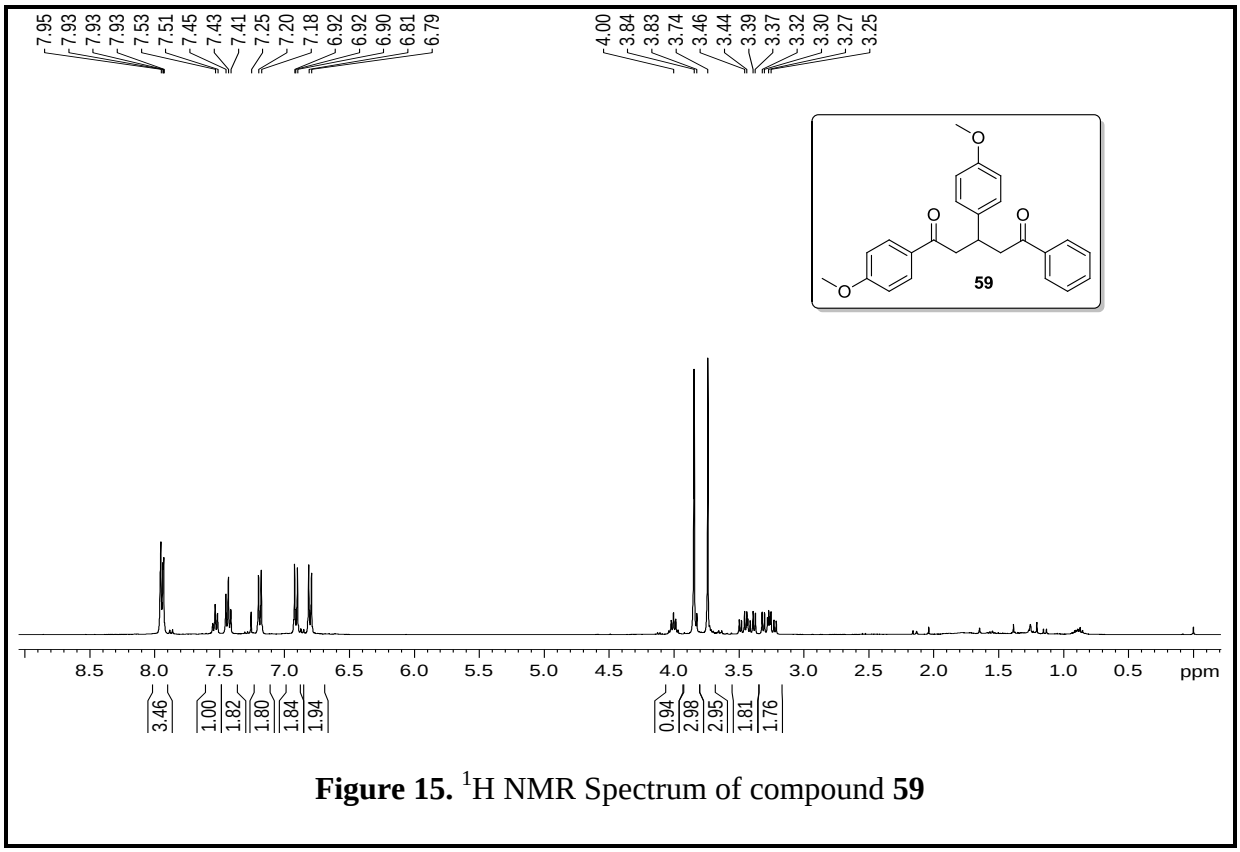

Figure 15. ^{1}H NMR Spectrum of compound **59**

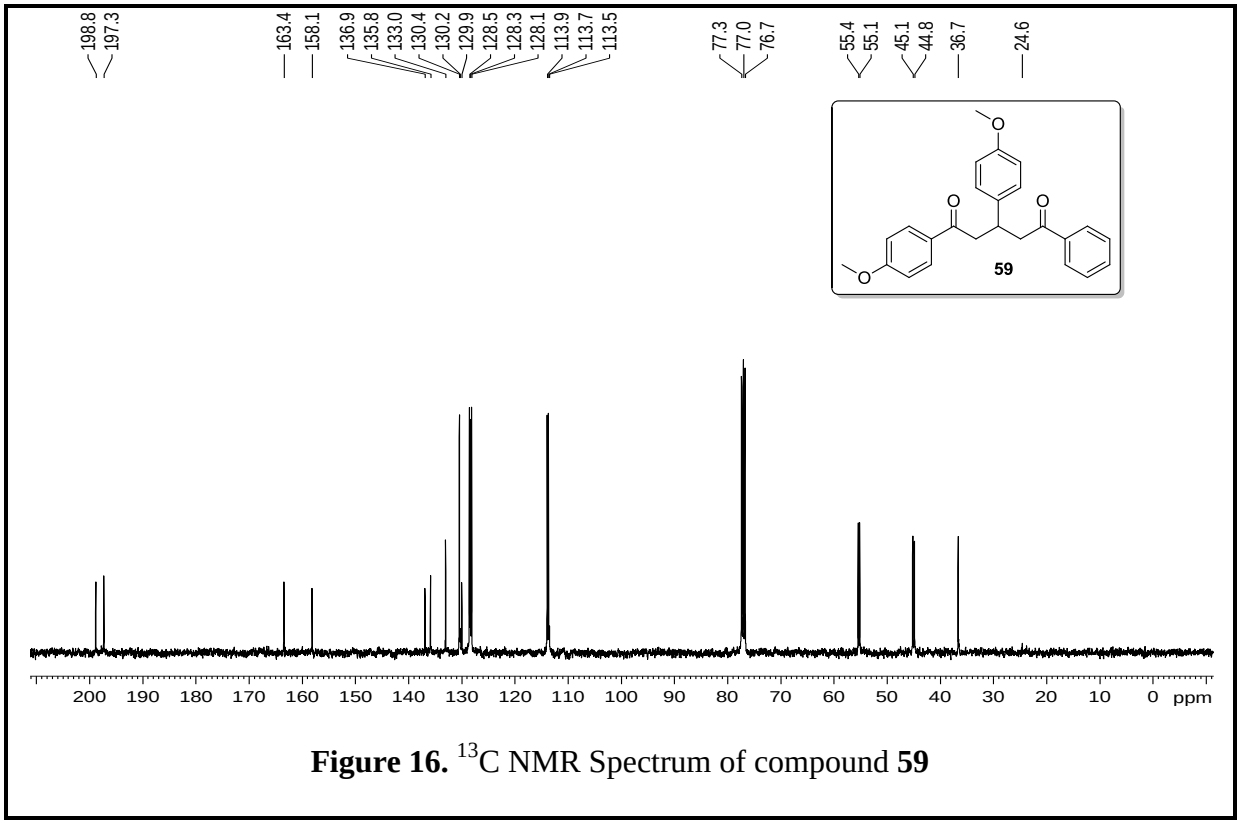

Figure 16. ^{13}C NMR Spectrum of compound **59**

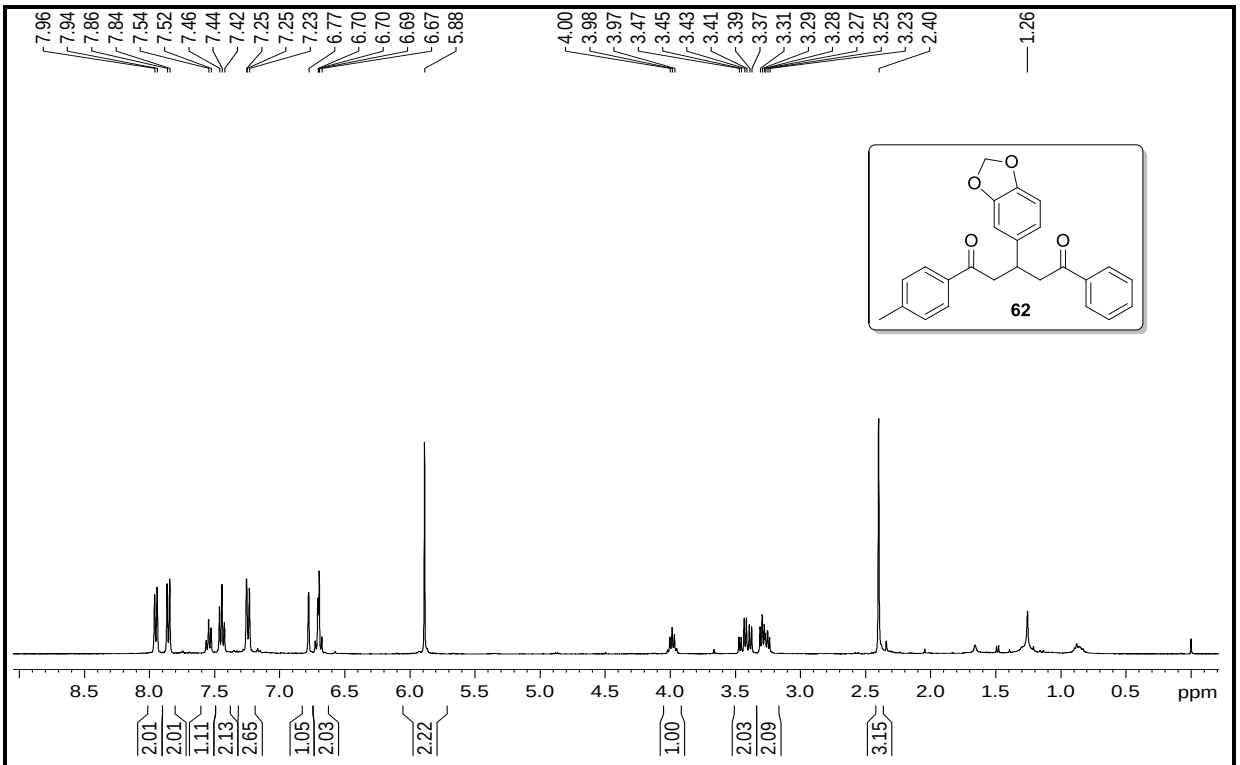

Figure 17. ^{1}H NMR Spectrum of compound **62**

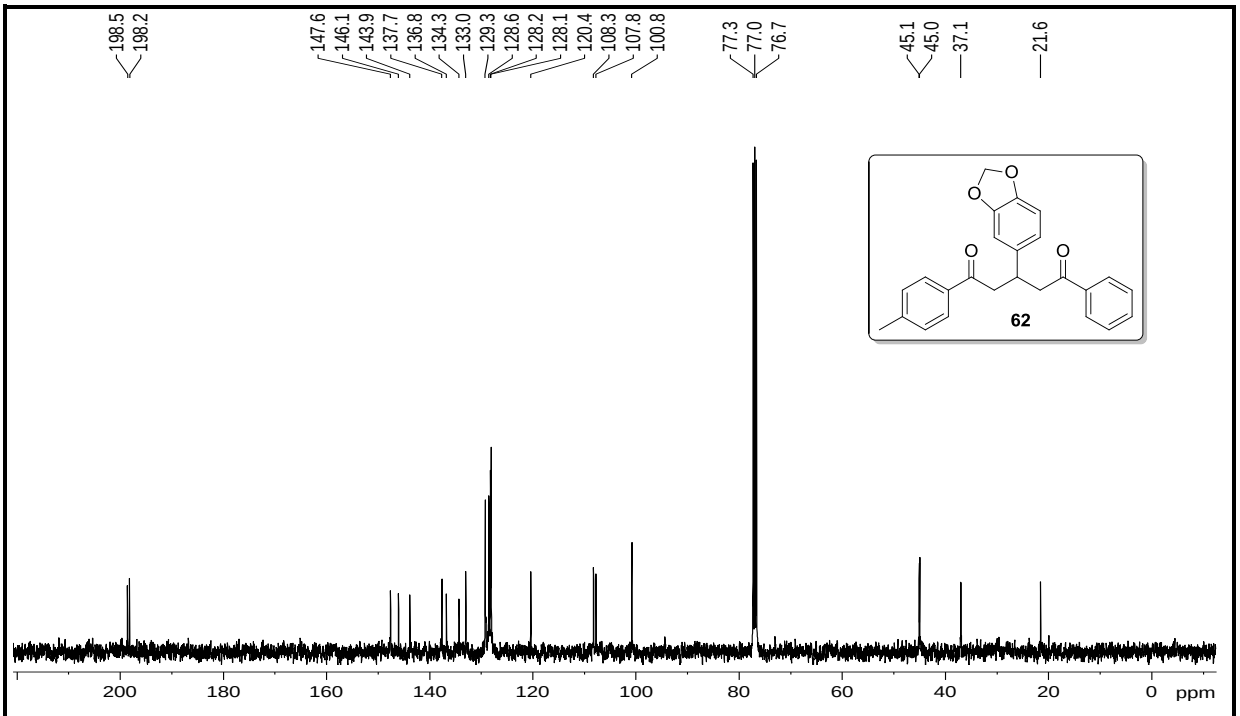

Figure 18. ^{13}C NMR Spectrum of compound **62**

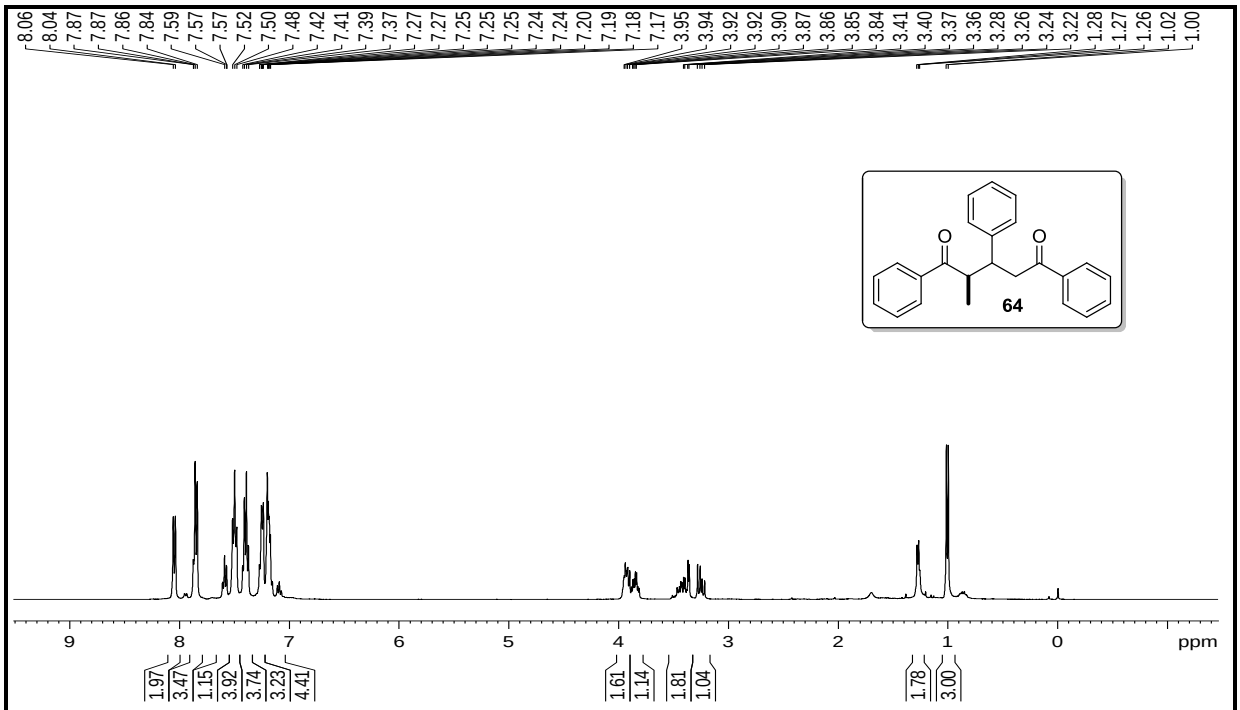

Figure 19. ^{1}H NMR Spectrum of compound **64**

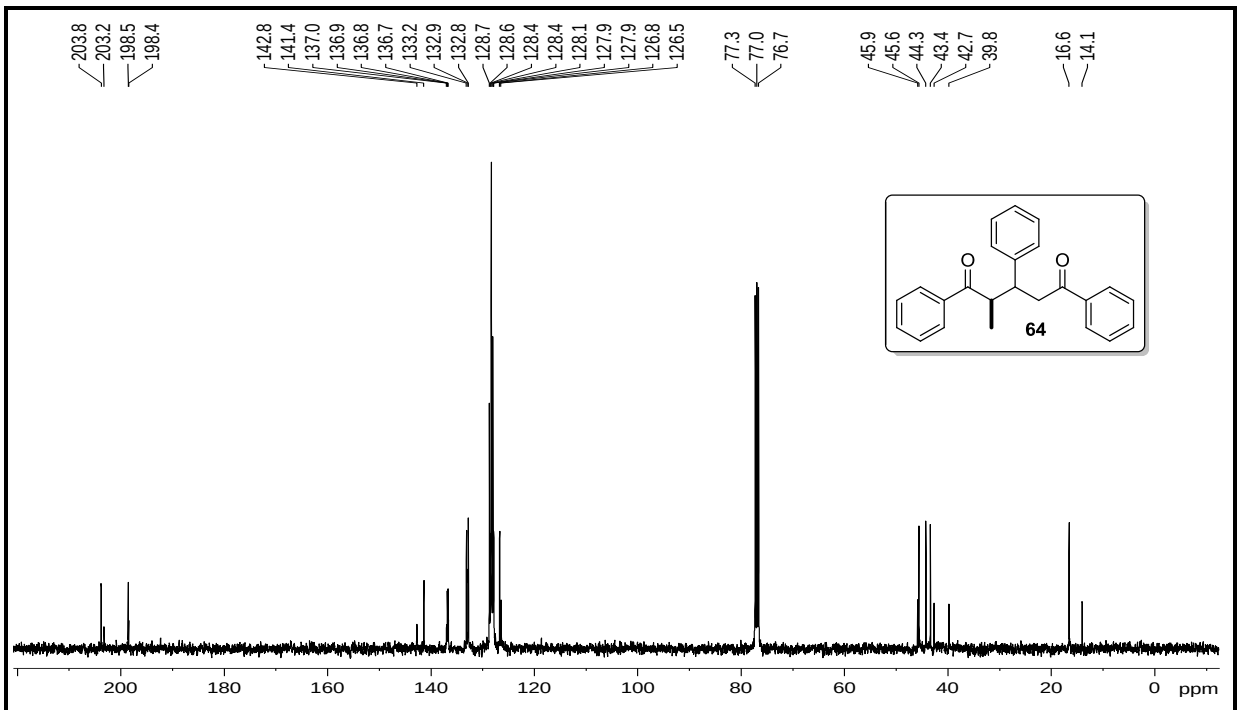

Figure 20. ^{13}C NMR Spectrum of compound **64**

List of Publications

1. Scope of $AuCl_3$ in the Activation of Per-*O*-acetyl-glycals.

   Balamurugan, R.; **Koppolu**, **S. R.** *Tetrahedron* **2009**, *65*, 8139.

2. Gold(III)-Catalysed Glycosylation Reaction: Development of an Easily Accessible Glycosyl Donor.

   Koppolu, S. R.; Balamurugan, R. *Manuscript under preparation*.

3. Triflic Acid-Promoted Direct α-Alkylation of Unactivated Ketones Using Alcohols *via In Situ* Formed Acetals

   Koppolu, S. R.; Naveen, N.; Balamurugan, R. *J. Org. Chem. Under revision.*

4. Lewis acid-Catalysed Direct α-Alkylation of Unactivated Ketones

   Naveen, N.; **Koppolu, S. R.**; Balamurugan, R. *Manuscript under preparation.*

5. Triflic acid-Promoted Synthesis of 1,5-Diketones from Unactivated Ketones.

   Koppolu, S. R.; Balamurugan, R. *Manuscript under preparation.*

Oral and Poster Presentations

1. Oral presentation was given titled "**Gold(III)-Catalysed Glycosylation Reactions**" at CHEMFEST-2012, 9^{th} in-house symposium held at University of Hyderabad, Hyderabad.

2. A poster was presented titled "**Gold(III)-Catalysed Glycosylation Reactions**" at CHEMFEST-2012, 9^{th} in-house symposium held at University of Hyderabad, Hyderabad.