Development of New Methodology for Different Organic Transformations

Thesis submitted for the Degree of

Doctor of Philosophy (Science)

of

Jadavpur University

2021

By

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কলকাতা-৭০০ ০৩২, ভারত

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Professor

CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled **"Development of New Methodology for Different Organic Transformations"** submitted by **Mrs. Sneha Nandy,** who got her name registered on ***05-11-2015*** for the award of ***Ph.D. (Science) degree of Jadavpur University***, is absolutely based upon her own work under my supervision and that neither this thesis nor any part of it has been submitted for either any degree / diploma or any other academic award anywhere before.

Sanjay Bhar
04/10/2021

(Signature of the Supervisor
with date and official seal)

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All of the work is dedicated to my parents who inspire, support and protect.

I couldn't have done it without you.

PREFACE

Investigations presented in this dissertation entitled "**Development of New Methodology for Different Organic Transformations**", submitted for the degree of Ph.D. (Science) of Jadavpur University, were initiated in November 2015 under the supervision of Professor Sanjay Bhar, Department of Chemistry, Organic Chemistry Section, Jadavpur University, Kolkata-700032.

The purpose of the study embodied in the aforesaid thesis was to develop alternative protocols for important organic reactions aiming at the functional group transformations along with the construction of important molecular skeletons. In order to proceed for a 'sustainable future' inexpensive and eco-compatible reagents as well as recyclable catalysts were involved under mild reaction conditions implementing good yield, unique reactivity and excellent chemoselectivity to the reaction outcome. All of the synthesized products were duly characterized with different spectroscopic and analytical techniques. Entire investigations have been divided into three Chapters. **Chapter-I** deals with a transition metal-free Cross Dehydrogenative Coupling (CDC) reaction for the synthesis of aryl esters starting from benzylic alcohols as the substrates using *t*-butyl hydroperoxide (TBHP) as a terminal oxidant in the presence of catalytic amount of tetrabutylammonium iodide (TBAI) and imidazole. In **Chapter-II,** commercially available Amberlyst®-15(H) has been utilised efficiently as an air-stable, heterogeneous, inexpensive solid acid catalyst which was reused consecutively up to several times with marginal loss of its catalytic activity. This catalytic system was utilized under different solvent systems for the formation of C–N as well as C–O bond in chemoselective fashion with wide structural variation. Additionally, differently substituted conjugated dienes were prepared through the cleavage of cyclopropane ring of aptly substituted cyclopropylcarbinols with good yield. **Chapter-III** includes the chemoselective reduction of α-heteroatomic esters using $NaBH_4$ in methanol as a mild reducing agent at room temperature.

Interesting results were obtained in course of the aforesaid investigations, some of which have been presented in National and International Symposia. A couple of them have been published in international journals while the manuscripts of the others are being prepared. The entire process has been delayed due to intermittent interruptions because of COVID-19 pandemic.

ACKNOWLEDGEMENTS

First and foremost I would like to express my sincere gratitude to my Supervisor, Professor Sanjay Bhar, Department of Chemistry, Organic Chemistry Section, Jadavpur University, Kolkata 700032, for his guidance, invaluable advice, insightful comments, constructive criticism and continuous support throughout my research programme. His immense knowledge, plentiful experience, professionalism, organizational art and above all his all time assistance have encouraged me to perform my research work along with every other work with utmost dedication and honesty.

I would also like to thank Professor Brindaban Chandra Ranu, Department of Chemistry, Indian Association for the Cultivation of Science (IACS) for his important suggestions in different occasions.

I express my deep regards to Professor Swapan Kumar Bhattacharya, Head, Department of Chemistry, Jadavpur University, Professor Rina Ghosh, Professor Gourhari Maiti, Professor Umasish Jana, Professor Umesh Chandra Halder, Dr. Shaubhik Haldar, Dr. Tanurima Bhaumik, Dr. Samit Guha, Dr. Arunabha Thakur, Dr. Amit Saha, Dr. Mohabul Alam Mondal and all other respected teachers of Jadavpur University for their constant support and encouragement throughout the journey, especially during the odd times.

I sincerely like to put on records my heartiest thanks to the authority of Jadavpur University for providing me infrastructural and instrumental facilities for my research investigations. Financial support which I have enjoyed from Innovation in Science Pursuit for Inspired Research (INSPIRE) of Department of Science & Technology (DST), Government of India in terms of Junior and Senior Research Fellowship is gratefully acknowledged.

I express my warm thanks to Mr. Raju Biswas of Jadavpur University and Mr. Nirmalya Dutta of IACS for their intimate help in recording most of the ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra presented in this thesis.

I convey my special thanks to my lab seniors and lab mates, Dr. Subrata Kumar Chaudhuri, Dr. Manabendra Saha, Dr. Sanchita Roy, Dr. Amit Pramanik, Dr. Sagar Khan, Dr. Rimi Roy, Dr. Avishek Ghatak and Mr. Asit Kumar Das for their whole-hearted co-operation throughout the entire tenure of my research work inside and outside the laboratory as well as during the preparation of my thesis.

My sincere thanks to Mrs. Pritha Das from CSIR – Indian Institute of Chemical Biology (IICB) for helping immensely with recording many of the instrumental characterisation data presented in this thesis.

I also convey my gratitude to Dr. Soumyadipta Rakshit, Mr. Debopam Sinha, Dr. Ankita Roy, Mr. Saikat Gayen, Mr. Sandip Munshi, Mrs. Promita Nandy, Mr. Biswajit Sen, Miss. Parinita Singhamahapatra, Mr. Indradip Mandal, Mr. Tarun Kumar Dinda, Mr. Biprajit Pal, Miss. Suvenira Jana, Mr. Sudip Ghosh and Miss. Pameli Ghosh for their motivation and help at many steps.

I always remain indebted over head and ears to my Father, Mr. Asoke Nandy, my Mother, Mrs. Minu Nandy and my husband Mr. Pramit Dutta for their continuous support and encouragement throughout my above-mentioned journey. At times when I felt depressed, these persons used to come up to put me back on my determination.

I gratefully acknowledge the constant support from Mr. Partha Pratim Datta and Mrs. Somali Datta for always believing in me and encouraging me to follow my dreams. I also express my special love to my nieces Dibyashree and Samriddhi for their relaxing company. Above all, without the immense patience and sacrifice of all my family members the research work would have been impossible.

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ABBREVIATIONS and SYMBOLS

Ac	acetyl
ACP	alkylidenecyclopropanes
BIAN	1, 2-((bis-2, 6-diisopropylphenyl)imino)acenaphthene
Bn	benzyl
bp	boiling point
Bu	butyl
CAN	cerium (IV) ammonium nitrate
CD	cyclodextrin
CDC	cross dehydrogenative coupling
DA	Diels-Alder
DAC	donor-acceptor cyclopropane
DCM	dichloromethane
DCE	1, 2-dichloroethane
DEPT	distortionless enhancement polarization transfer
DFT	density-functional theory
DIBAL	di-isobutyl aluminium hydride
DME	dimethoxyethane
DMF	*N, N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNBSA	2, 4-dinitrobenzenesulfonic acid
dppp	1, 3-bis(diphenylphosphino)propane
DPAT	diphenylammonium triflate
EA	ethyl acetate
EAA	ethyl acetoacetate
EDG	electron donating group
ee	enantiomeric excess
Equiv	equivalent
EWG	electron withdrawing group
Et	ethyl
h / hrs	hours
GHB	gamma-hydroxy butyric acid

HAT	hydrogen atom transfer
HFIP	hexafluoroisopropanol
HRMS	high resolution mass spectrum
HMF	hydroxymethylfurfural
IR	infrared
J	coupling constant
LAH	lithium aluminum hydride
LED	light emitting diode
MCP	methylenecyclopropane
Me	methyl
min	minutes
mL	mililitre
mp	melting point
MW	microwave
NFSI	N-fluorobenzenesulfonimide
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
PEG	polyethylene glycol
PFPAT	pentafluorophenyl ammonium triflate
Ph	phenyl
PMHS	polymethylhydrosiloxane
PNN	2-(di-tert-butylphosphinomethyl)-6-(diethylaminomethyl) pyridine
ppm	parts per million
rt	room temperature
SET	single electron transfer
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TBDMS	tert-butyldimethylsilyl
TBHP	tert-butyl hydroperoxide
TCNE	tetracyanoethylene
TCT	2, 4, 6 trichloro-[1, 3, 5]-triazine
TEMPO	2, 2, 6, 6-tetramethylpiperidinyloxy
THF	tetrahydrofuran

TLC	thin layer chromatography
TMS	tetramethylsilane
TMSCN	trimethylsilyl cyanide
$TMSN_3$	azidotrimethylsilane
Ts	tosyl
UV	ultraviolet
δ	chemical shift
ν	frequency

CONTENTS

Copy of the reprint from:

(a) *Synlett* **2018**, *29*, 2208-2212

(b) *Synth .Commun. **2020**, 50, 3326-3336*

Abstracts, pictures and certificates of the presented posters:

List of papers presented in National and International symposia

(In the form of posters)

1. "Synthesis of alkyl and aryl esters from the corresponding alcohols in aqueous medium using TBHP/TBAI as an efficient catalyst", Nandy, S.; Ghatak, A.; Das, A. K.; Chakraborty, D.; Bhar, S. in the National Symposium on Indian Chemical Industries: Retrospect and Prospect by Department of Chemistry, Jogesh Chandra Chaudhuri College, Kolkata on 27th February, 2017. (Book of Abstract was not published)

2. "C–N bond formation in wet acetonitrile using Amberlyst®-15(H) as a catalyst", Nandy, S.; Das, A. K.; Bhar, S. in the National Symposium on Current Developments in Chemical Sciences by Department of Chemistry, Jadavpur University, Kolkata on 7th March, 2018. (Poster No. P27)

3. "C–O bond formation using Amberlyst®-15(H) as a recyclable catalyst", Nandy, S.; Dinda, T. K.; Bhar, S. in the National Symposium on Chemical Sciences: Today and Tomorrow by Department of Chemistry, Jadavpur University, Kolkata on 14th March, 2019. (Book of Abstract page no. 22)

4. "Amberlyst®-15(H) – a versatile and recyclable catalyst for organic transformations", Nandy, S.; Das, A. K.; Bhar, S. in the International Symposium on Chemistry for Human Development (ICCHD-2020) by Professor Asima Chatterjee Foundation, Heritage Institute of Technology, Kolkata on 9th-11th January, 2020. (Poster No. P-017, Book of Abstract page no. 162)

CHAPTER-I

Chemoselective and metal-free synthesis of aryl esters from the corresponding benzylic alcohols in aqueous medium using TBHP/TBAI as an efficient catalytic system

CHAPTER-I

Chemoselective and metal-free synthesis of aryl esters from the corresponding benzylic alcohols in aqueous medium using TBHP/TBAI as an efficient catalytic system

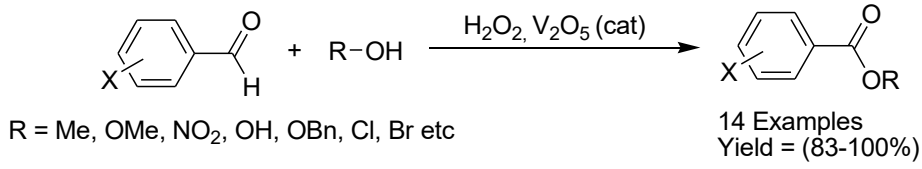
I.1. Introduction:

Esters represent an important and beneficial class of functional groups of all times with immense applications in the cosmetic industry for their characteristic smell as well as in both medicinal and pharmaceutical industries for being a part of important molecular scaffolds. Apart from widely being used as an organic solvent, polyesters are mainly used to make plastics. Some natural esters are found in pheromones that are capable of acting like hormones outside the body of the secreting individual, to influence the behaviour of another individual. Esters are used in a parallel way to make different surfactant scaffolds holding plenty of uses in our everyday life. In spite of the vivid general use, specific fatty acid esters of glycerol are mostly identified for being the constituent of naturally occurring fats and oils. Where nitrate esters, such as nitroglycerin, are recognized for their explosive properties, phosphoester is the main component to figure the backbone of nucleotide molecules. Due to this plethora of significant applications and interesting properties, development of efficient synthetic methodologies for the construction of the ester moiety has gathered important attention all over the globe till date. A concise account of current developments in this area involving mainly the oxidative transformation is being presented in the following review.

I.2. Recent methods for esterification: A Review

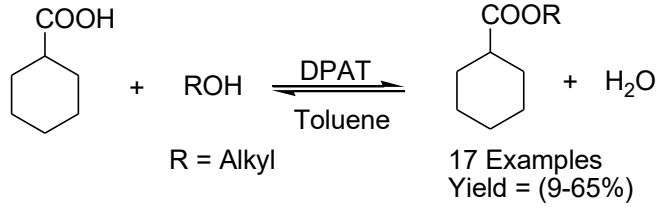
A simple yet highly efficient method was designed[1] for the synthesis of esters from the corresponding aldehydes using catalytic amounts of vanadium pentoxide in combination with hydrogen peroxide as an oxidant (Scheme 1). This method had the advantages over other methods with respect to cost-effectiveness, environmentally benign catalyst and reagent, mild reaction conditions, shorter reaction times, high efficiency and simple product isolation procedure. According to the substrate scope, the *m*- and *p*- substituents at the ring favoured the reaction while the *o*- substituents impeded suggesting that steric effect had an important role to play in the reaction pathway as it disfavoured the intermediate formation. For the nitro group as the substituent, the reaction was sluggish at first but refluxing the reaction in the water bath accelerated the reaction rate.

According to their proposition, the aldehydes were first oxidized by V_2O_5-H_2O_2 to their corresponding acid, and then esterified immediately with alcohol following a hemiacetal intermediate pathway.



Scheme 1: Esterfication of aldehydes using V_2O_5-H_2O_2

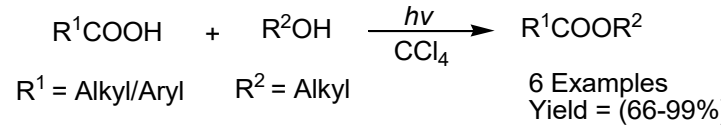
Jenner *et al*. established[2] a novel method for the esterification of bulky acids and alcohols in fluorous media, mostly in perfluorohexane, under the presence of diphenylammonium triflate (DPAT), a cheap and mild catalyst, as shown in Scheme 2. The fluorous hydrocarbons provided enhanced advantages associated with their environmental innocuity, easy recovery by simply extraction and re-usability in subsequent runs. Other fluorous compounds with higher boiling points could also serve as a medium provided that they had non-amphiphilic properties. This particular esterification process involving hindered reagents though came out as an effective method; the yields of the products were not so much satisfactory as they were less miscible resulting in hydrolysis to some extent.



Scheme 2: Esterfication of carboxylic acids using DPAT

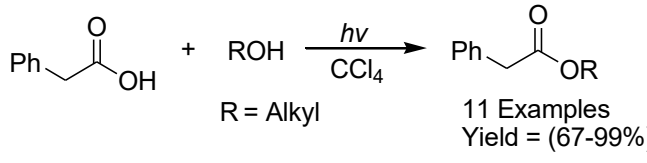
Another esterification of carboxylic acids with different alcohols in carbon tetrachloride (CCl_4) was accomplished[3] efficiently by exposing the solution to UV irradiation (Scheme 3). This photolytic reaction showed major selectivity between primary and secondary alcohols, but there was no reaction if tertiary alcohols were used as the substrates. The team performed control experiments and detected the *p*H values for the reaction medium during the photolytic conversion of phenylacetic acid and methanol to the desired ester in CCl_4 (Scheme 4).

The *p*H value was initially 4.3 but dropped to 0.30 after 3 hours. These *p*H values indicated that acids were formed during photolysis.



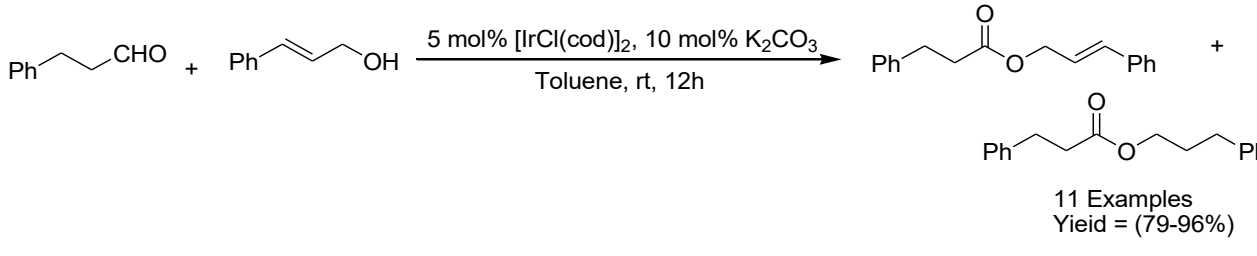
Scheme 3: Photochemical esterfication of carboxylic acids with alcohols

Thus they proposed an acid-catalyzed mechanism for the photolytic esterification where an acid was generated in-situ photochemically reacting with CCl_4 and alcohols under optimised conditions. The performance of these esterification involved easy manipulation; any Lewis acid or other mineral acid was not mandatory as the external catalyst.



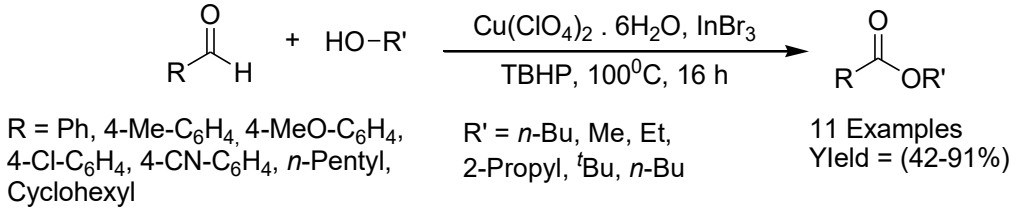
Scheme 4: Photochemical esterfication of benzylic acids with alcohols

A novel iridium-catalyzed oxidative esterification of aliphatic aldehydes with olefinic alcohols was carried out[4] by Syun-ichi Kiyooka, Mahuyu Ueno and Eri Ishii under mild reaction condition using the transition metal complex $[IrCl(cod)]_2$ (Scheme 5). In this process several aldehydes, primary and secondary allylic alcohols underwent the oxidative esterification reaction despite having the structural difference to afford the corresponding esters. According to the team the rate of reaction was drastically enhanced by the presence of a catalytic amount of base (K_2CO_3) using toluene as the solvent and taking a 1:2 molar ratio of the starting aldehyde to alcohol.



Scheme 5: Esterfication using transition metal complex $[IrCl(cod)]_2$

An oxidative esterification reaction between aldehydes and alcohols catalyzed by a combination of $Cu(ClO_4)_2$. $6H_2O$ and $InBr_3$ using *tert*-butyl hydroperoxide (TBHP) as an oxidant (Scheme 6) was reported[5] by Li *et al.* In this case both aliphatic and aromatic aldehydes were suitable for the reaction conditions and no excess alcohol was required to obtain the desired ester. But due to the oxidative nature of the reaction conditions, substrates which contain readily oxidizable functional groups, such as allylic alcohols and sulfides were not so much compatible with the reaction condition.



Scheme 6: Oxidative esterfication catalyzed by a combination of $Cu(ClO_4)_2$.$6H_2O$ and $InBr_3$

They had given a tentative mechanism for the oxidative esterification of aldehydes with simple alcohols where the reaction might go through the formation of a hemiacetal intermediate followed by oxidation using TBHP to provide the corresponding ester as shown in Figure 1.

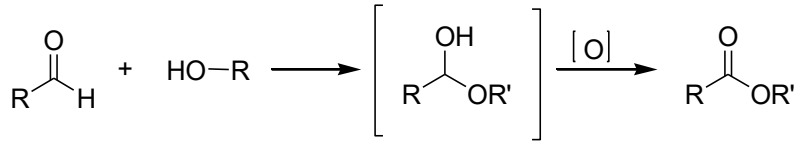
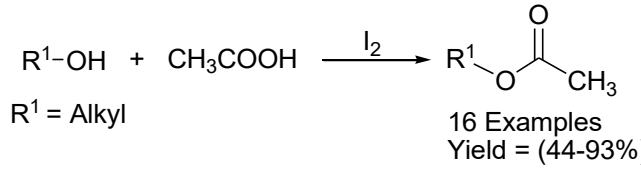


Figure 1: Mechanism for the oxidative esterfication catalyzed $Cu(ClO_4)_2$. $6H_2O$ and $InBr_3$

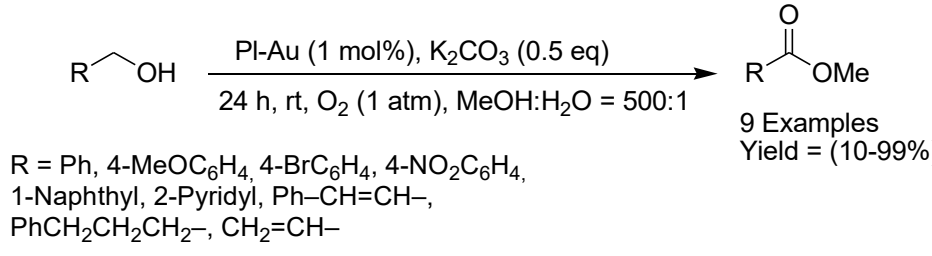
Zupan *et al.* reported[6] dual behaviour of iodine for the oxidative transformation of alcohols to their corresponding acetate esters under solvent-free reaction conditions (Scheme 7). They investigated both the electronic and steric effects of the substituents on benzylic alcohol and observed reaction with acetic acid even without I_2, but the conversion in presence of I_2 was higher. This method was surprising as water had a modest deteriorating influence on the reaction. The experimental results strongly suggested that at first iodine activated the alcohol forming a cationic intermediate which subsequently led to the product.

It was established that primary and secondary benzylic alcohols were more reactive than aliphatic alcohols, while the introduction of a methoxy group further increased the reactivity to a subtle extent.



Scheme 7: Esterfication catalyzed by molecular I_2

Kobayashi *et al.* reported[7] an aerobic oxidative technique for the esterification of primary alcohols using a polymer-incarcerated gold nanocluster catalyst (Scheme 8). Notable feature of this reaction was that it took place at room temperature under normal atmospheric conditions. Moreover, the catalyst could be recovered by simple filtration followed by washing with water and MeOH and could be reused for a few times by cautious handling with marginal loss of catalytic activity, thus having the advantages in terms of energy efficiency and green chemistry.



Scheme 8: Aerobic oxidative esterfication using a polymer-incarcerated gold nanocluster catalyst

They also performed kinetic experiments and proposed the mechanism through a hemiacetal pathway (Figure 2).

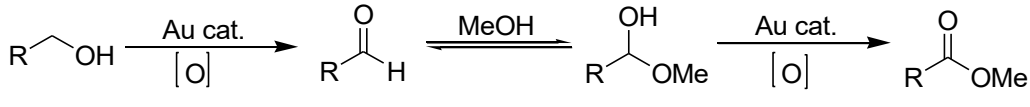
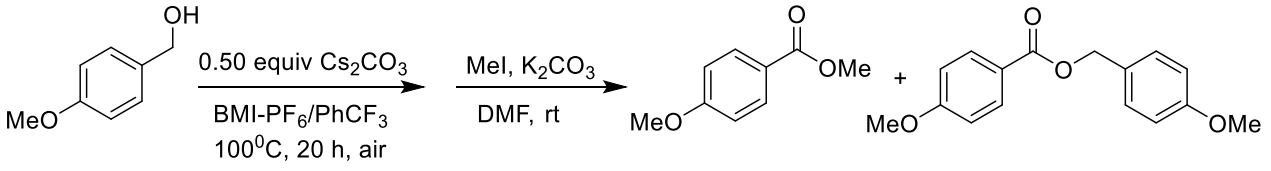


Figure 2: Proposed mechanism for the aerobic oxidative esterfication

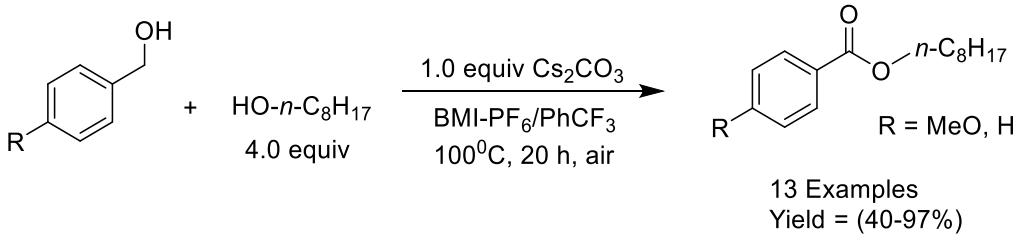
Several transition-metal-free strategies were also implemented to achieve the self and cross esterification reaction, among which a BMI-PF_6 promoted aerobic esterification along with

oxidation of benzylic alcohols to aryl ketones was developed[8] by Miura and his group (Scheme 9 and Scheme 10).



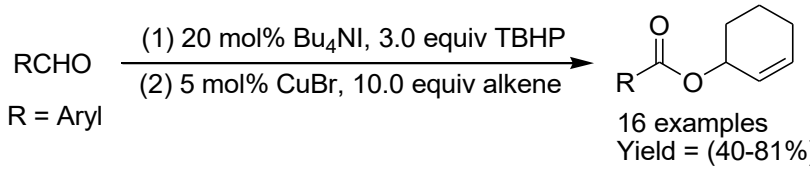
Scheme 9: Aerobic oxidative self esterfication using BMI-PF_6

The aerobic oxidation system was highly advantageous from the viewpoint of atom economy but here also the attempt to apply this protocol for the esterification of aliphatic and allylic alcohols remained unsuccessful. Although the exact mechanism was not disclosed, the outcome in their results suggested the efficiency of the ionic liquid-promoted aerobic oxidation system.



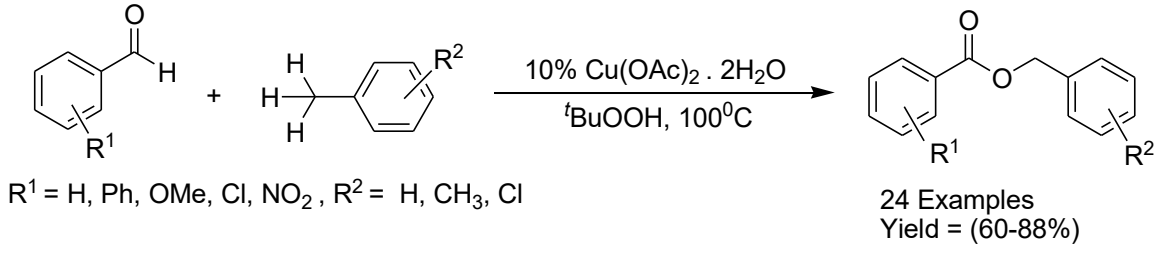
Scheme 10: Aerobic oxidative cross esterfication using BMI-PF_6

Wan *et al.* implemented[9] the combination of the aldehyde C-H oxidation and the Kharasch-Sosnovsky reaction unlocking a novel way for the generation of allylic ester directly from simple olefins and aldehydes via. a two-step one-pot procedure as shown in Scheme 11. Here the first step was the C-H oxidation of aldehydes followed by CuBr catalyzed allylic oxidation of alkene, leading to the formation of required allylic esters in good yields. They suggested about an acyl radical mediated catalytic cycle for the transformation.



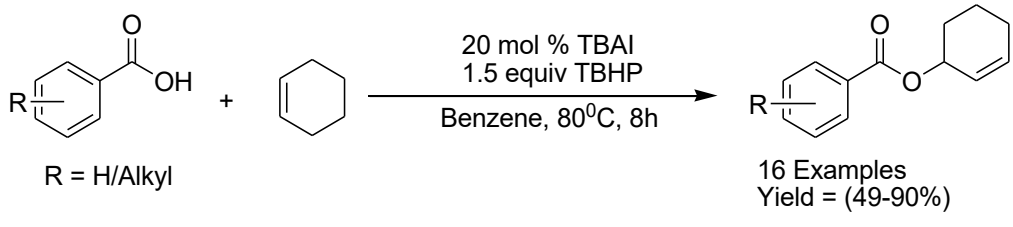
Scheme 11: Allylic esterfication via a two-step one-pot procedure

Patel and his group reported[10] a CDC (cross dehydrogenative coupling) based approach for the formulation of benzylic esters from aryl aldehydes and alkylbenzenes using Cu(II) as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme 12). The necessity of both the copper catalyst and the oxidant was confirmed as no desired product was obtained when H_2O_2 was used as an oxidant instead of TBHP. The experiments carried out with either a copper catalyst or TBHP at a single time did not serve the purpose, as no formation of the product could be detected. After indulging several substrates to the reaction protocol it was observed that aldehydes with electron-donating substituents gave much high yields of benzylic esters within a shorter time, but with electron-withdrawing substituents, the reaction proceeded slowly providing the desired product in only moderate yields.



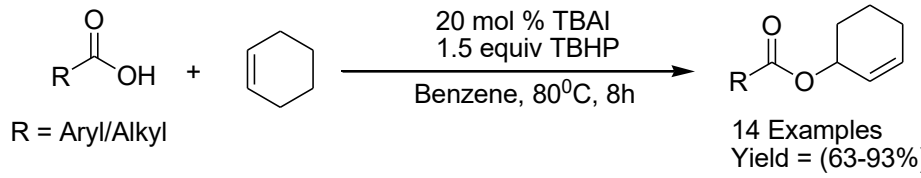
Scheme 12: Formation of benzylic esters from using Cu(II) acetate and *tert*-butyl hydroperoxide

Wan and his team successfully developed[11] the metal-free allylic ester synthesis allowing selective coupling of acyloxy and allylic radicals using TBAI as a commercially available and inexpensive catalyst and TBHP as a readily available oxidant without requiring an inert atmosphere (Scheme 13).



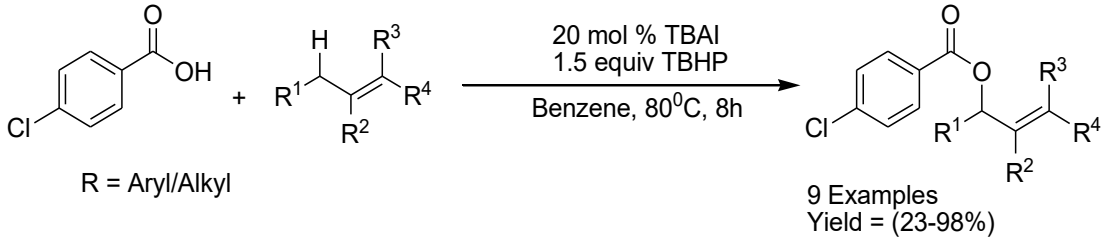
Scheme 13: Formation of esters using TBHP/ TBAI in benzene from aryl carboxylic acids

In this process both electron-donating and electron withdrawing aryl carboxylic acids were successfully converted to their corresponding allylic esters in good to excellent yields thus having the advantage of high level functional group tolerance. Alkanoic acids also participated efficiently in this protocol (Scheme 14).



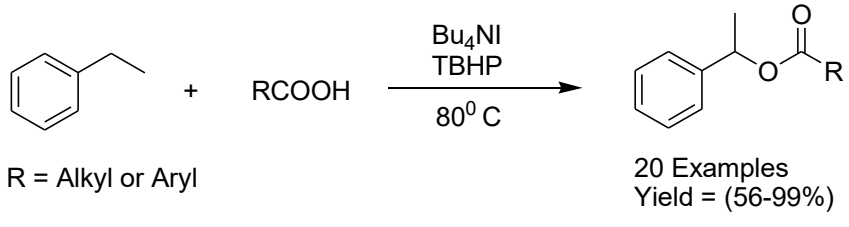
Scheme 14: Formation of esters using TBHP/ TBAI in benzene from alkyl carboxylic acids

In fact, under this reaction pathway several alkenes reacted successfully for their allylic ester synthesis; making the strategy recognised as the first reported example of allylic C-H oxidation using tetrasubstituted alkenes as reactants (Scheme 15). Based upon their results, it was thought that the reaction involved the coupling of acyloxy and allylic radicals in the catalytic cycle for the allylic ester synthesis.



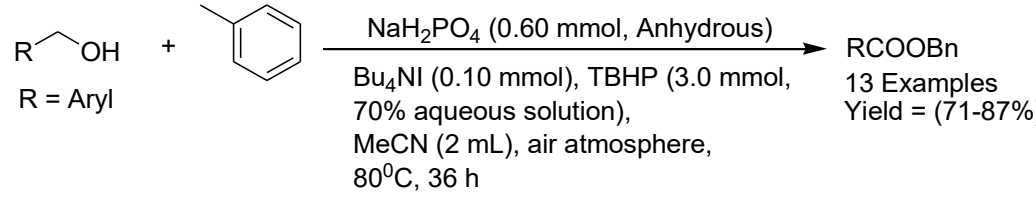
Scheme 15: Formation of esters using TBHP/TBAI from halogenated aryl carboxylic acids

Feng *et al*. came up[12] with a direct esterification process of benzyl C-H bond using TBHP as co-oxidant and tetrabutyl-ammonium iodide (TBAI) as an effiecient catalyst (Scheme 16). This catalytic system was metal-free and compatible for coupling reactions between large numbers of carboxylic acids with several benzyl substrates. Even the protocol was conveniently applied for benzyl protection of amino acids at the oxygen centre. Additionally, non-protected amino acids did not furnish the ester product depicting that free amino group was not suitable for the reaction. They also executed control experiments based on which a catalytic cycle involving radical intermediate was proposed.



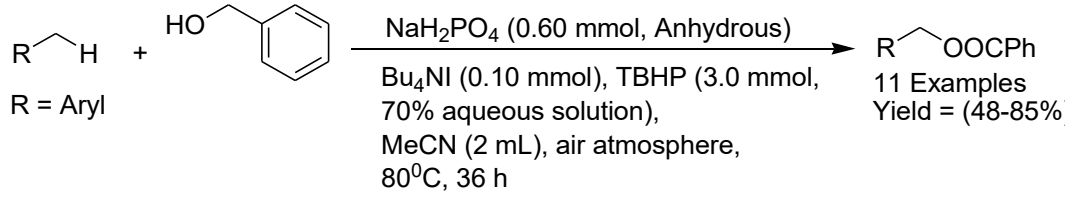
Scheme 16: Metal-free oxidative esterification of the benzyl C-H bond

A transition metal-free direct esterification of alcohols with toluene was proposed[13] by the team of Chun-hua Yan using Bu_4NI as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant. The mechanistic investigations indicated that the alcohols were sequentially oxidized to aldehydes, carboxylic acids, and then to benzyl esters in single pot with good to excellent yield (Scheme 17).



Scheme 17: Conversion of alkanes to benzyl esters using TBHP and Bu_4NI

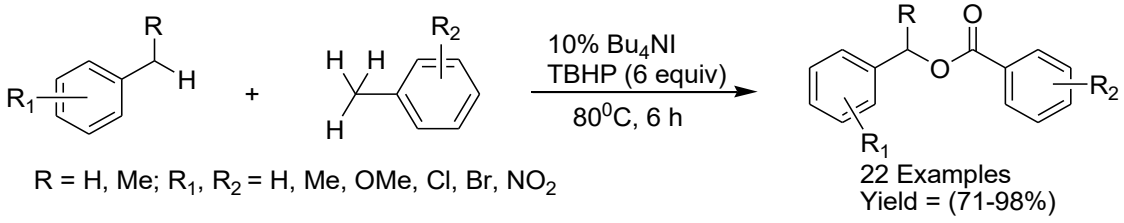
This protocol provided another novel strategy for the rational design and functionalization of sp^3 C–H bonds with a varied range of suitable substrates including good tolerance of halogens and heteroatoms of carboxylic acid and toluene to form phenyl ester (Scheme 18). As suggested by the team, the esterification reaction occurred through a sequential oxidation involving a radical initiated oxidation of alcohol to aldehyde followed by the oxidation of aldehyde to carboxylic acid via a carbonyl radical intermediate then finally the oxidative coupling. They also proposed a dual role of Bu_4NI helping the reaction in two ways; while Bu_4N+ cation functioned as the phase-transfer reagent the counter anion iodide acted as a catalyst as the employment of Bu_4NBr led to a drastic decrease of the product yield.



Scheme 18: Conversion of primary alcohols to phenyl esters using TBHP and Bu_4NI

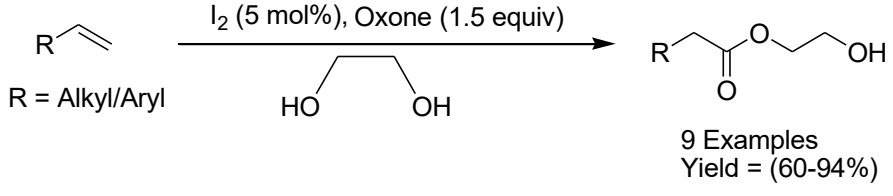
Patel and his team reported[14] another CDC based technique under TBAI/TBHP conditions, where the pathway led to the synthesis of symmetrical as well as unsymmetrical benzyl ester involving the cleavage of four sp^3 benzylic C–H bonds (Scheme 19). Under the reaction condition, toluene molecules possessing electron-withdrawing substituents provided the respective benzylic esters in good yields but the reactions were a bit slow. The sluggishness

was well reflected with the substrate bearing strongly electron withdrawing group as NO_2 in toluene as it gave a poor yield of the desired ester. Moreover, even for di/tri-alkylated benzenes only monoesterification was observed and no trace of diesters was recorded.



Scheme 19: Synthesis of symmetrical as well as unsymmetrical benzyl ester

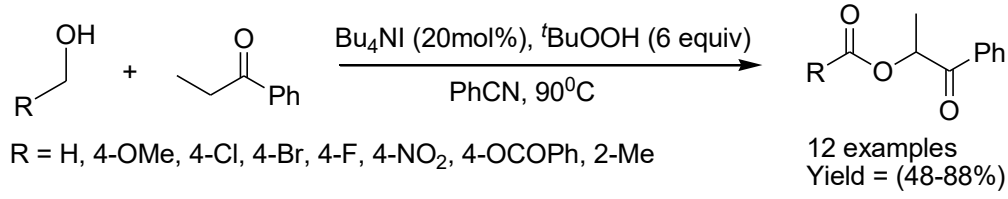
A remarkably mild, efficient, selective, metal-free and one-pot procedure was reported[15] for the preparation of glycol mono esters from olefins by using iodine and oxone as the oxidative reagent system. Styrene produced the desired product with excellent yield in just 1.3 h. but, relatively longer reaction times were required for activating or deactivating groups present on the aromatic ring of styrene to provide high yields (Scheme 20). It was assumed that there was an electrophilic addition of iodine on the olefin to give a three membered cyclic iodonium ion intermediate which underwent nucleophilic ring opening by ethylene glycol to finally form the ester. This was distinguished as one of the few procedures where alkenes were successfully converted to esters having well to excellent yields.



Scheme 20: Synthesis of of glycol mono esters from olefins by using iodine and oxone

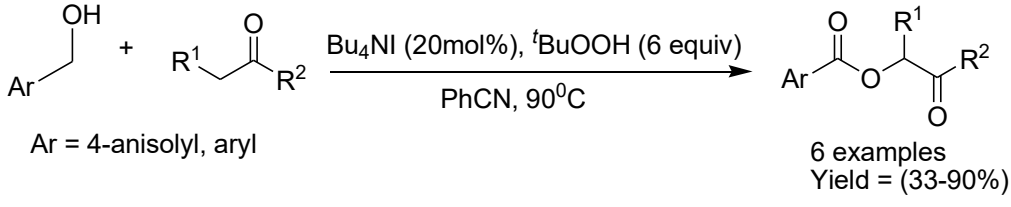
Jiang Cheng and his team developed[16] a TBAI-catalyzed α-acyloxylation reaction of ketones with benzylic alcohols using TBHP as an oxidant (Schemes 21 and 22). The reaction was independent of the electronic nature of the benzylic alcohols as both electron-withdrawing and electron-donating substrates worked well to produce the corresponding α-acyloxylated products in moderate to excellent yields.

Even, halogens like chloro and bromo also survived under this procedure. Aliphatic alcohol such as isobutyl alcohol also provided the desired product, though the yield was a little low. Steric hindrance had a little effect on this transformation, as visualised by the high yield of the corresponding esters.



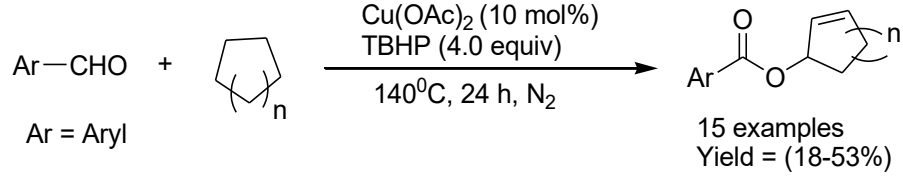
Scheme 21: α-acyloxylation reaction of phenyl ketones with primary alcohols

Based on the experimental results, a plausible mechanism was proposed either involving the oxidation of TBAI by TBHP, then abstraction of α-H of the ketone to produce the α-carbonyl radical, or involving the oxidation of benzylic alcohol in presence of TBHP which subsequently converted to the *tert*-butyl perester. This procedure focused on the wide application of commercially available starting materials as an alternative to existing transition metal catalysed reaction conditions.



Scheme 22: α-acyloxylation reaction of ketones with primary alcohols

Pan *et al.* reported[17] novel example of Cu-catalyzed dehydrogenation-olefination and esterification of C(sp^3)-H bond of cycloalkanes along with aromatic aldehydes in the presence of TBHP as the oxidant (Scheme 23). A wide range of aromatic aldehydes were examined under this process to generate their corresponding cycloallyl esters.



Scheme 23: Cu-catalyzed dehydrogenation-olefination and esterification

Benzaldehyde with electron-donating alkyl groups on the phenyl ring, reacted easily with cyclohexane and gave the desired products in moderate yields, but with electron withdrawing groups, such as Br, Cl, and NO_2 the yields dropped significantly. Based on the experimental data, they further proposed a plausible mechanism (Figure 3), including the dehydrogenation-olefination of cycloalkanes followed by CDC.

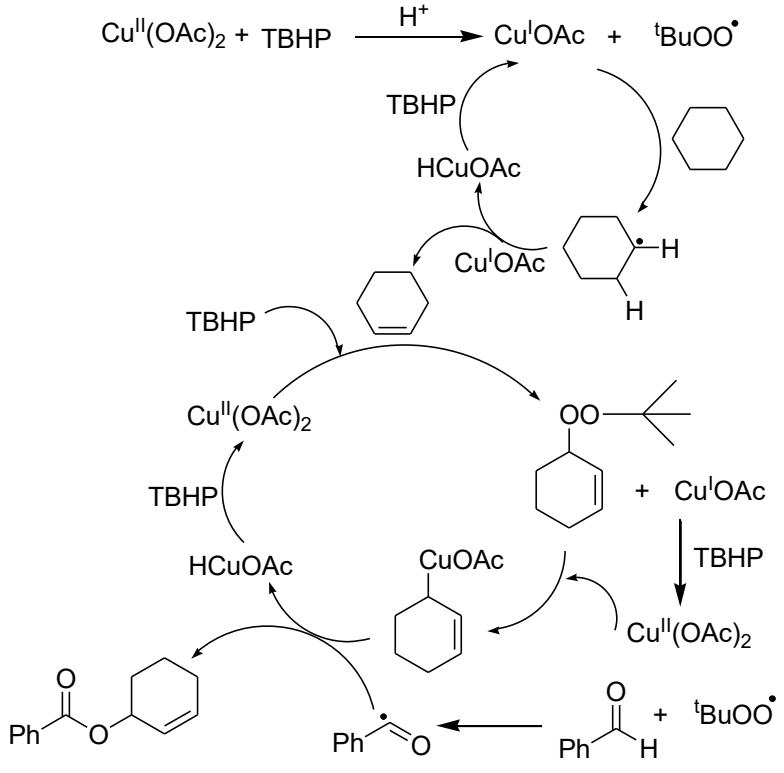
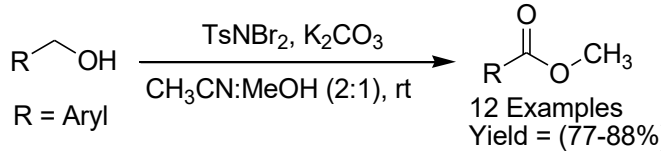


Figure 3: Mechanism of Cu-catalyzed dehydrogenation-olefination and esterification

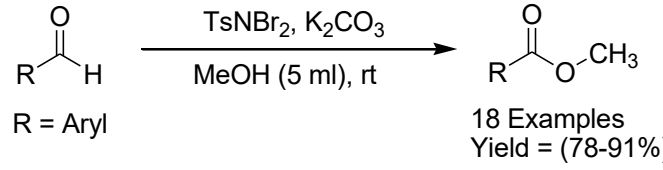
A simple, fast and efficient procedure for the direct conversion of alcohols and aldehydes to their corresponding methyl ester was also developed[18] using $TsNBr_2$ without any use of catalyst (Scheme 24).



Scheme 24: Synthesis of methyl esters from primary alcohols

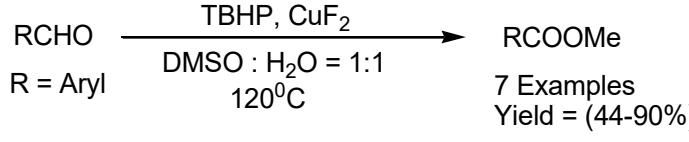
This one-pot reaction was promoted in the presence of a base (K_2CO_3) at room temperature in methanol, as the reaction in the absence of base gave very poor yield of the product.

In most of the cases, the reaction required very less time to produce the corresponding methyl ester in excellent yield (Scheme 25). Further investigation suggested the use of a 2:1 mixture of acetonitrile and alcohol produced the ester with maximum yield.



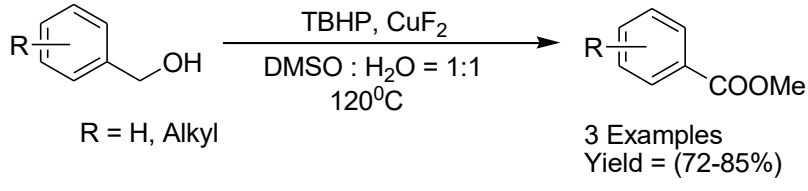
Scheme 25: Synthesis of methyl esters from aldehydes

Copper-catalyzed oxidative transformation of methyl esters from aromatic aldehydes (Scheme 26) and primary alcohols (Scheme 27) was reported[19] by Li *et al.* in the presence of TBHP where the reaction followed a radical reaction mechanism. Other metal catalysts for oxidation, such as iron, silver, palladium, ruthenium and rhodium were found to be ineffective for this protocol.



Scheme 26: Synthesis of methyl esters from aldehydes using TBHP

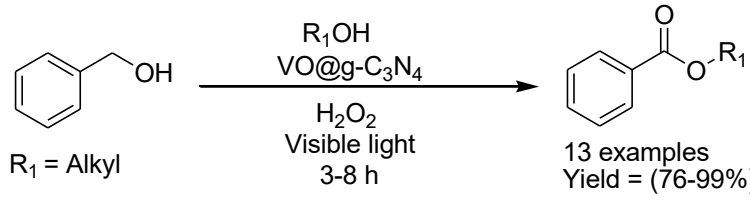
In this particular case TBHP not only acted as an efficient oxidant, but also as a potential methyl source. The catalytic procedure was also counted as a sustainable alternative to the procedure where mostly noble metal and base are required for such transformation.



Scheme 27: Synthesis of methyl esters from primary alcohols using TBHP

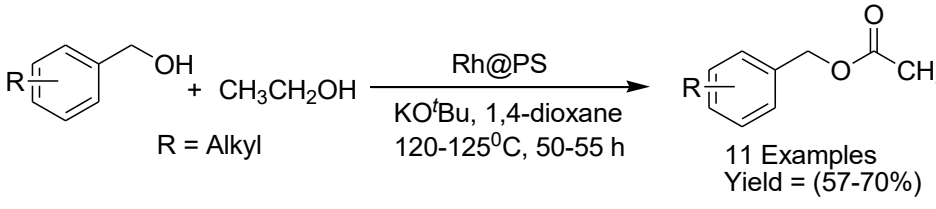
A simple and competent method for the esterification of alcohol via photocatalytic C–H activation was accomplised[20] by Verma *et al.* using oxovanadium–graphitic carbon nitride

(VO@g-C_3N_4) as a suitable catalyst (Scheme 28). They performed thorough study on the direct oxidative esterification of aromatic primary alcohols using a range of metal catalysts supported over graphitic carbon nitride under visible light irradiation. The optimised method of the esterification of alcohols utilised the oxo-vanadium complex with the in-built nitrogenous framework which provided an adequate mild basic environment using visible light as the source of energy.



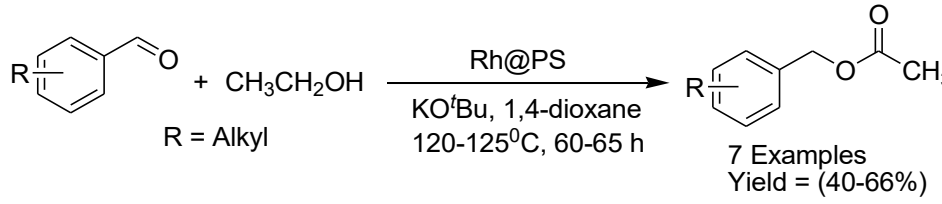
Scheme 28: Synthesis of esters from primary alcohols using VO@g-C_3N_4

Das *et al.* established[21] the application of polystyrene stabilized rhodium (Rh@PS) nanoparticles as supported catalyst, promoting oxidative "reverse-esterification" of ethanol and benzyl/alkyl alcohols (Scheme 29) or aldehydes (Scheme 30) to their corresponding acetate esters following a very unusual and unexplored pathway in a one pot consecutive approach. Here the catalyst system exhibited a slow and sustainable process for the oxidative esterification under *in situ* redox reaction conditions using tandem strategy.



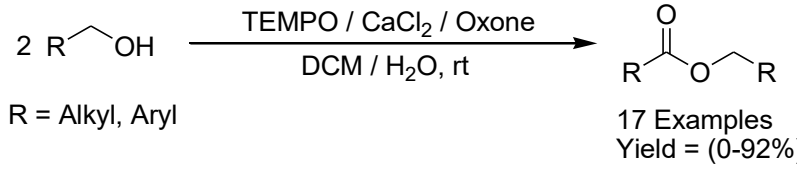
Scheme 29: Synthesis of methyl esters from primary alcohols using Rh@PS

The team demonstrated that the catalyst retained its catalytic activity up to six cycles of reaction with minor loss of catalytic activity due to metal leaching. They performed several cross studies to understand the intermediates and reaction mechanism and found that without ethanol, benzyl alcohol was oxidized to benzaldehyde, which showed that ethanol here played a crucial role not only in preventing the oxidation of primary alcohols as well as promoting their facile nucleophilic attack for generating the ultimate product.



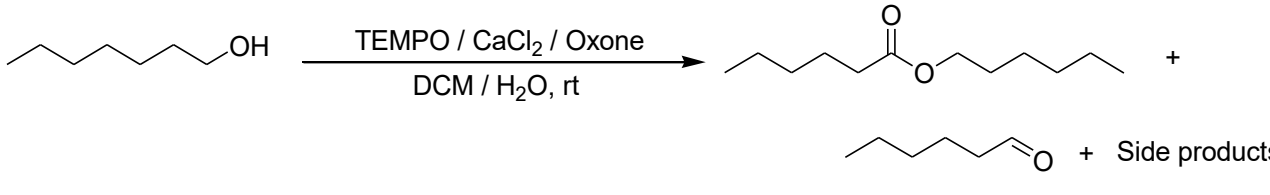
Scheme 30: Synthesis of methyl esters from aldehydes using Rh@PS

Franz *et al.* formulated[22] a convenient catalytic system for the synthesis of symmetrical esters starting from primary alcohols (Scheme 31) in a biphasic dichloromethane–water solvent mixture using a combination of TEMPO, $CaCl_2$ and Oxone. Moreover, the reaction was metal-free and did not require any anhydrous condition. But, this reaction was not so much successful in case of cross-esterification where the main products were the corresponding to those obtained by self-esterification.



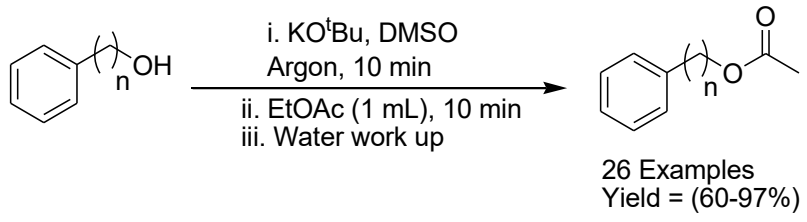
Scheme 31: Synthesis of symmetrical esters starting from primary alcohols

This reaction protocol had certain drawbacks as a mixture of products containing hexanal, hexyl hexanoate and other un-identified by-products was obtained from the aliphatic alcohol, namely, hexanol (Scheme 32). Alcohols containing β-oxygen substitution failed to give the products with promising yields. In the same way, alcohols with ketone and ester functionalities at the β-position did not give the desired esterification products.



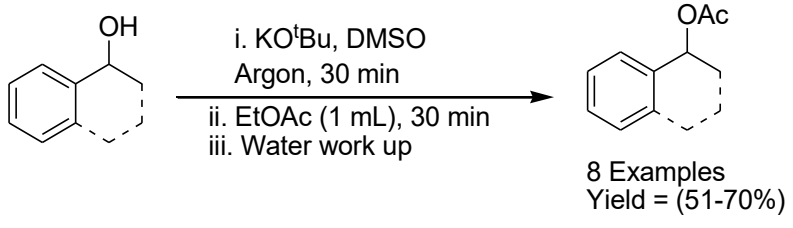
Scheme 32: Synthesis of alkyl symmetrical esters starting from primary alcohols

Ray *et al.* reported[23] a KO^{t}Bu and ethyl acetate (EA) mediated competent methodology for the acetylation of acyclic (Scheme 33) and alicyclic (Scheme 34) alcohols at room temperature using EA as the source of acetyl moiety. It was noted that the electron rich substrates gave a higher yield than electron deficient substrates, while the halogen containing substrates gave the products in comparatively fair yields.



Scheme 33: Acetylation of acyclic primary alcohols

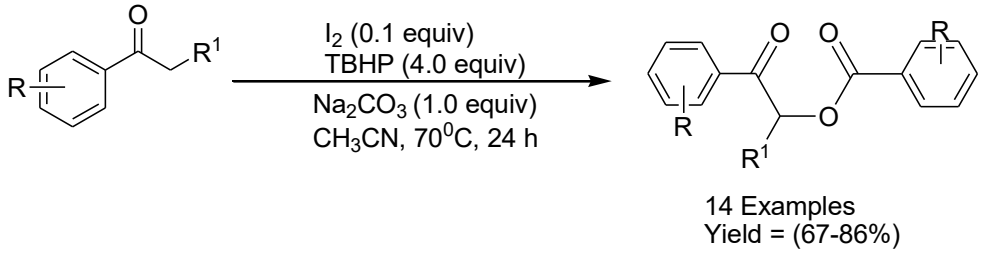
The thiophene-2-ylmethanol and furan-2-ylmethanol were converted to the products in lower yields might be due to the decomposition of such substrates under basic conditions. Though the reaction procedure was mild, fast, highly efficient and quite applicable for a range of aliphatic, benzylic, allylic and propargylic alcohols, from the thorough experimental studies only primary alcohols came out as the most preferred substrates.



Scheme 34: Acetylation of cyclic alcohols

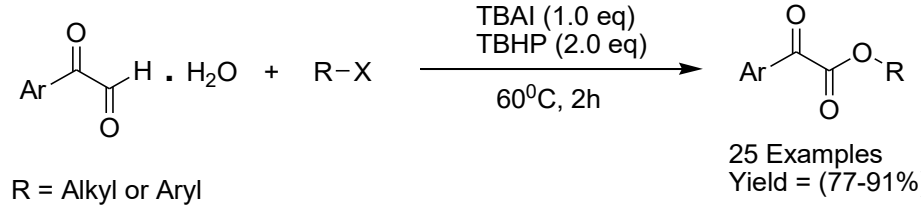
I_2–TBHP was also utilised[24] as an effective oxidative system for the construction of α-acetoxyaryl ketones from aryl ketones via intermolecular oxidative self-coupling which under the optimum reaction condition reacted with various aryl ketones to give the corresponding products in fair to excellent yield (Scheme 35). This was one of the pioneering examples for using TBHP as the oxidant for the construction of α-acetoxyaryl ketones via intermolecular oxidative self-coupling. The reaction condition used to furnish the desired product was mild and the substrate scope was also quite large.

Along with this, though a series of control experiments were performed to justify the reaction mechanism indicating mostly a radical pathway, the mechanism was not clarified in details.



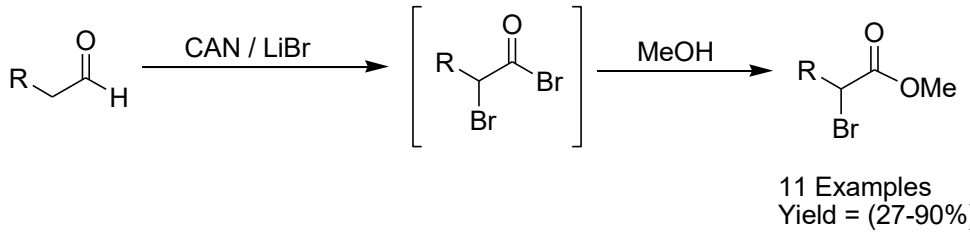
Scheme 35: Synthesis of α-acetoxyaryl ketones from aryl ketones

The TBHP/TBAI system was again utilised[25] for another efficient synthesis of α-ketoesters from α-carbonyl aldehydes and alkyl halides under metal-free conditions. This strategy involved the oxidative esterification of aldehydes with alkyl halide using TBAI as promoter and TBHP as terminal oxidant (Scheme 36). The resultant α-ketoesters were produced in less reaction time providing remarkable product yield with huge substrate scope. Use of inexpensive and commercially available substrates, high substrate scope and functional group tolerance were the noteworthy features of this particular procedure.



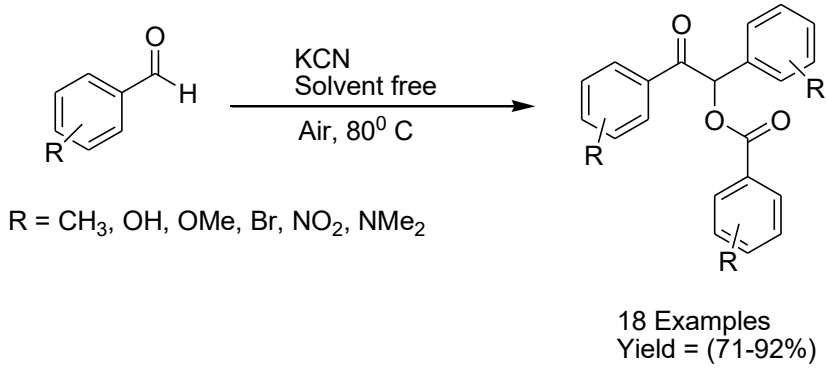
Scheme 36: Oxidative esterification of a-carbonyl aldehydes and alkyl halides

Nikishin *et al.*introduced[26] a solvent-free oxidation system involving Cerium (IV) ammonium nitrate (CAN) and LiBr, which after the addition of methanol afforded methyl α-bromocarboxylates following a two-step, one-pot pathway (Scheme 37). This method of preparing the methyl esters was quite facile and without any special equipment facility it was able to generate 2-bromoesters from aliphatic aldehydes from 5 to 10 carbon chain lengths.



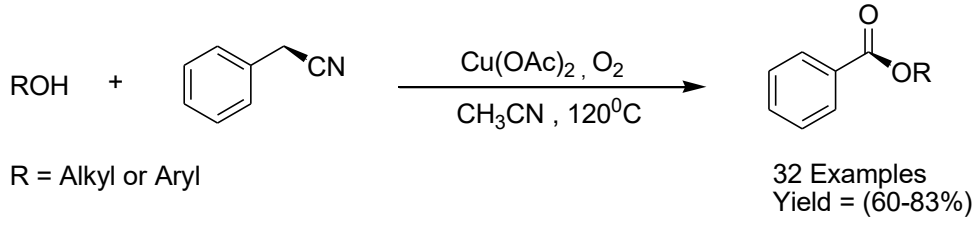
Scheme 37: Synthesis of methyl esters from aldehydes with CAN / LiBr

An aerobic oxidation of aromatic aldehydes in presence of potassium cyanide under no solvent condition was reported[27] by Elham *et. al*. to generate the corresponding esters with high yields (Scheme 38). This simple and convenient technique was applicable to a number of aromatic aldehydes. For finding out the mechanism when benzoin was treated with benzaldehyde without potassium cyanide, there was no esterified product, but in the presence of cyanide salt, the esters were obtained with satisfactory yield assuming the association of benzoyl cyanide. This procedure carefully avoided toxic and explosive organic solvents using air as the safe oxidant.



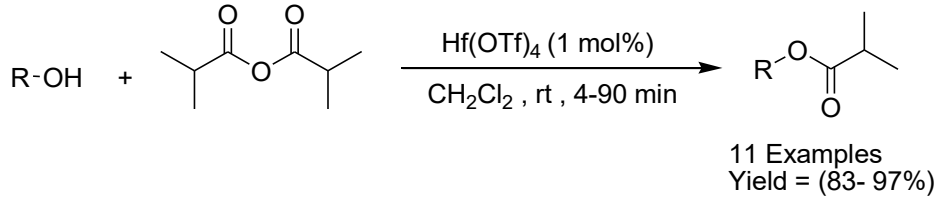
Scheme 38: KCN catalyzed aerobic oxidation of aromatic aldehydes

Another simple and efficient methodology for aerobic oxidative esterfication[28] by copper salt was applied for easily available arylacetonitrile derivatives and alcohols or phenols without any additives (Scheme 39). In this reaction a lower loading of the copper salt was used for alcohols and a higher loading of copper salt was used for phenols. The current process successfully promoted C-H bond oxygenation, C-C bond activation along with C-O bond formation successively in one pot providing a variety of functionalized esters.



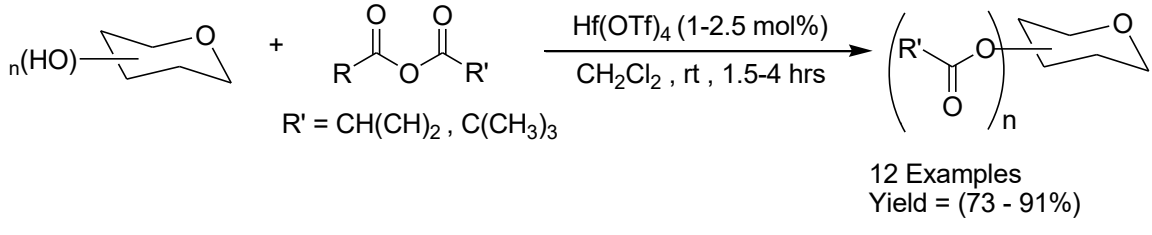
Scheme 39: Cu-mediated direct aerobic oxidative esterification

A highly efficient protocol was developed[29] for activating hindered acid anhydrides and to direct the reaction towards acylation using hafnium triflate catalyst in DCM (Scheme 40).



Scheme 40: Synthesis of esters from alcohols using $Hf(OTf)_4$

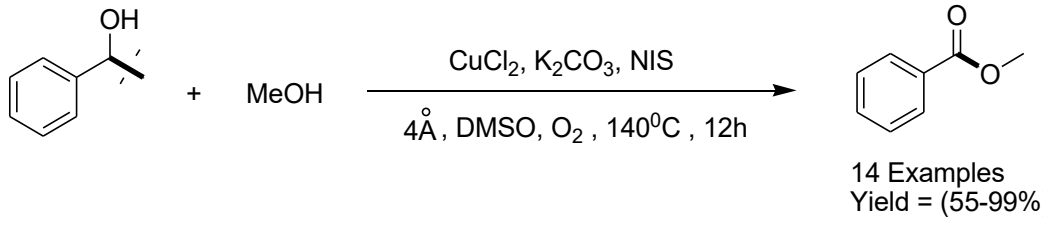
The versatile procedure was mild and able to proceed at room temperature extending its scope to different alcohol substrates including sterically crowded ones as well as carbohydrate derived polyols generating the corresponding esters in good to excellent yields (Scheme 41).



Scheme 41: Synthesis of bulky esters from alcohols using $Hf(OTf)_4$

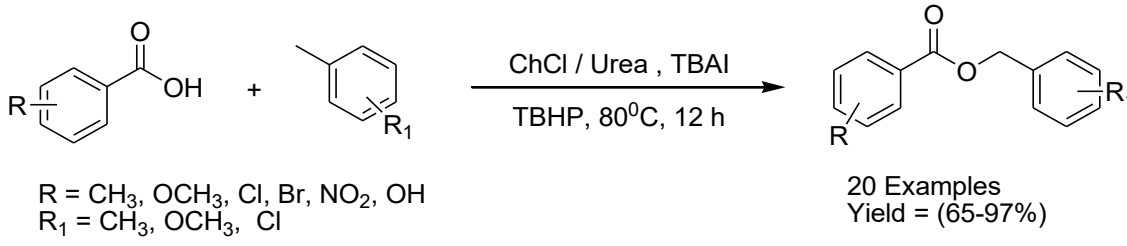
Han and his team developed[30] a novel and selective method to functionalize C(OH)–C bonds using environmentally safe O_2 as the oxidant and commercially available copper salts as catalysts to provide esters with excellent yields (Scheme 42).

A wide range of phenylethanol derivatives containing C(OH)–C bonds were efficiently converted into corresponding methyl benzoates. The selective cleavage and esterification was catalyzed by inexpensive copper salts where the mechanistic study indicated that inspite of the major esterification route; olefins and acids were obtained as side products under the oxidative condition.



Scheme 42: Aerobic oxidative esterification catalyzed by copper salts

Moayyed *et al*. utilised[31] ChCl/urea in TBHP/TBAI for the construction of substituted benzyl benzoates. Several conventional benzoic acids, cinnamic acid along with 2-naphthanoic acid were converted to their corresponding esters using toluene in high yields. *o*-xylene and *p*-xylene participated successfully in the esterification reaction with no mixture of products. But gallic acid failed to do the reaction in toluene and was quantitatively recovered after the stipulated time.



Scheme 43: Oxidative esterification of carboxylic acids in Choline chloride/Urea

Thus, a comprehensive overview of recent protocols for esterification reaction with a plethora of reagents, solvents and catalysts has been presented to substantiate the importance, necessity and timeliness of the present investigation going to be described in the next section.

I.3. Present investigation:

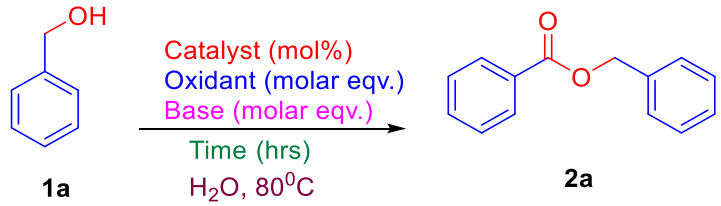
I.3.1. Background of the investigation:

The choice of a suitable solvent for a desired synthetic pathway can have profound economic and environmental implications from the standpoint of 'Green Chemistry'. In order to proceed for a 'sustainable future' aqueous medium has drawn considerable attention[32] not only due to its innocuous, inexpensive and non-flammable nature but also its widespread applicability, unique reactivity and excellent selectivity imposed to the reaction outcome. Therefore, the development of an efficient and eco-compatible method for an organic reaction in aqueous medium constitutes an essential and formidable target to the synthetic organic chemists in recent times.

Oxidative transformation where α-acyloxycarbonyl compounds are prepared by the reaction of different alcohols to form highly useful ester functionality is of great demand in the present scenario and several protocols have been suggested for this reaction. But many of the previously reported methods suffer from drawbacks, such as, moisture-sensitivity of the sophisticated reagent systems,[4, 5, 8, 18, 21, 24] relatively long reaction time,[4, 5, 7, 8, 13, 16, 19, 21, 22, 24] involvement of exotic reagents containing expensive metals,[4, 7, 19, 20, 21, 22] lack of chemoselectivity,[4, 7, 8, 20, 21, 22] formation of by-products and limited applicability to selected domain of substrates.[4, 7, 8, 13, 19, 22] Therefore, our intention was to develop of a highly chemoselective metal-free oxidative protocol for esterification of a number of primary alcohol. As a part of our recent explorations[33] in the field of organic transformations in aqueous medium we have developed a novel, highly chemoselective, metal-free oxidatative protocol transformations of primary benzylic alcohols employing by combination of TBHP, TBAI and imidazole to obtain a variety of aryl esters in aqueous medium. The detailed investigation is being presented in the following sections.

I.3.2. Results and Discussion:

The efficiency of TBHP-TBAI couple towards the proposed reaction was checked by carrying out the reaction with benzyl alcohol (1 mmol) using H_2O_2 and TBHP (2 mmol) as the oxidant in presence of various catalysts along with different bases in water at 80^oC to obtain the product benzyl benzoate (**2a)** (Scheme 36), as presented in Table 1.



Scheme 36: Reaction of benzyl alcohol using different catalyst, oxidant and base in aqueous medium

Table 1: Optimization of esterification of benzyl alcohol

Entry	Catalyst	Mole (%)	Oxidant	Molar equiv.	Base	Molar equiv.	Time (h)	Yield of 2a (%)
1	KI	10	H_2O_2	1	KOH	2	8	-
2	KI	10	H_2O_2	2	KOH	4	10	-
3	I_2	10	H_2O_2	1	K_2CO_3	2	10	-
4	I_2	10	H_2O_2	2	K_2CO_3	4	10	Trace
5	TBAI	10	TBHP	1	Imidazole	1	6	65
6	TBAI	15	TBHP	2	Imidazole	2	8	73
7	**TBAI**	**20**	**TBHP**	**2**	**Imidazole**	**2**	**8**	**86**
8	TBAI	15	TBHP	3	Imidazole	3	8	74
9	TBAB	20	TBHP	2	Imidazole	2	8	24[a]
10	KBr	20	TBHP	2	Imidazole	2	8	-
11	SDS	20	TBHP	2	Imidazole	2	8	-
12	TBAI	20	-	-	Imidazole	2	8	9[b]
13	TBAI	20	TBHP	2	Imidazole	2	8	12[c]
14	TBAI	20	H_2O_2	2	Imidazole	2	8	-

[a] Extent of unreacted alcohol, aldehyde, ester is 34%, 42% and 24% respectively by 300 MHz ^{1}H NMR

[b] Extent of unreacted alcohol and ester is 91% and 9% respectively, no aldehyde was detected by 300 MHz ^{1}H NMR

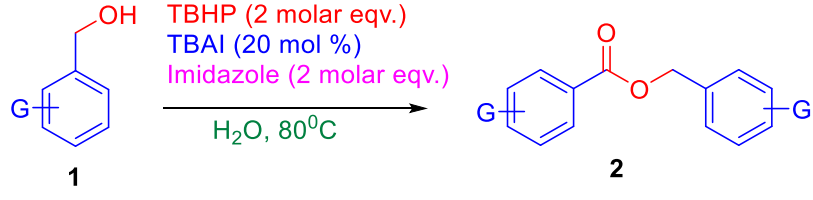
[c] The reaction was carried out under inert (argon) atmosphere and the extent of unreacted alcohol, aldehyde, ester is 47%, 41% and 12% respectively by 300 MHz ^{1}H NMR

The reaction did not occur in the absence of either any iodide salt or a base. Initially H_2O_2 was used as oxidant using KI as catalyst and KOH as the base in different molar proportions, but no reaction did not take place (Entries 1 and 2 in Table 1). When I_2 and K_2CO_3 were used for their respective purpose the results were not satisfactory (Entries 3 and 4 in Table 1). In the contrary, TBHP in the presence of TBAI (as iodide source) and imidazole (as the base) at different relative concentrations promoted the oxidative transformation of **1a** more efficiently

and produced **2a** with better yield (Entries 5 to 8 in Table 1). Most satisfactory result was obtained following the stoichiometry corresponding to the Entry 7 in Table 1 which was subsequently selected as the optimized condition for further reactions in order to extend the substrate scope and establish the general applicability as well as the selectivity of the aforesaid protocol. This reaction was less effective with TBAB and extent of alcohol, aldehyde and ester was detected in the reaction mixture as 34%, 42% and 24% respectively (Entry 9 in Table 1). The reaction did not take place at all using KBr instead of TBAB (Entry 10 in Table 1). Similarly, using SDS as a surfactant in place of quaternary ammonium halides ended up with no transformation of the substrate (Entry 11 in Table 1).

It is very important to note that the reaction was much slower in the presence of aerial oxygen as the sole oxidant in the absence of TBHP, but no aldehyde was detected in the reaction mixture although the extent of conversion of the substrate was very low (Entry 12 in Table 1). Similarly, this reaction with TBHP under inert (Ar) atmosphere in the absence of aerial oxygen was quite sluggish and the extent of unreacted alcohol, aldehyde and ester was detected as 47%, 41% and 12% respectively (Entry 13 in Table 1). Benzyl alcohol was also treated with TBAI and H_2O_2 in the presence of imidazole. No conversion was noted in the aforesaid reaction and benzyl alcohol was recovered totally unaffected (Entry 14 in Table 1). Therefore, simultaneous necessity of TBHP and aerial oxygen towards this oxidative transformation has been firmly established along with a quaternary ammonium iodide. This reaction bodes for eco-compatibility in terms of the reaction medium (water), limited toxicity of the reagents and involvement of acceptable organic solvent (ethyl acetate) for the isolation of product during work-up and recyclability of TBAI.

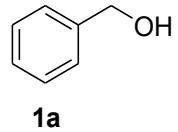
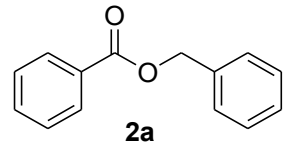
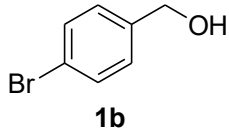
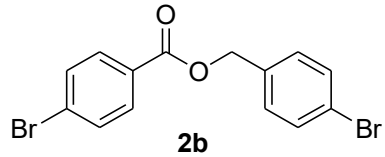
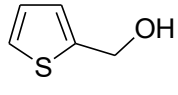
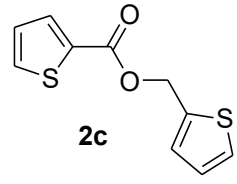
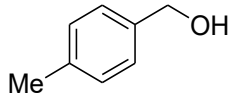
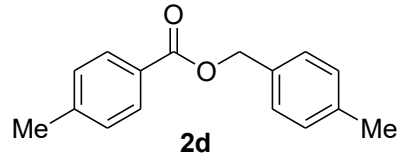
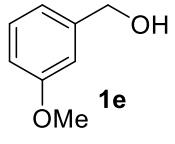
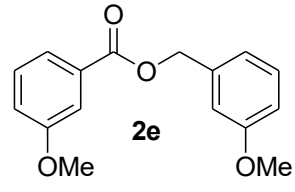
As a continuity of this theme, benzyl carbinols **1** with different substituents at the aromatic ring were subjected to the oxidative reaction under the optimized condition (Scheme 37) where the corresponding benzyl benzoates **2** were obtained with good yield (Table 2).



1 2

Scheme 37: Reaction of substituted benzyl alcohols under optimized condition

Table 2: Reaction of different primary alcohols with TBHP/TBAI under optimized reaction conditions using imidazole as a base

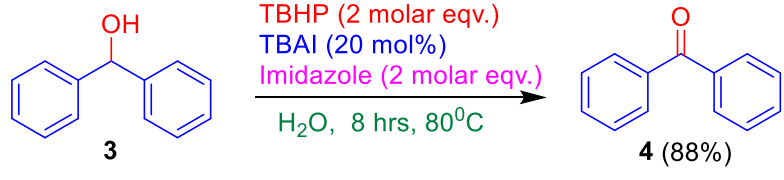
Entry	Primary alcohols (1)	Ester (2)	Time (h)	Yield (%)
1	 **1a**	 **2a**	8	86
2	 **1b**	 **2b**	7	88
3	 **1c**	 **2c**	8	85
4	 **1d**	 **2d**	7	86
5	 **1e**	 **2e**	8	84

Under the optimized condition unsubstituted benzyl alcohol (**1a)** produced benzyl benzoate (**2a)** in satisfactory yield (yield of the isolated pure product fully characterised spectroscopically). The formation of **2a** was confirmed by the occurrence of a new singlet at δ 5.41 in ^{1}H NMR along with a signal at δ 70.2 in ^{13}C NMR spectra due to –COOCH_2– moiety as well as the complete disappearance of the singlet at δ 4.79 ^{1}H NMR and the signal at δ 68.1 in ^{13}C NMR spectra due to the benzylic –CH_2– moiety in benzyl alcohol (**1a**). This oxidative self-esterification also took place very efficiently with the substrate (**1c**) having

high susceptibility to oxidative decomposition to afford **2c** with good yield. The formation of the product **2c** was confirmed by the appearance of a new singlet at δ 5.47 in ^{1}H NMR and a signal at δ 61.1 in ^{13}C NMR spectra coming from –COO*CH*$_2$–. Complete disappearance of the signals at δ 4.79 in ^{1}H NMR and δ 59.6 in ^{13}C NMR spectra (due to the –CH$_2$– in **1c** and subsequent changes in the heterocyclic ring in both ^{1}H and ^{13}C NMR spectra indicated complete consumption of the substrate. Benzylic carbinols bearing halogen, alkyl and alkoxy substituents at the aromatic ring also responded smoothly to yield the corresponding benzyl benzoates **2b**, **2d** and **2e** respectively.

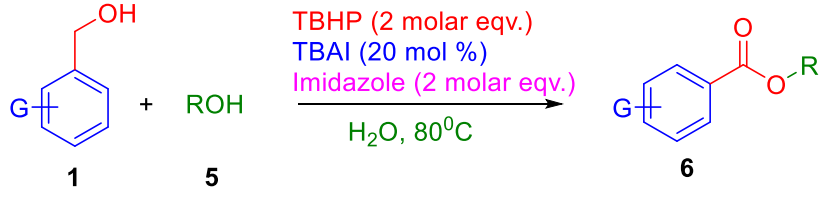
This reaction did not take place with aliphatic primary alcohols where the substrates were recovered unchanged. Therefore this protocol can serve as an alternative to Tischenko reaction for the synthesis of differently substituted benzyl benzoates using the corresponding benzylic primary alcohols as the substrates instead of aryl aldehydes.

Quite interestingly, **1a** was converted to **2a** with I$_2$ in KOH, but other alcohols failed to react. The diarylcarbinol **3** was converted to the corresponding ketone **4** in 88% yield without any cleavage of aryl-carbonyl C-C bond (Scheme 38) from under the present oxidative reaction.



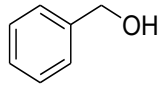
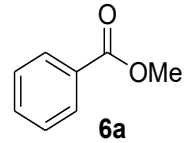
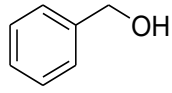
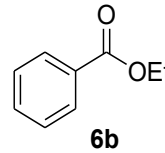
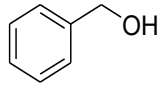
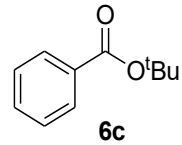
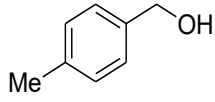
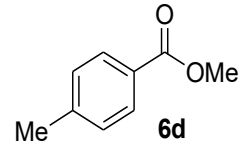
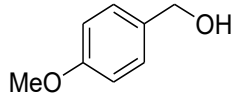
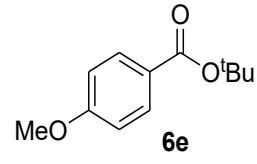
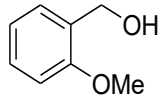
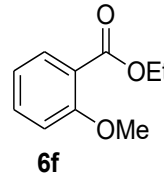
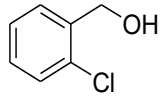
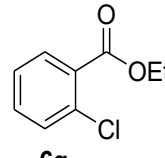
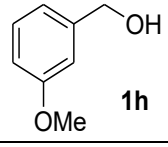
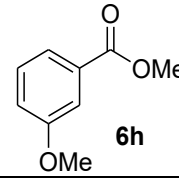
Scheme 38: Oxidation of diarylcarbinol

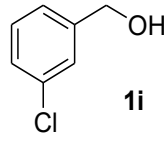
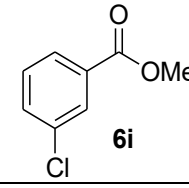
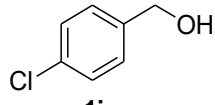
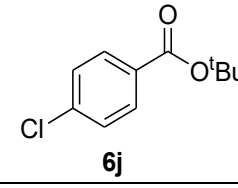
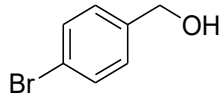
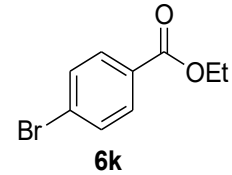
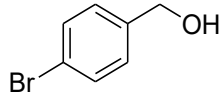
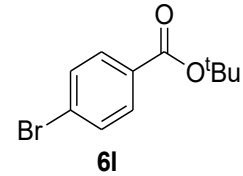
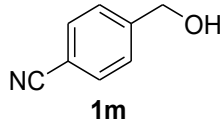
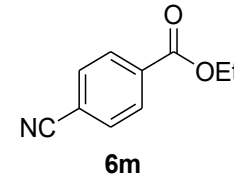
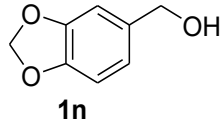
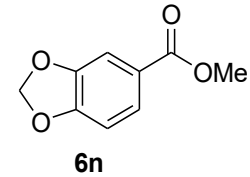
Inspired by the aforesaid results with a promise of showing chemoselectivity, we attempted for the synthesis of alkyl benzoates from a mixture of alkyl and aryl alcohols using this oxidative protocol (Scheme 39). The results are presented below in Table 3.



Scheme 39: Reaction of substituted benzyl alcohols with aliphatic alcohols under optimized condition

Table 3: Reaction of different primary alcohols with TBHP/TBAI under optimized reaction conditions using imidazole as a base

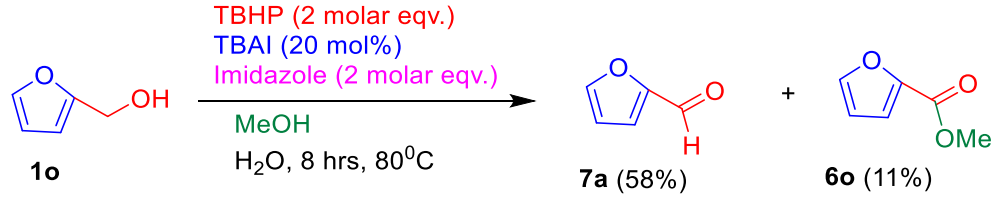
Entry	Primary alcohols (1) (Substrate)	Reagent alcohol (5)	Ester (6)	Time (h)	Yield (%)
1	 **1a**	MeOH (**5a**)	 **6a**	6	82
2	 **1a**	EtOH (**5b**)	 **6b**	6	84
3	 **1a**	^{t}BuOH (**5c**)	 **6c**	6	87
4	 **1d**	MeOH (**5a**)	 **6d**	6	82
5	 **1e**	^{t}BuOH (**5c**)	 **6e**	6	85
6	 **1f**	EtOH (**5b**)	 **6f**	8	84
7	 **1g**	EtOH (**5b**)	 **6g**	10	80
8	 **1h**	MeOH (**5a**)	 **6h**	9	83

9	 **1i**	MeOH (**5a**)	 **6i**	7	86
10	 **1j**	^{t}BuOH (**5c**)	 **6j**	8	84
11	 **1b**	EtOH (**5b**)	 **6k**	8	85
12	 **1b**	^{t}BuOH (**5c**)	 **6l**	7	87
13	 **1m**	EtOH (**5b**)	 **6m**	17	89
14	 **1n**	MeOH (**5a**)	 **6n**	7	80

As evident from Table 3, a number of substituted benzyl alcohols (**1**) reacted smoothly with a good number of structurally different aliphatic alcohols (**5**) to produce the corresponding alkyl benzoates (**6**) in good yield (yield of the isolated pure product fully characterised spectroscopically). Benzyl benzoate (**2a**) acts as a potential saviour for the patients affected with human scabies, lice infestation, asthma and whooping cough; while methyl benzoate (**6a**) is used as pesticide. Sterically crowded benzylic alcohols having substituents at *ortho* positions reacted smoothly to furnish the products **6f** and **6g** respectively. Even the bulky and less reactive tertiary alcohol (t-butyl alcohol) responded efficiently to produce the corresponding t-butyl esters (for example, **6c, 6e, 6j** and **6l**) which are otherwise difficult to prepare. The incorporation of *tert*-butyl group in **6j** was established by the occurrence of a singlet at δ 1.40 in ^{1}H NMR and at δ 26.2 in ^{13}C NMR. Hydrolysable functional groups, like –CN and methylenedioxy, also survived in the present protocol of cross dehydrogenative

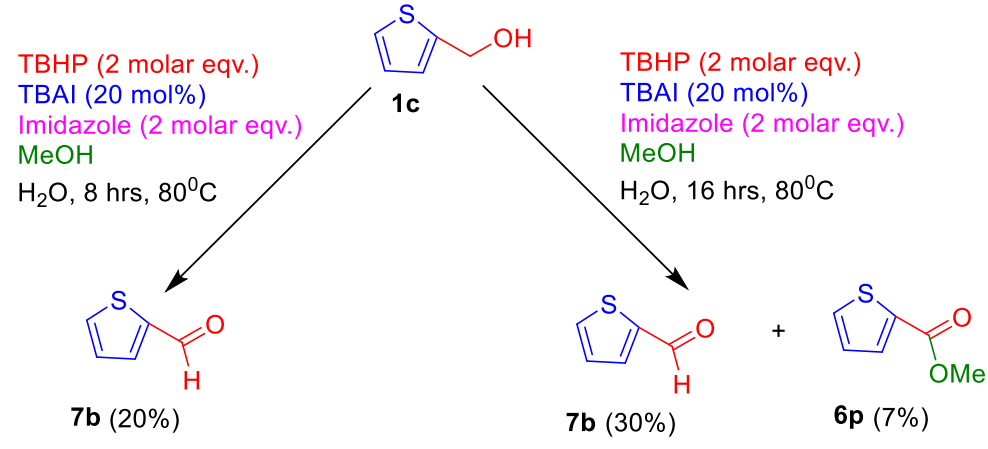
coupling reaction in aqueous medium to produce the esters **6m** and **6n** respectively. The survival of the methylenedioxy group was confirmed by a singlet at δ 3.86 in ^{1}H NMR and a signal δ 101.7 in ^{13}C NMR due to the –C*H*$_2$– moiety of the methylenedioxy group. Excess TBHP (6 molar equivalents in three equal instalments) was needed to get **6m** and the reaction was quite sluggish.

Among heteroarylcarbinols, highly vulnerable furfuryl alcohol (**1o**) reacted under the present oxidative protocol in the presence of methanol to furnish a mixture of methyl furoate (**6o**), furfural (**7a**) and unreacted furfuryl alcohol (**1o**) in 58:11:31 ratio (Scheme 40) (percentage of conversion determined by 400 MHz ^{1}H NMR).



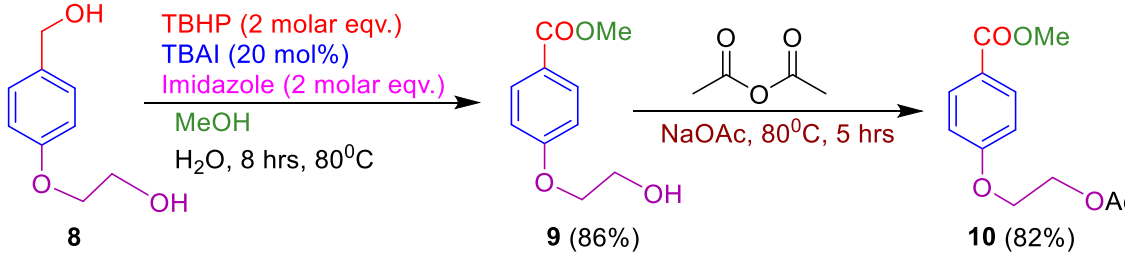
Scheme 40: Reaction of furan-2-yl-methanol under optimised condition

Thiophen-2-yl-methanol (**1c**) under the optimized condition in presence of methanol was found to be quite sluggish and was converted to thiophene-2-carbaldehyde (**7b**) only to the extent of 20% (determined by 400 MHz ^{1}H NMR). After prolonged reaction (16 hours), methyl thiophene-2-carboxylate (**6p**), thiophene-2-carbaldehyde (**7b**) and unreacted thiophen-2-yl-methanol (**1c**) were obtained (Scheme 41) as a mixture in 7:30:63 ratio (percentage of conversion determined by 400 MHz ^{1}H NMR). Pyridin-2-yl-methanol did not respond to the present protocol.



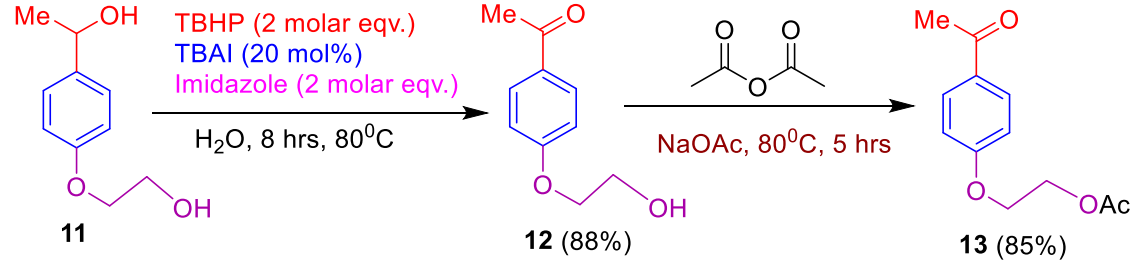
Scheme 41: Reaction of thiophen-2-yl-methanol under optimised condition

In order to establish further the chemoselectivity of the said protocol, intramolecular competition experiment was carried out. When the substrate **8**, with both the benzylic and aliphatic primary alcohols present in the same molecule, reacted under this oxidative method in MeOH, primary benzylic alcohol underwent oxidation and esterified selectively to the corresponding methyl ester (**9**) whereas the primary aliphatic alcohol moiety remained unaffected, as shown in Scheme 42. The selective formation of aromatic methoxycarbonyl group was confirmed by the presence of only one singlet (at δ 3.87) at a relatively downfield region in its ^{1}H NMR spectrum as well as from one signal (at δ 166.9) in the ^{13}C NMR spectrum. The presence of unreacted aliphatic primary alcohol was further established through acetylation of **9** (Scheme 42) which was confirmed by a singlet at δ 2.10 (in ^{1}H NMR) as well as a signal at δ 170.9 (in the ^{13}C NMR spectrum) in compound **10**. The acetylation was confirmed by the disappearance of IR band at 3292.79 cm^{-1} in **10** which was present in **9** as an evidence of aliphatic primary alcohol group.



Scheme 42: Chemoselective oxidation of 1°-benzylic alcohol

Similar chemoselectivity was also observed with the compound **11** where the secondary benzylic alcohol was selectively oxidized to the ketomethyl moiety under the present oxidative protocol to yield the compound **12** leaving the aliphatic primary alcohol group intact (Scheme 43). The occurrence of aromatic ketomethyl moiety in **12** was confirmed by the singlet δ 2.54 (in ^{1}H NMR) as well as a signal at δ 200.4 (in the ^{13}C NMR spectrum). Survival of the 1°-aliphatic alcohol moiety was further substantiated through the acetylation of **12** to **13**.



Scheme 43: Chemoselective oxidation of 2°-benzylic alcohol

The mechanistic study of the reaction suggested that, the reaction might be initiated by *in situ* formation of $[Bu_4N^+]$ $[IO^-]$[34] obtained from TBHP and TBAI where no I_2 was detected at any stage as evident from the absence of any blue coloration in the reaction mixture containing starch solution. Moreover, benzaldehyde was isolated from the reaction mixture after limited time period and subsequently transformed to benzyl benzoate and ethyl benzoate when subjected to the present protocol in the absence and presence of ethanol respectively. The reaction was highly suppressed in the presence of TEMPO where the ethyl benzoate, benzaldehyde and unreacted benzyl alcohol was obtained in 5:9:36 ratio. Therefore, an oxidative radical process might be speculated involving the intermediacy of benzaldehyde (Figure 4). Alkyl–oxygen bond formation[14, 35] to obtain the ester seems unlikely because sterically demanding *tert*-butyl alcohol also reacted efficiently. Alternatively, they can either be resulted by the oxidation of hemiacetal intermediate[10] (path A), or more possibly through the formation of benzoyl radical followed by benzoylium cation *via* two successive oxidative steps through single electron transfer mechanism (path B). Subsequent nucleophilic attack at sterically more accessible linear benzoylium cation even by the bulky tertiary alcohol took place to produce the ester through acyl-oxygen bond formation.

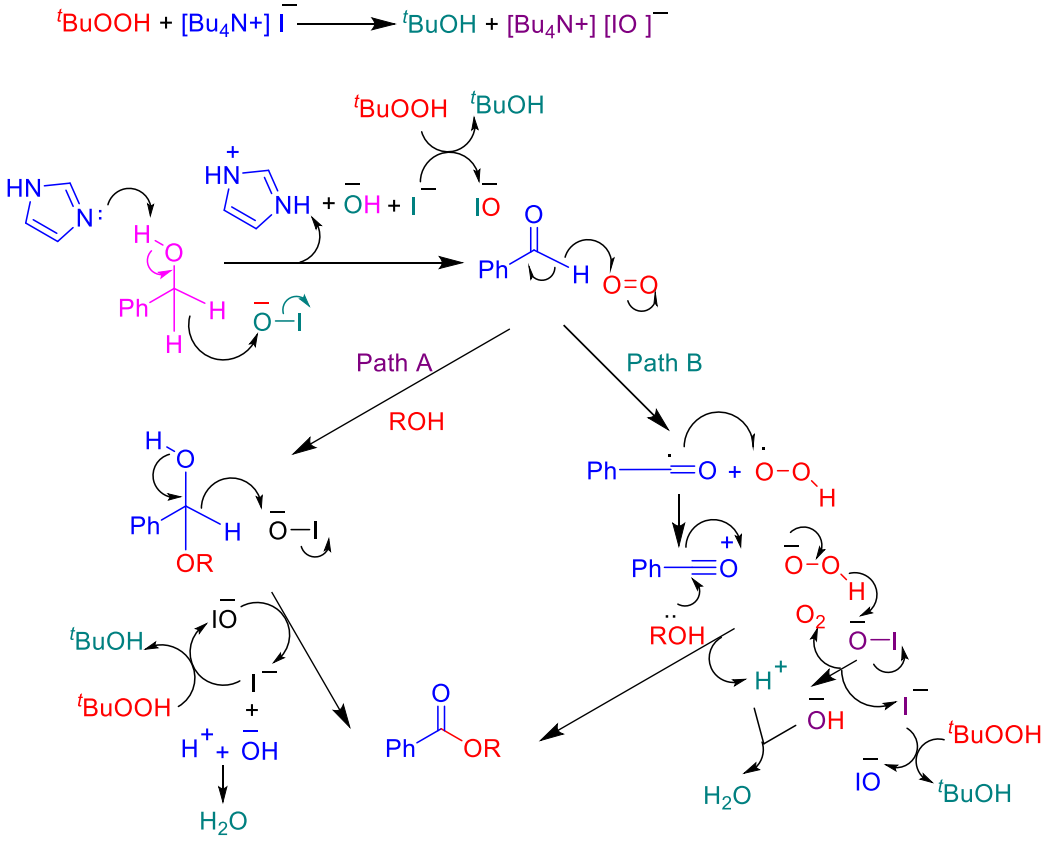
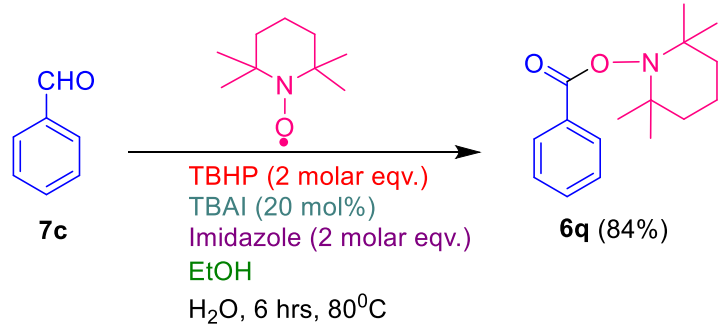


Figure 4: Plausible mechanism for cross dehydrogenative coupling

When the speculated intermediate, namely, benzaldehyde (**7c**) reacted (Scheme 44) with ethanol in the present protocol in the presence of TEMPO, 2, 2, 6, 6-tetramethyl-piperidin-1-yl benzoate (**6q**) was isolated in place of ethyl benzoate. The structure of **6q** was established by ^{1}H NMR analysis, where two singlets appeared at δ 1.12 and δ 1.28 in ^{1}H NMR as a result of the included *gem*-dimethyl moieties from TEMPO. No triplet and quartet due to ethoxycarbonyl functionality were found around δ 1.35 as well as δ 4.35 which were present in ethyl benzoate (**6b**). In ^{13}C NMR the signals at δ 17.2, δ 21.0, δ 26.4, δ 32.1, δ 39.3 and δ 60.6 were accounted for the aliphatic carbons present in **6q**, after doing DEPT-135 experiment the peaks on the positive side at δ 20.9 and δ 31.9 proved the presence of $-CH_3$ groups, two peaks at the negative side at δ 17.0 and δ 39.1 proved the presence of $-CH_2-$ groups and the disappearance of the two peaks at δ 26.4 and δ 60.6 proved the presence of the quaternary carbons in **6q** respectively.



Scheme 44: Reaction of benzaldehyde and TEMPO under optimized condition

This observation substantiated the formation of benzoyl radical from benzaldehyde, as proposed in path B. Chemoselectivity is induced at the initial oxidation step due to higher tendency of the benzylic alcohols towards oxidation compared to the simple alkanols where the TBHP-TBAI system seems to be aptly fine-tuned to promote selective oxidation.

The plausible mechanism suggested in Figure 4 also accounts for the catalytic behavior of TBAI, necessity for the co-existence of TBHP and aerial oxygen, role of imidazole and neutrality of the reaction medium (pH is nearly 6.8 after the reaction) in the present protocol of cross dehydrogenative coupling reaction.

On the basis of the aforesaid experimental findings, essentiality of TBHP/TBAI couple for the aforesaid chemical transformation is quite obvious. Although the exact reaction pathway and mode of catalysis is still uncertain to us, yet the synthetic importance of the esterification based on cross dehydrogenative coupling has been well-established here.

I.3.3. Conclusion:

A cost-effective, operationally simple, transition-metal free, chemoselective, eco-compatible protocol in aqueous medium has been developed for the synthesis of a variety of aryl esters directly from primary benzylic alcohols where aliphatic alcoholic moiety remained unaffected. Moreover this was one of the few cross dehydrogenative coupling protocols available where excellent chemoselectivity was also observed during the reaction.

I.3.4. Experimental

General:

All organic solvents used for the reaction were purchased from Merck, and were distilled before use. Melting points were recorded in open capillary on electrical bath which are uncorrected. ^{1}H NMR, ^{13}C NMR and DEPT spectra were obtained on a Bruker–300 (300 MHz) and Bruker–400 (400 MHz) spectrometer in $CDCl_3$ solvent with TMS as internal reference. IR spectrums were done in Perkin-Elmer Spectrum Version 10.4.1 and Mass spectrums were measured on HRMS (Qtof micro YA263). Column chromatography were performed on silica gel (60–120 mesh) supplied by SRL, India. Thin layer chromatographic separations were performed on pre-coated glass plates using silica gel G for TLC (E. Merck).

(i) Purification and drying of solvents and reagents:

A. **Methanol:**

Commercial grade methanol was left overnight on calcium oxide. It was then filtered and refluxed adding metallic sodium for one hour. Finally it was distilled as constant boiling fraction 64–65^{o}C and was stored in a well stoppered round bottom flask containing 4Å molecular sieves.

B. **Ethanol:**

Commercial grade ethanol was left overnight with calcium oxide. It was then filtered and refluxed over metallic sodium for one hour. Finally it was distilled at constant boiling fraction 78–79^{o}C and was stored in a well stoppered round bottom flask containing 4Å molecular sieves.

C. **^{t}Butanol:**

Commercial grade ethanol was left overnight with calcium oxide. It was then filtered and refluxed over metallic sodium for one hour. Finally it was distilled at constant boiling fraction 80-85^{o}C and was stored in a well stoppered round bottom flask containing 4Å molecular sieves.

(ii) Representative procedure for the reaction:

A. To a mixture of benzyl alcohol (108 mg, 1.0 mmol), and TBHP (180 mg, 2.0 mmol) in water (5 ml), the catalyst TBAI (73.8 mg, 0.2 mmol) and imidazole (136 mg, 2.0 mmol) were added and the mixture was stirred at 80^{o}C for 8 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. Then the organic product was extracted with ethyl acetate (3x10 ml), repeatedly washed with distilled water (4x5 ml) to remove the unreacted TBHP, dried with anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to afford benzyl benzoate (182 mg, Yield 86%).

B. To a mixture of benzyl alcohol (108 mg, 1.0 mmol), and TBHP (180 mg, 2.0 mmol) in water (3 ml), the catalyst TBAI (73.8 mg, 0.2 mmol), imidazole (136 mg, 2.0 mmol) and MeOH (2 ml) were added and the mixture was stirred at 80^{o}C for 8 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. Then MeOH was distilled out and the organic product was extracted with ethyl acetate (3x10 ml), repeatedly washed with distilled water (4x5 ml) to remove the unreacted TBHP, dried with anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to afford methyl benzoate (112 mg, Yield 82%). Some of the other products were purified by filtration chromatography on a short column of silica gel using 1-4% ethyl acetate-hexane as eluent.

(iii) Spectral and analytical data of the compounds:

1. **benzyl benzoate (2a)**[36]**:** White solid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.41 (2H, s), 7.40-7.48 (5H, m), 7.50-7.60 (3H, m), 8.13 (2H, d, *J* = 9.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 70.2, 131.1, 134.4, 135.1, 138.3, 145.6, 169.1

2. **4-bromobenzyl 4-bromobenzoate (2b)**[37]**:** Yellowish solid (Yield 88%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.52 (2H, s), 7.11-7.13 (2H, m), 7.38-7.41 (2H, m), 7.55-7.57 (2H, m) 7.89-7.92 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 72.2, 124.4, 128.2, 131.4, 133.5, 143.1, 169.8

3. **(thiophen-2-yl) methyl thiophene-2-carboxylate (2c):** Yellow oil (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.47 (2H, s), 7.00-7.02 (1H, m), 7.07-7.10 (1H, m), 7.17-7.18

(1H,m), 7.33-7.35 (1H, m) 7.55-7.57 (1H, m), 7.82-7.83 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.1, 126.8, 126.9, 127.7, 128.3, 132.7, 133.4, 133.7, 137.7, 161.9; HRMS (ESI-TOF, m/z) calculated for $C_{10}H_8O_2S_2$ [M + Na^+] 246.9866, found 246.9868

4. **4-methylbenzyl 4-methylbenzoate (2d)**[37]**:** White solid (Yield 86%); ^{1}H NMR (300 MHz; CDCl3): δ 2.38 (6H, s), 5.64 (2H, s), 7.02-7.20 (2H, m), 7.25-7.38 (4H, m), 7.97-8.01 (2H, d); ^{13}C NMR (75 MHz; $CDCl_3$): δ 24.8, 68.7, 127.7, 129.4, 137.4, 138.6, 143.1, 167.1

5. **3-methoxybenzyl 3-methoxybenzoate (2e):** Yellowish oil (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.81 (3H, s), 3.88 (3H, s), 5.58 (2H, s), 7.05-7.09 (3H, m), 7.28-7.33 (2H, m), 7.53-7.54 (1H, m), 7.60-7.62 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 56.2, 69.1, 112.4, 113.7, 114.8, 119.3, 120.2, 122.9, 131.2, 132.7, 143.1, 161.4, 167.2

6. **benzophenone (4)**[38]**:** White solid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.44-7.60 (6H, m), 7.78-7.80 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 128.1, 129.8, 132.2, 137.4, 196.8

7. **methyl benzoate (6a)**[20]**:** White semisolid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.89 (3H, s), 7.49 (2H, m), 7.56-7.57 (1H, m) 8.01-8.03 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 52.0, 128.4, 129.6, 130.3, 132.9, 167.1

8. **ethyl benzoate (6b)**[20]**:** White semisolid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.35-1.38 (3H, m), 4.34-4.36 (2H, m), 7.42 (2H, m), 7.53 (1H, m), 8.07-8.08 (2H, m)**;** ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.3, 60.9, 128.3, 129.6, 130.6, 132.8, 166.5

9. ***tert*-butyl benzoate (6c)**[39]**:** Yellowish solid (Yield 87%)**;** ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.42 (9H, s), 7.43-7.64 (3H, m), 7.94-8.14 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 26.2, 84.0, 128.6, 129.1, 130.2, 133.3, 133.7, 164.5

10. **methyl 4-methylbenzoate (6d)**[20]**:** Yellowish solid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.40 (3H, s), 3.89 (3H, s), 7.23 (2H, d, *J* = 8.2 Hz), 7.93 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.2, 51.1, 127.9, 129.6, 130.1, 142.6, 167.8

11. ***tert*-butyl 4-methoxybenzoate (6e)**[40]**:** Yellowish oil (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.47-1.44 (9H, s), 3.81 (3H, s), 6.93-6.97 (2H, m), 7.94-8.12 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 29.1, 56.2, 82.3, 115.2, 123.1, 131.7, 165.2, 166.4

12. **ethyl 2-methoxybenzoate (6f)**[41]**:** Yellow oil (Yield 84%)**;** ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.36 (3H, t), 3.88-3.94 (3H, s), 4.30-4.38 (2H, m), 6.93-6.98 (2H, m), 7.41-7.47 (1H, m), 7.75-7.78 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.7, 56.2, 61.8, 114.3, 121.8, 131.4, 134.9, 162.1, 167.1

13. **ethyl 2-chlorobenzoate (6g)**[41]**:** Yellowish oil (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.25-1.42 (3H, m), 4.36-4.43 (2H, m), 7.27-7.45 (3H, m), 7.79-7.82 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.8, 61.2, 127.3, 129.6, 132.1, 134.9, 169.9

14. **methyl 3-methoxybenzoate (6h)**[42]**:** Yellowish oil (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.81 (3H, s), 3.89 (3H, s), 7.05-7.09 (1H, m), 7.28-7.33 (1H, m), 7.53-7.62 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 52.1, 55.3, 113.9, 119.4, 121.9, 129.3, 131.4, 159.5, 166.9

15. **methyl 3-chlorobenzoate (6i)**[43]**:** Yellow oil (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.94 (3H, s), 7.34-7.38 (1H, m), 7.51-7.57 (1H, m), 7.92-7.97 (1H, m), 8.01-8.06 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 52.3, 129.1, 131.1, 133.7, 134.9, 167.1

16. ***tert*-butyl 4-chlorobenzoate (6j)**[44]**:** Yellowish oil (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.40 (9H, s), 7.42 (2H, d, J = 8.6 Hz), 7.88 (2H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 26.2, 84.1, 126.1, 128.7, 130.5, 139.8, 163.5

17. **ethyl 4-bromobenzoate (6k)**[18]**:** Yellow oil (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.39 (3H, t), 4.33-4.40 (2H, m), 7.57 (2H, d, J = 8.6 Hz), 7.89 (2H, d, J = 10.8 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.1, 61.7, 128.2, 130.5, 131.8, 133.1, 167.3

18. ***tert*-butyl 4-bromobenzoate (6l)**[45]**:** Yellowish oil (Yield 87%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.42 (9H, s), 7.55 (2H, d, J = 6.3 Hz), 7.84 (2H, d, J = 6.6 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 29.4, 86.2, 127.5, 129.2, 131.3, 142.2, 164.3

19. **ethyl 4-cyanobenzoate (6m)**[46]**:** Yellow oil (Yield 89%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.39-1.42 (3H, m), 4.39-4.43 (2H, m), 7.72-7.74 (2H, m), 8.13-8.14 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.9, 61.3, 116.4, 117.5, 131.5, 132.7, 135.1, 167.6.

20. **methyl benzo[1, 3]dioxole-5-carboxylate (6n)**[47]**:** Colourless viscous oil (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.86 (3H, s), 6.05 (2H, s), 6.82 (1H, d, J =

8.8 Hz), 7.45 (1H, d, J = 1.4 Hz), 7.64 (1H, dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 51.9, 101.7, 107.9, 109.5, 124.2, 125.3, 147.7, 151.6, 166.4

21. **methyl 4-(2-hydroxyethoxy)benzoate (9)**[48]**:** White solid (m.p.65^{o}C) (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.39 (1H, s), 3.87 (3H, s), 3.96-3.97 (2H, m), 4.10-4.13 (2H, m), 6.91 (2H, d, J = 8.7 Hz), 7.97 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 51.9, 61.1, 69.4, 114.1, 122.7, 131.6, 162.5, 166.9

22. **methyl 4-(2-acetoxyethoxy)benzoate (10):** White solid (m.p.76^{o}C) (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.10 (3H, s), 3.87 (3H, s), 4.22-4.23 (2H, m), 4.44 (2H, t, J = 4.3 Hz), 6.92 (2H, d, J = 8.7 Hz), 7.99 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 20.8, 51.9, 62.5, 65.9, 114.1, 123.1, 131.6, 162.2, 166.7, 170.9

23. **1-(4-(2-hydroxyethoxy)phenyl)ethanone (12):** Yellowish oil (Yield 88%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.54 (3H, s), 3.98 (2H, t, J = 4.3 Hz), 4.13 (2H, t, J = 4.4 Hz), 6.93 (2H, d, J = 8.7 Hz), 7.91 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 26.3, 60.9, 69.5, 114.2, 130.7, 162.8, 197.4

24. **2-(4-acetyl-phenoxy)-ethyl acetate (13):** Colourless semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.08 (3H, s), 2.54 (3H, s), 4.13-4.23 (2H, m), 4.43 (2H, t, J = 4.4 Hz), 6.93 (2H, d, J = 8.6 Hz), 7.92 (2H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 20.8, 26.3, 62.5, 66.0, 114.2, 130.6, 130.7, 162.3, 170.9, 196.7

25. **2, 2, 6, 6-tetramethyl-piperidin-1-yl benzoate (6q):** White solid (m.p.150^{o}C) (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.12 (6H, s), 1.28 (6H, s), 1.43-1.48 (2H, m), 1.57-1.60 (2H, m), 1.68-1.82 (2H, m), 7.46 (2H, t, J = 7.6 Hz), 7.57 (1H, t, J = 7.2 Hz), 8.07 (2H, d, J = 8 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 17.2, 21.0, 26.4, 32.1, 39.3, 60.6, 128.6, 129.3, 132.9, 166.5

^{1}H, ^{13}C, DEPT, IR and HRMS spectra of some representative compounds:

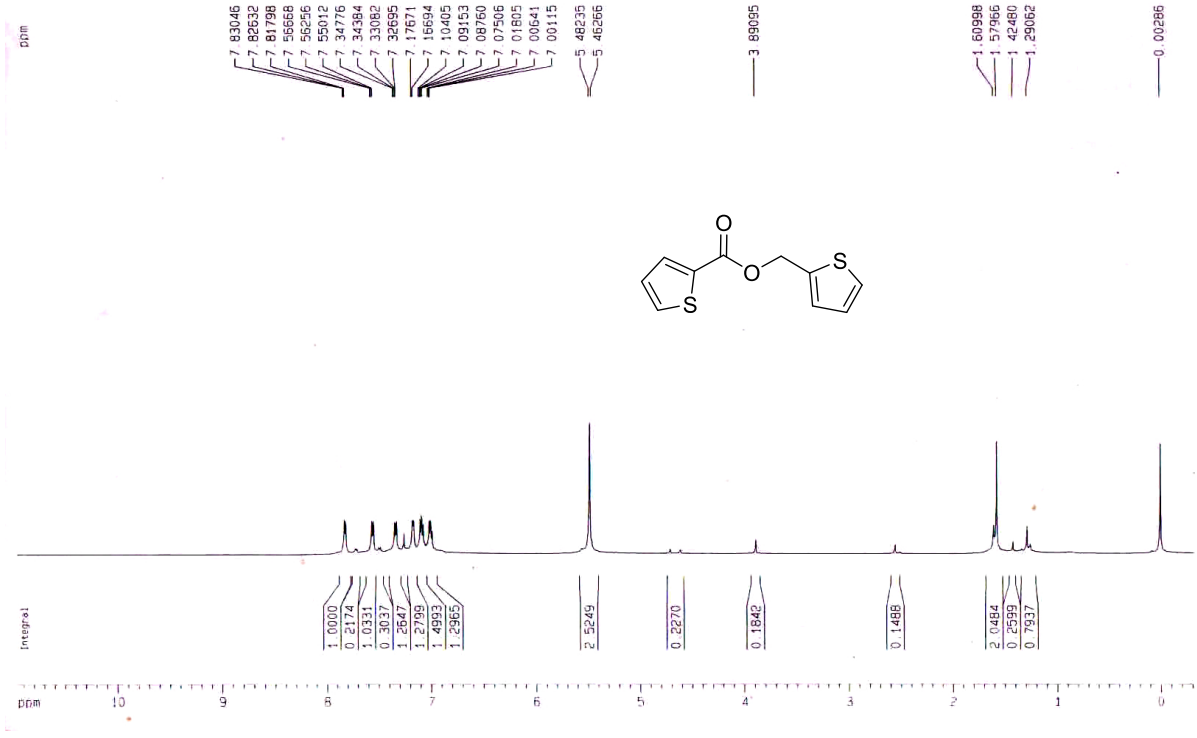


Figure 1: ^{1}H NMR of (thiophen-2-yl) methyl thiophene-2-carboxylate **(2c)**

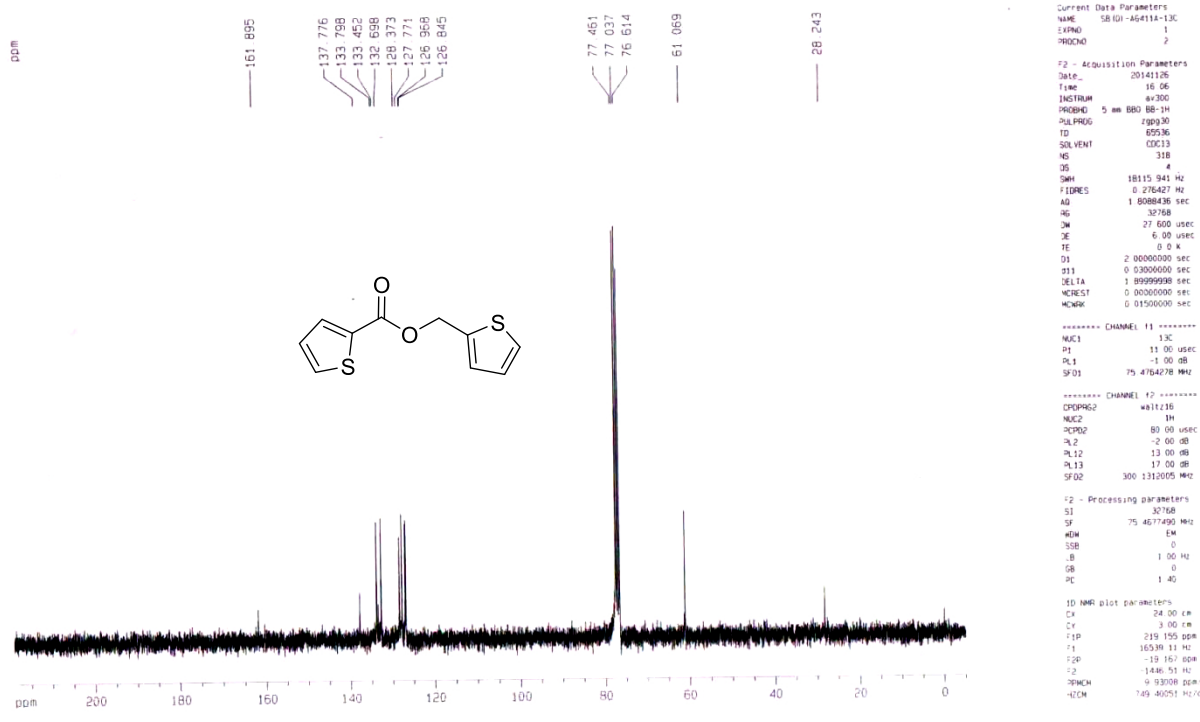


Figure 2: ^{13}C NMR of (thiophen-2-yl) methyl thiophene-2-carboxylate **(2c)**

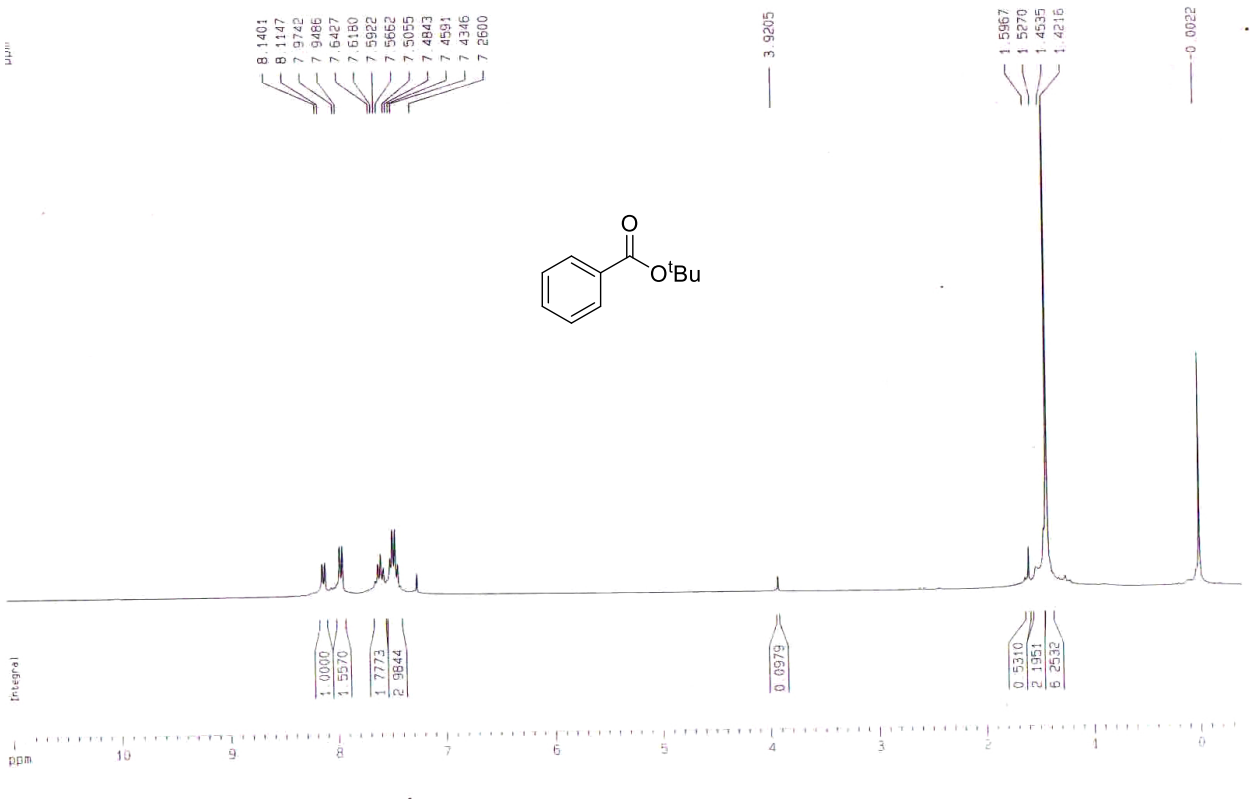


Figure 3: ^{1}H NMR of *tert*-butyl benzoate **(6c)**

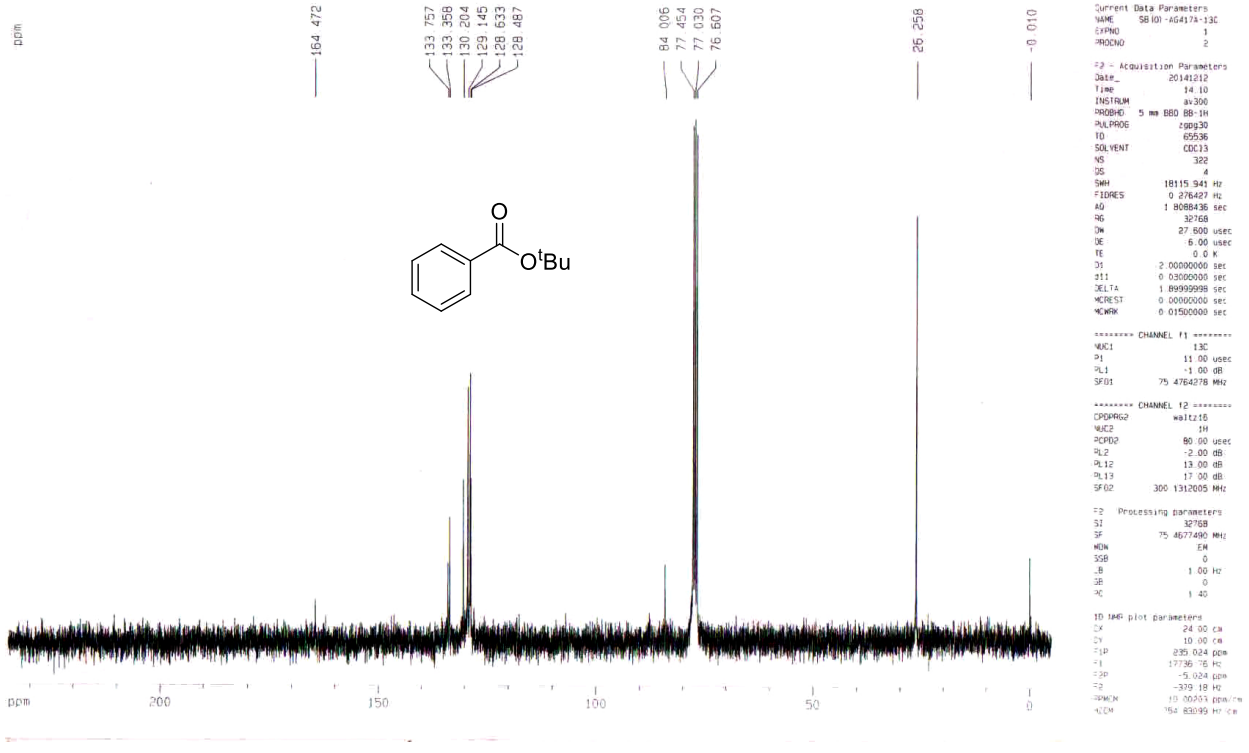


Figure 4: ^{13}C NMR of *tert*-butyl benzoate **(6c)**

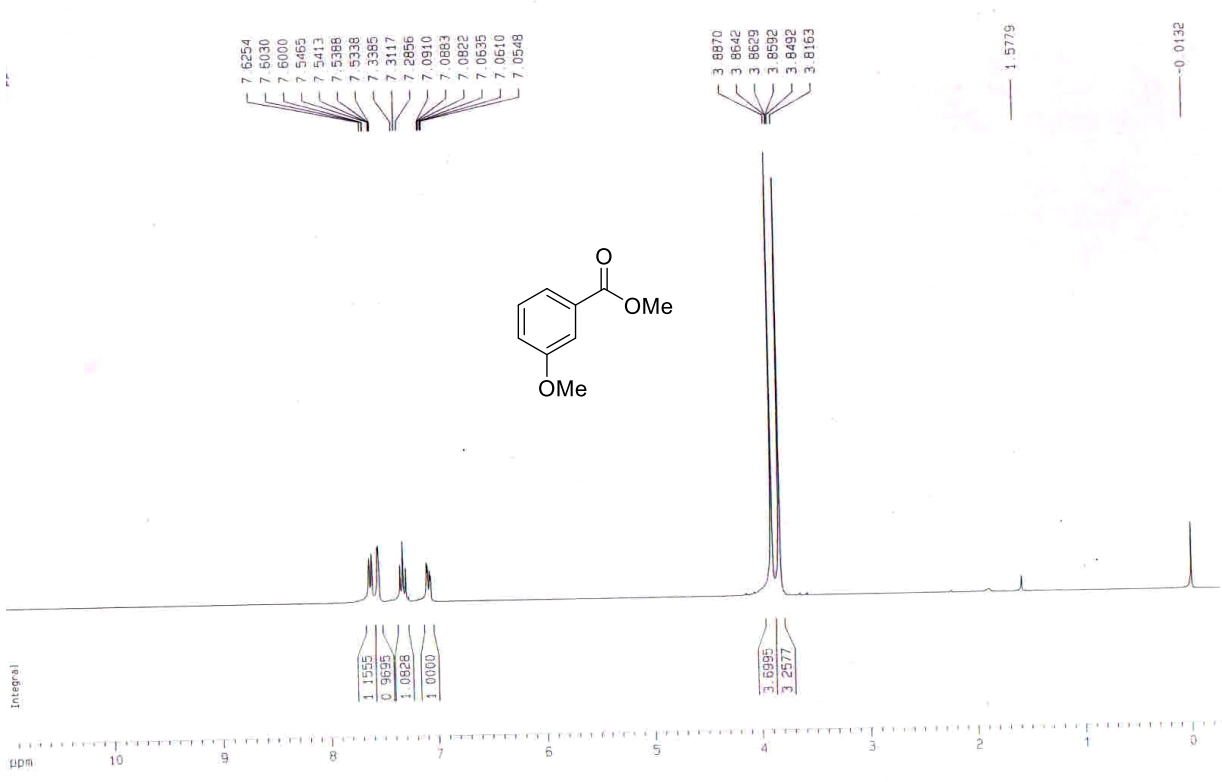


Figure 5: ^{1}H NMR of methyl 3-methoxybenzoate **(6h)**

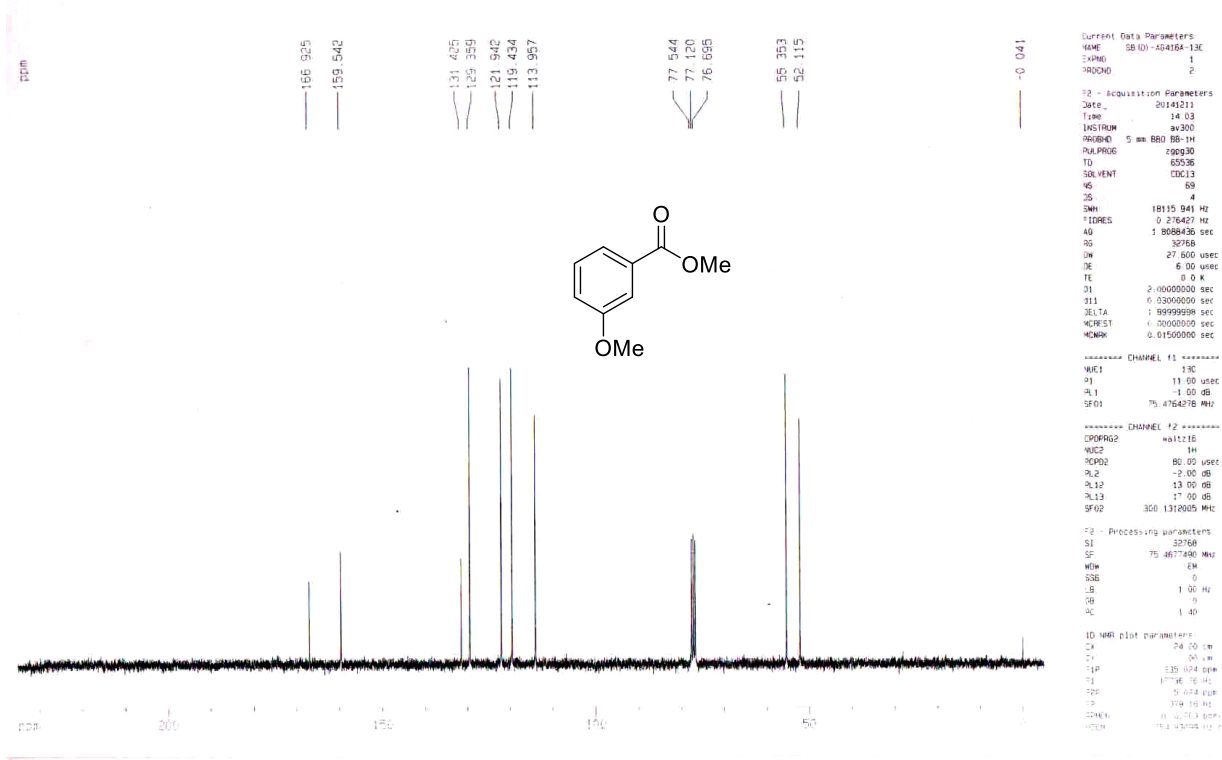


Figure 6: ^{13}C NMR of methyl 3-methoxybenzoate **(6h)**

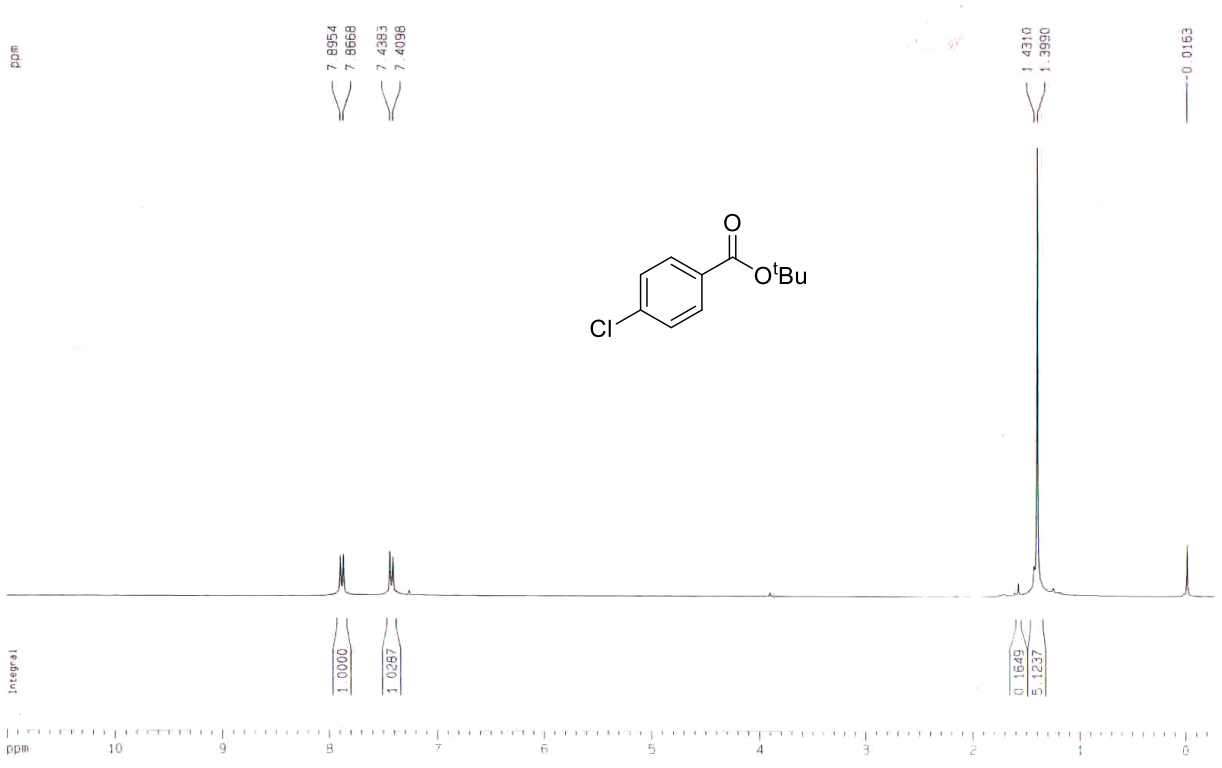


Figure 7: ^{1}H NMR of *tert*-butyl 4-chlorobenzoate **(6j)**

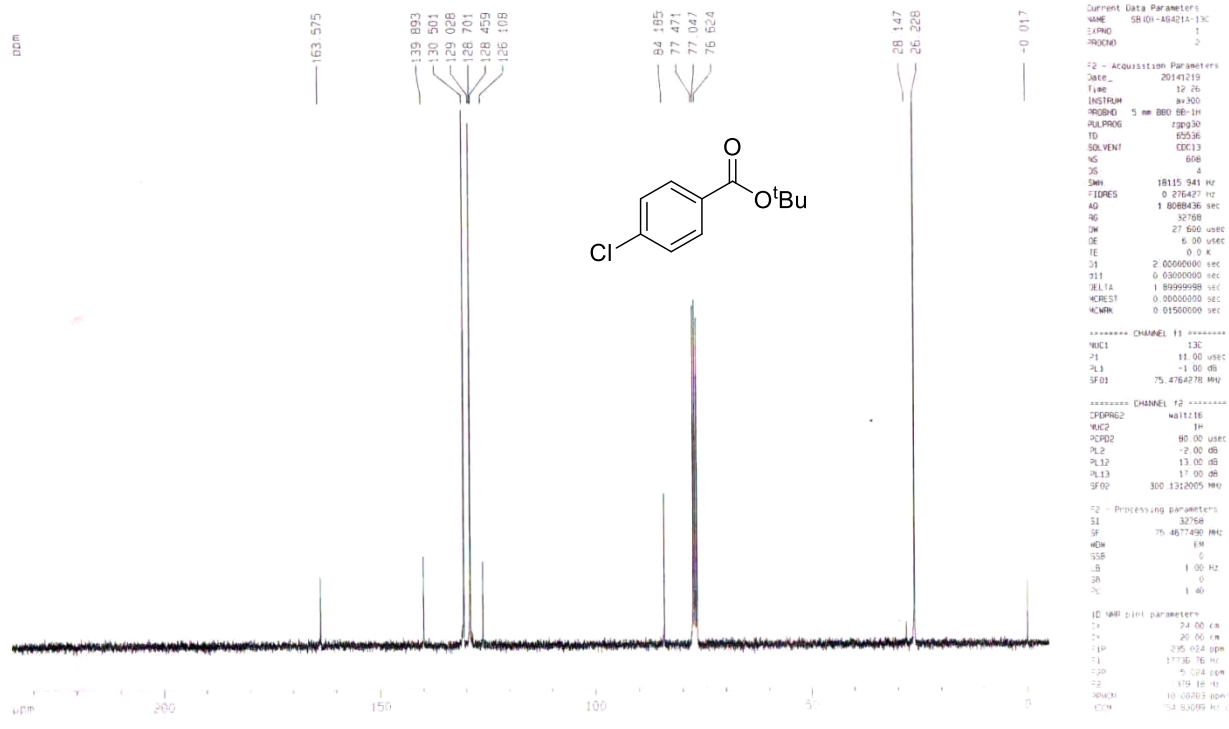


Figure 8: ^{13}C NMR of *tert*-butyl 4-chlorobenzoate **(6j)**

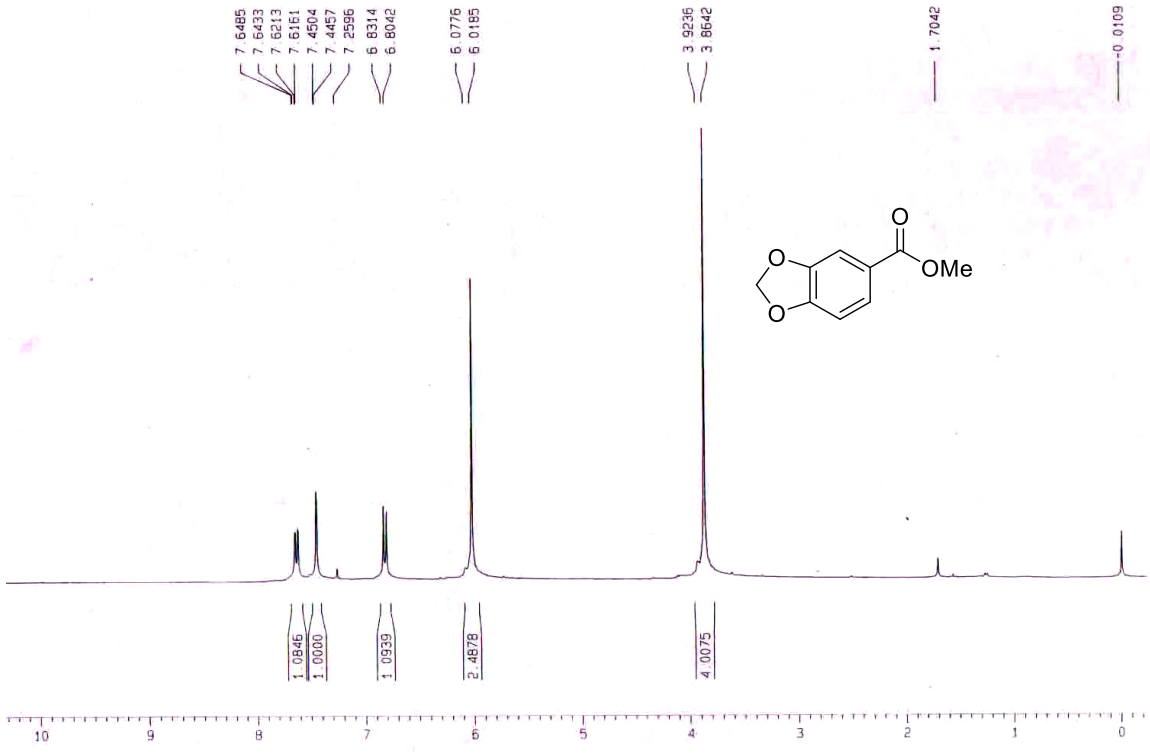


Figure 9: ^{1}H NMR of methyl benzo[1, 3]dioxole-5-carboxylate **(6n)**

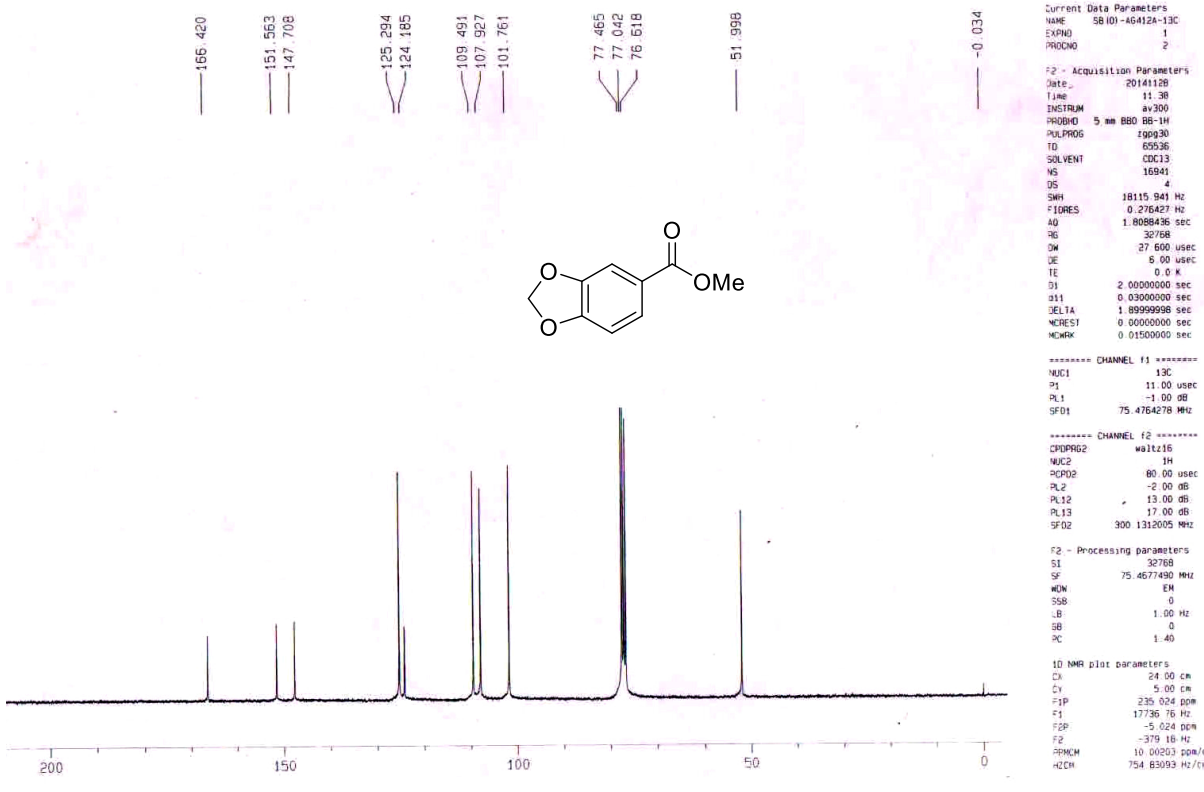


Figure 10: ^{13}C NMR of methyl benzo[1, 3]dioxole-5-carboxylate **(6n)**

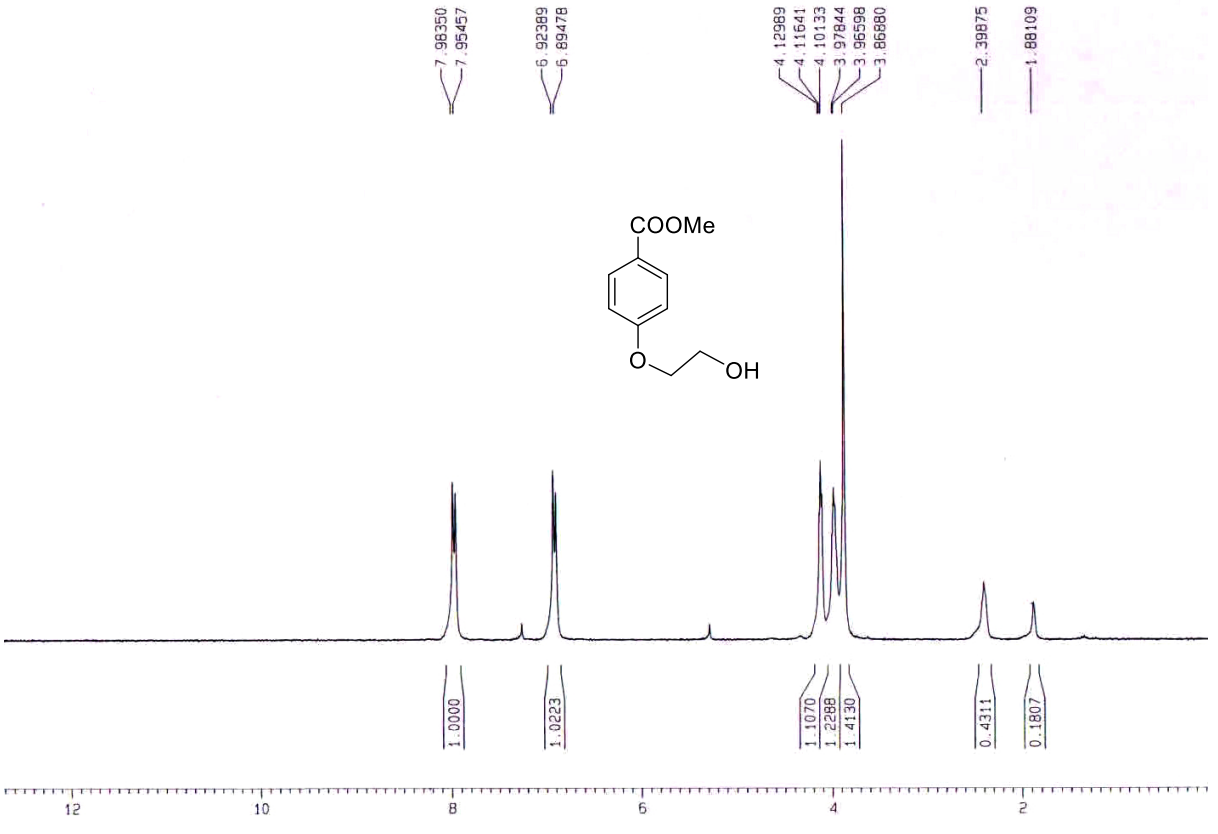


Figure 11: ^{1}H NMR of methyl 4-(2-hydroxyethoxy)benzoate **(9)**

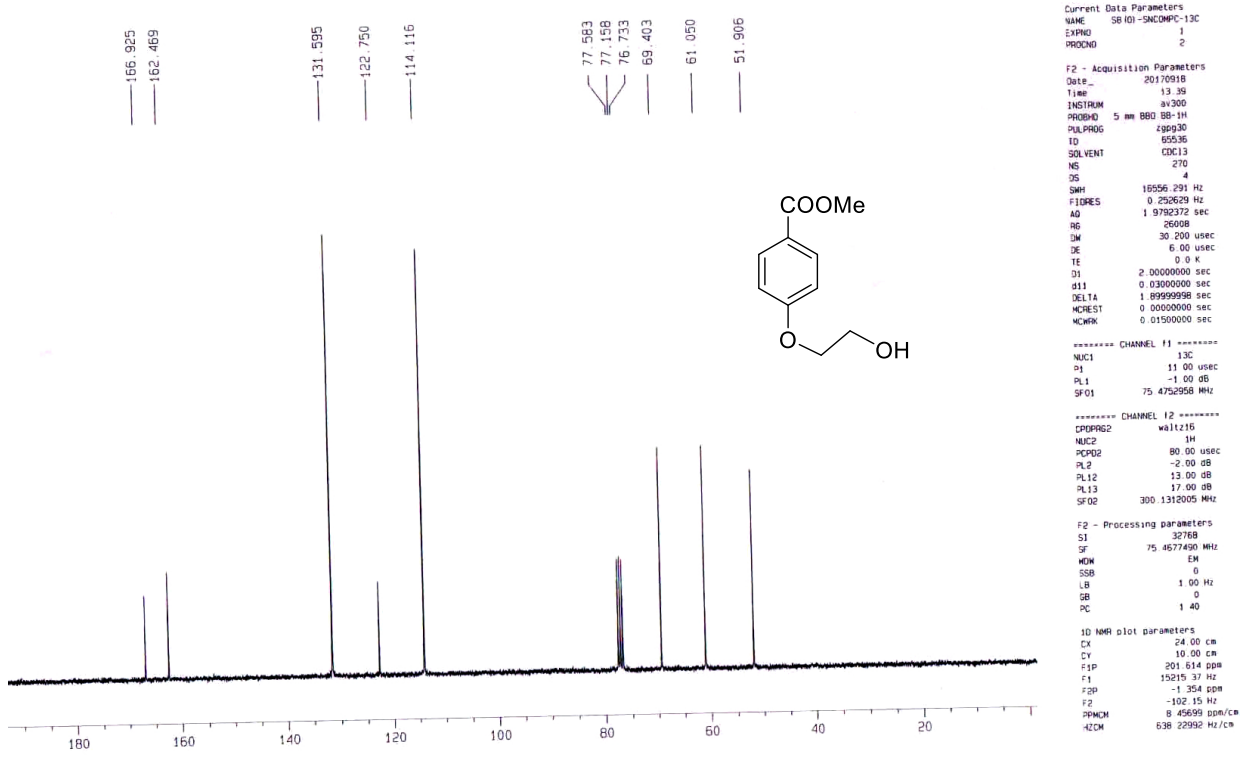


Figure 12: ^{13}C NMR of methyl 4-(2-hydroxyethoxy)benzoate **(9)**

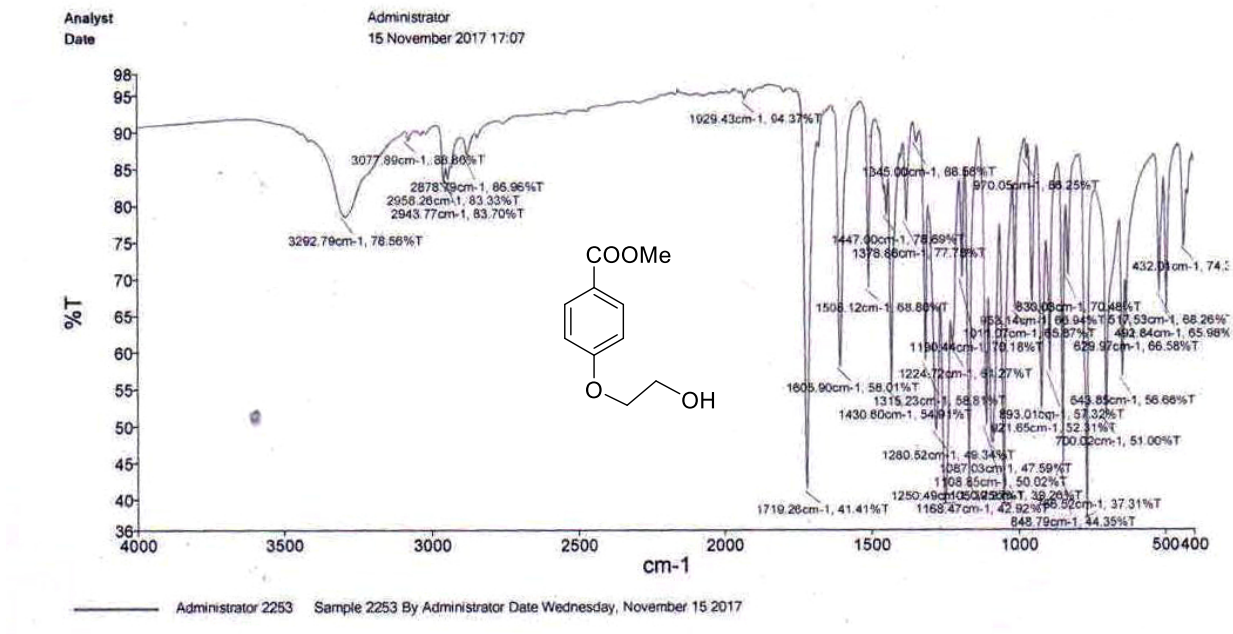


Figure 13: IR Spectra of methyl 4-(2-hydroxyethoxy)benzoate **(9)**

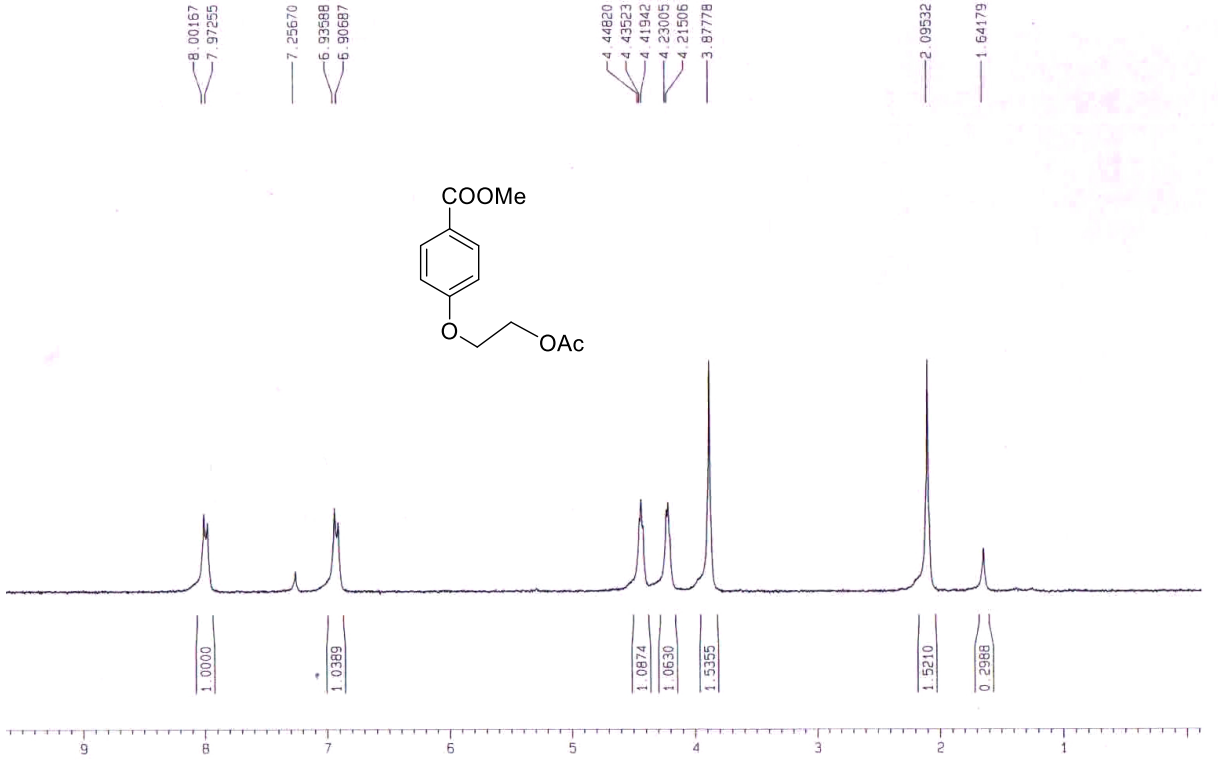


Figure 14: ^{1}H NMR of methyl 4-(2-acetoxyethoxy)benzoate **(10)**

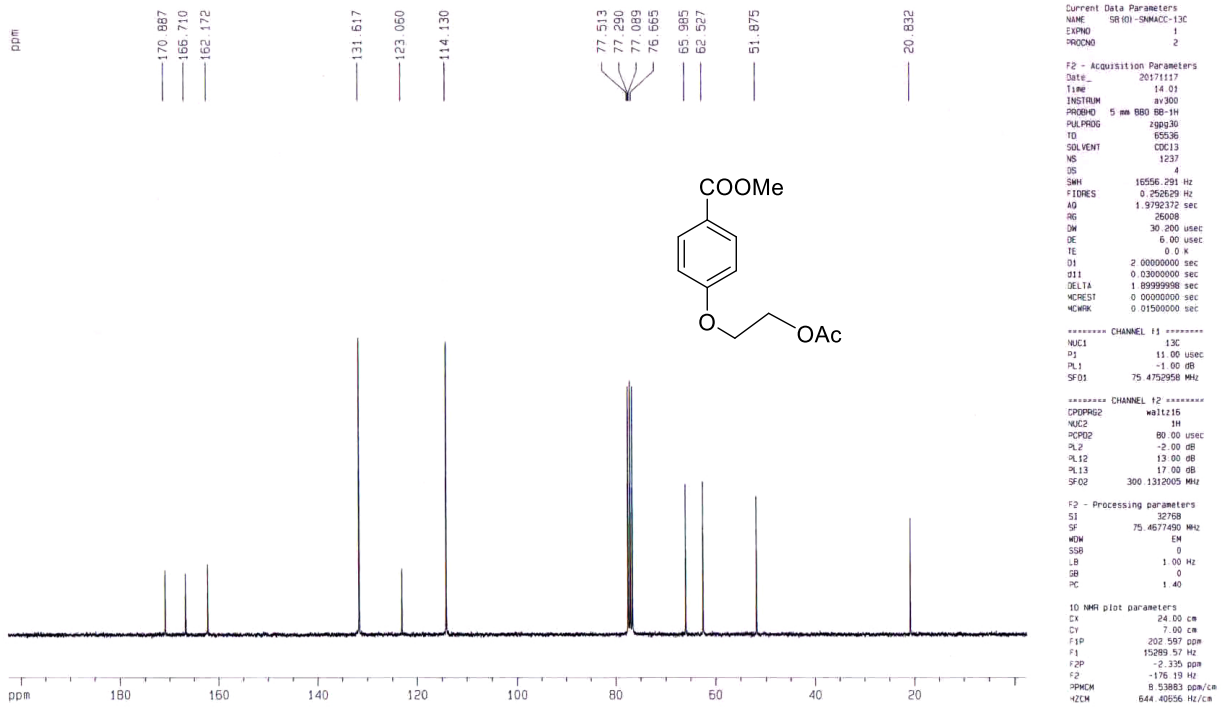


Figure 15: ^{13}C NMR of methyl 4-(2-acetoxyethoxy)benzoate **(10)**

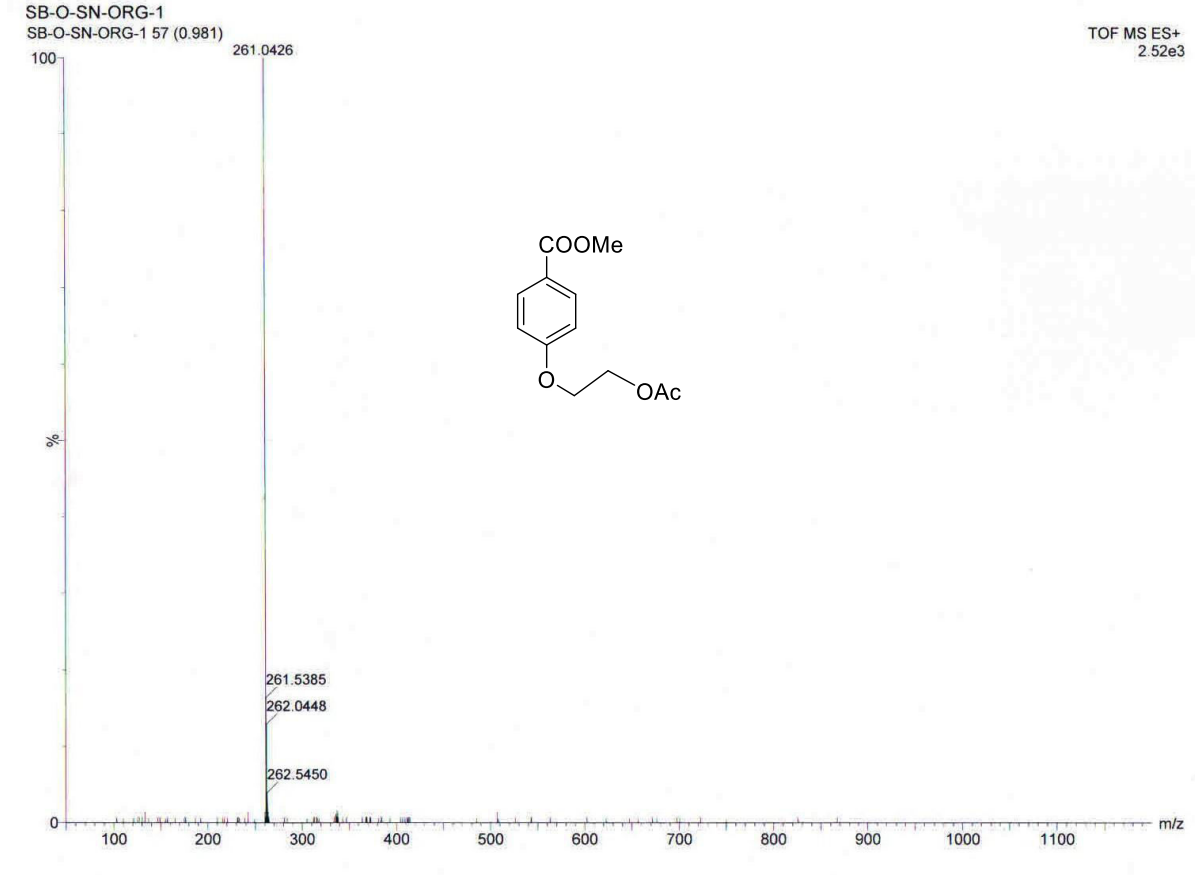


Figure 16: HRMS of methyl 4-(2-acetoxyethoxy)benzoate **(10)**

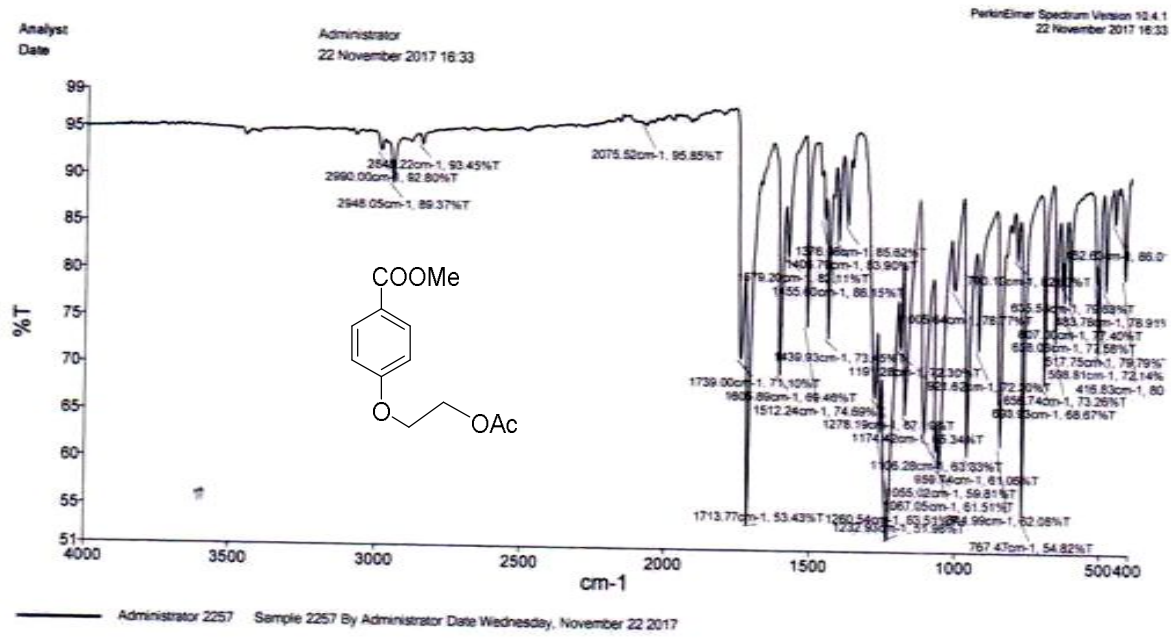


Figure 17: IR Spectra of methyl 4-(2-acetoxyethoxy)benzoate **(10)**

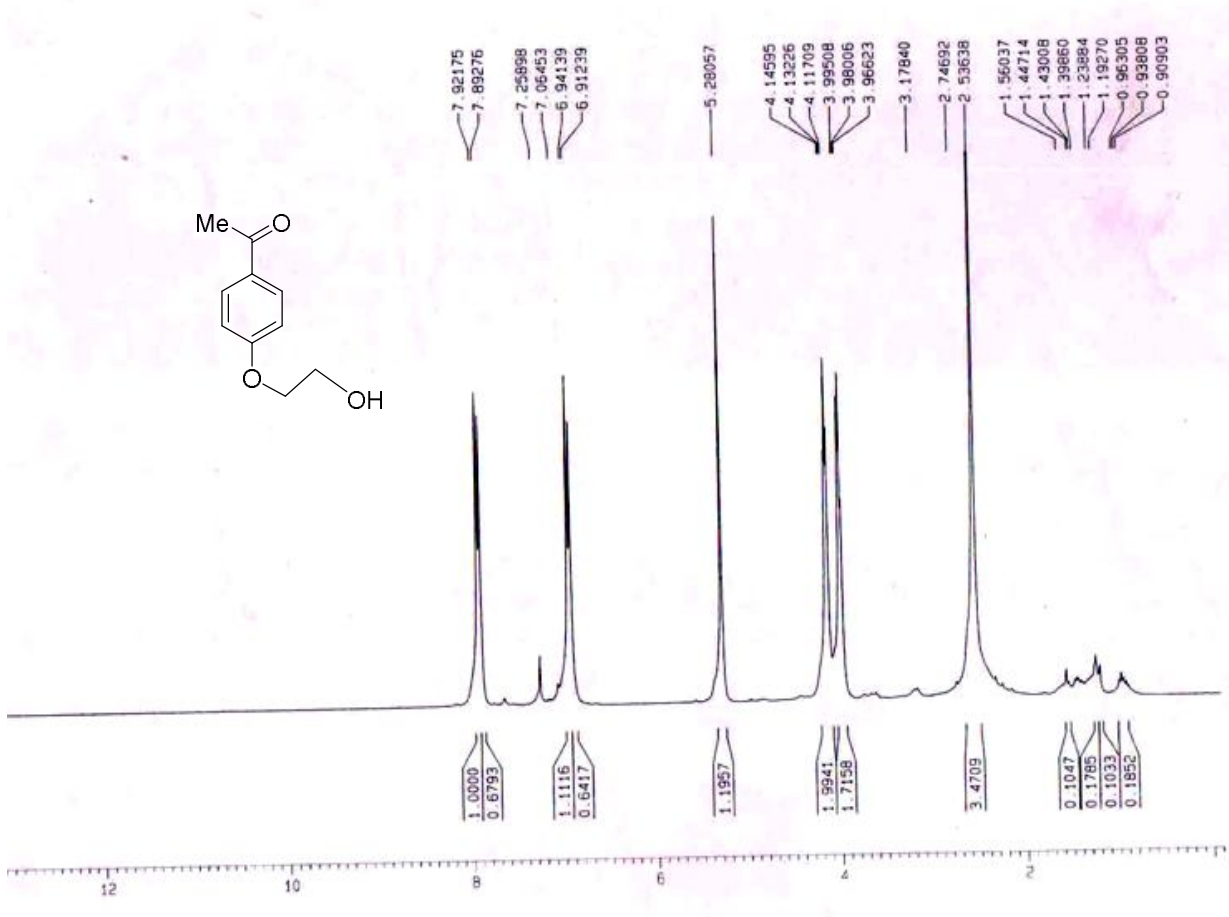


Figure 18: ^{1}H NMR of 1-(4-(2-hydroxyethoxy)phenyl)ethanone **(12)**

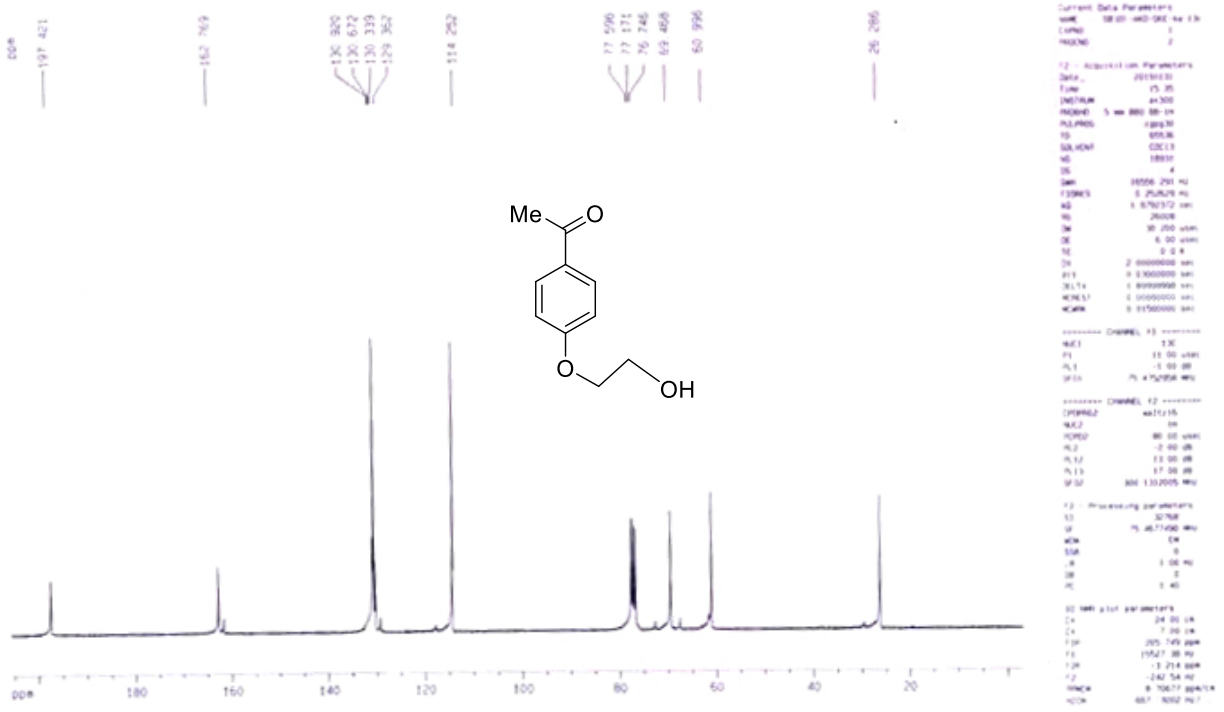


Figure 19: ^{13}C NMR of 1-(4-(2-hydroxyethoxy)phenyl)ethanone **(12)**

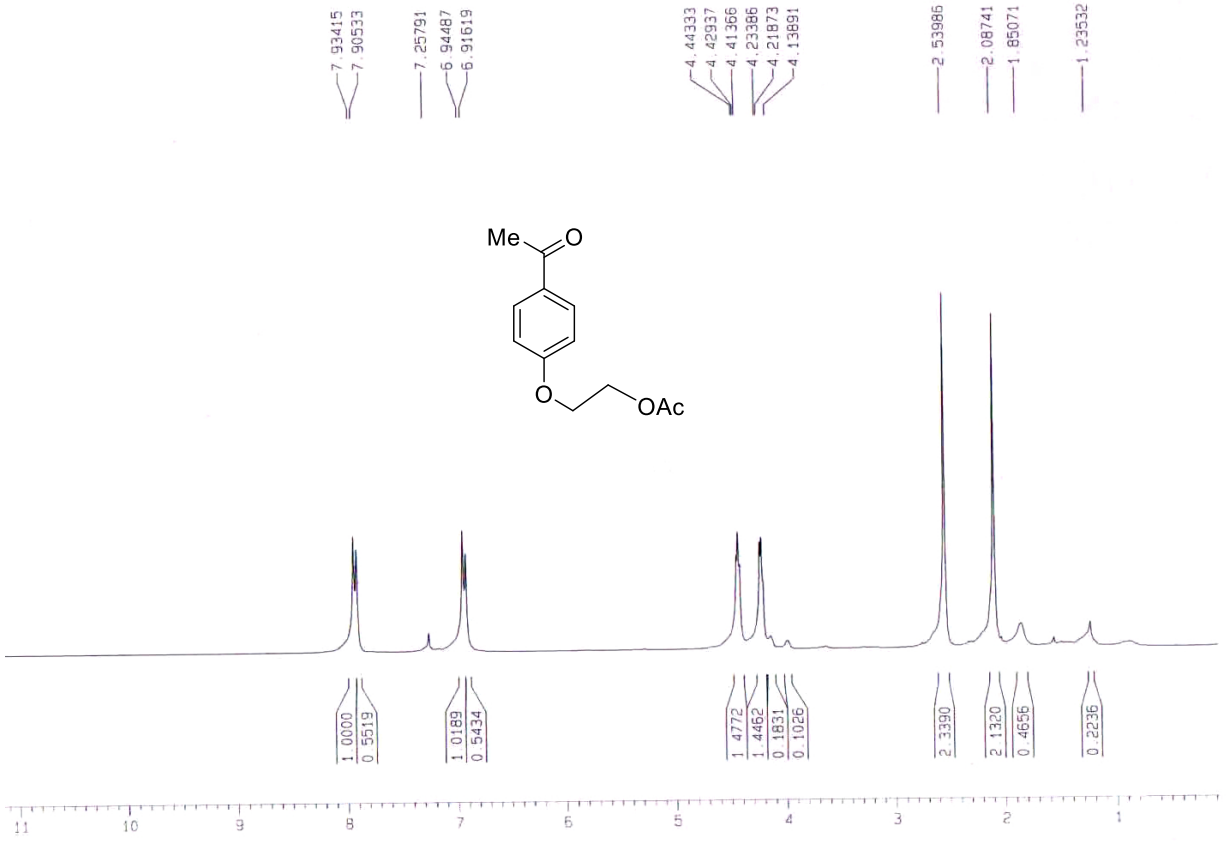


Figure 20: ^{1}H NMR of 2-(4-acetyl-phenoxy)-ethyl acetate **(13)**

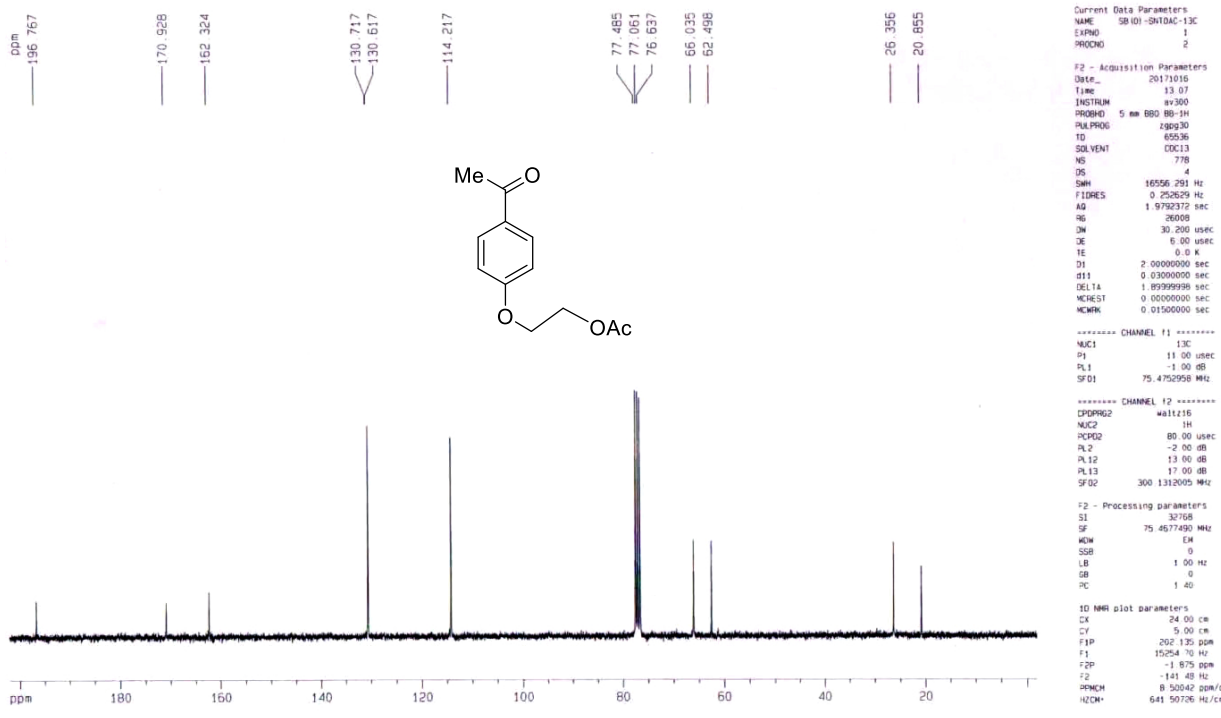


Figure 21: ^{13}C NMR of 2-(4-acetyl-phenoxy)-ethyl acetate **(13)**

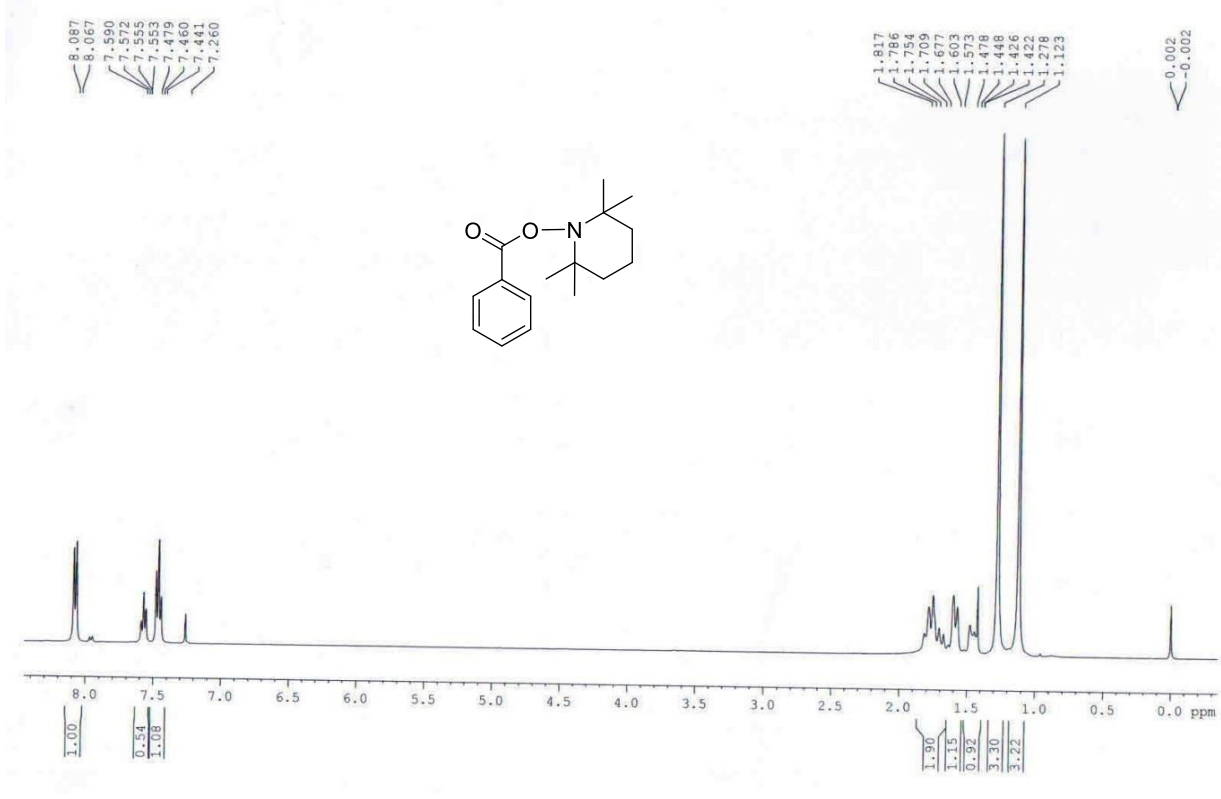


Figure 22: ^{1}H NMR of 2, 2, 6, 6-tetramethyl-piperidin-1-yl benzoate **(6q)**

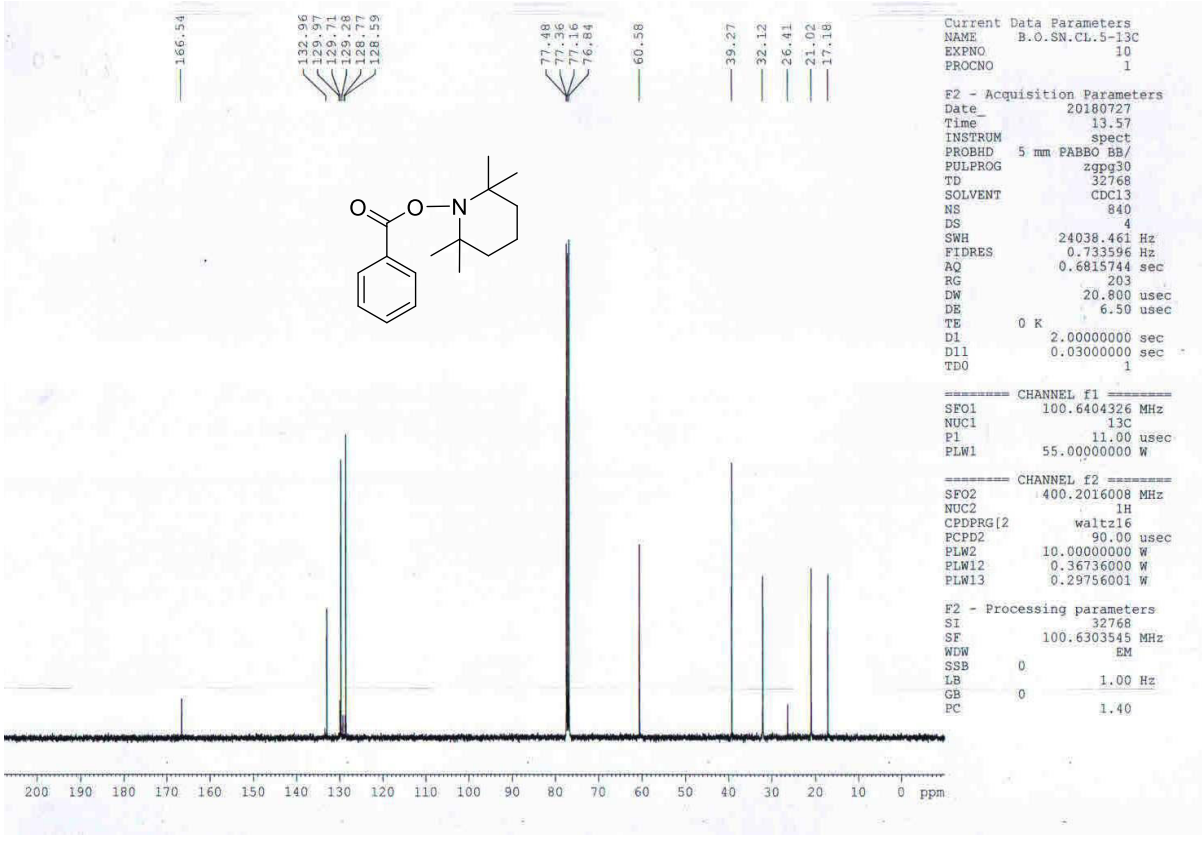


Figure 23: ^{13}C NMR of 2, 2, 6, 6-tetramethyl-piperidin-1-yl benzoate **(6q)**

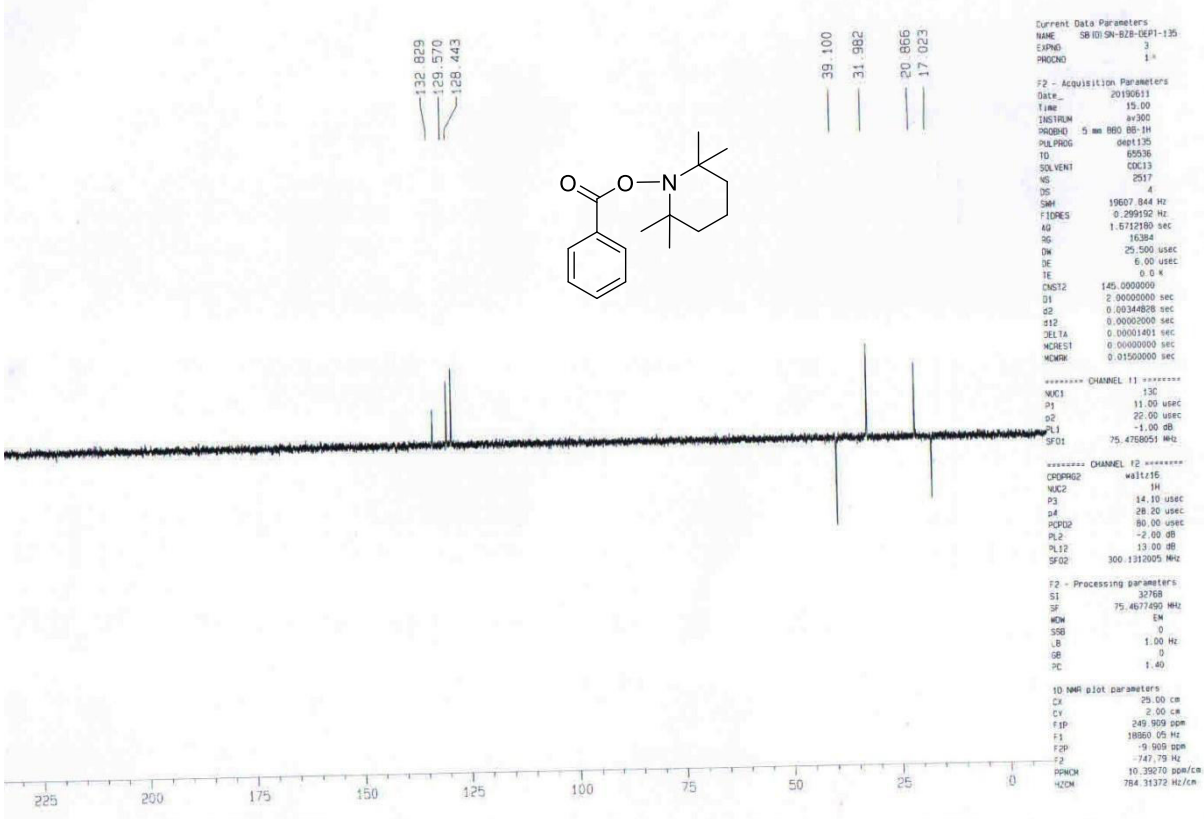


Figure 24: DEPT 135 of 2, 2, 6, 6-tetramethyl-piperidin-1-yl benzoate **(6q)**

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CHAPTER-II; SECTION-1

Versatile recyclable catalyst for different organic transformations: Amberlyst® - 15

CHAPTER-II; SECTION-1

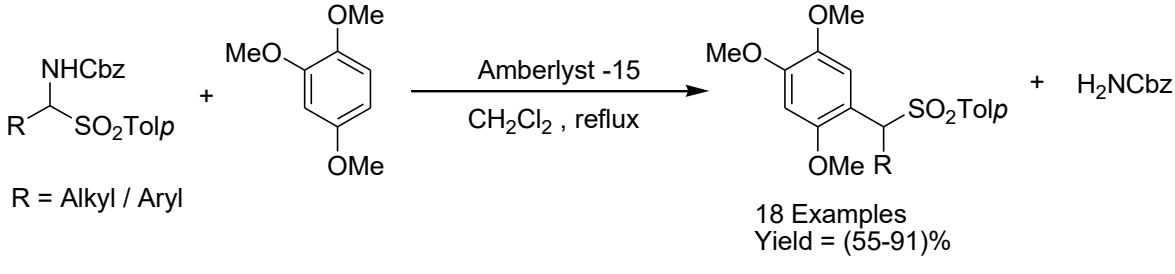
II.1. Versatile recyclable catalyst for different organic transformations: Amberlyst® - 15

II.1.1. Introduction:

Amberlyst-15 is one of the widely used polymeric resins with sulfonic acid functionality which is used as heterogeneous catalyst in both non-aqueous and aqueous media. The use of Amberlyst-15 as a catalyst in different solvent systems had experienced a huge development for the past few decades. This increasing interest in Amberlyst-15 is mainly due to its attributes of being commercially available, physically and chemically stable, non-toxic and non-corrosive nature. This cation-exchange polymer resin has excellent benefits like convenient recovery from the reaction mixture by simple filtration and recyclability without much variation in the catalytic activity, mild reaction conditions avoiding harmful solvents and transition metals. Furthermore due to its environmentally benign nature Amberlyst-15 is now regularly used in several organic syntheses as heterogeneous reusable acid catalyst for various types of transformations generating important simple and complex structural motifs.

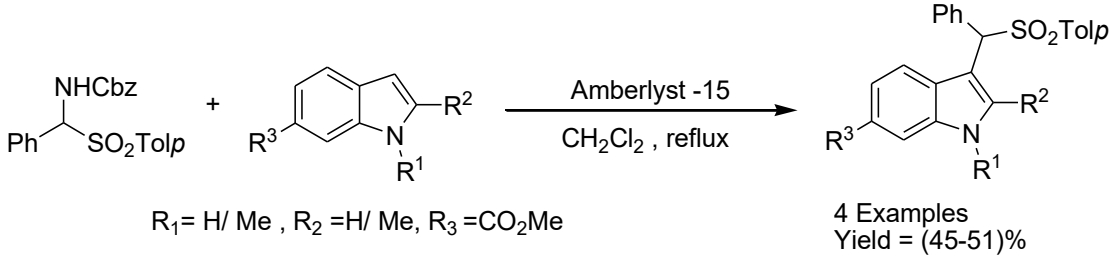
II.1.2. Use of Amberlyst-15 in different organic transformations: A Review

An efficient and novel catalytic method was developed[1] by Kadam *et al.* for the preparation of diarylsulfones through Friedel–Crafts reactions of α-amidosulfones with activated arenes and heteroarenes using Amberlyst-15 as a heterogeneous catalyst which could be the first example of Amberlyst-15-catalyzed synthesis of diarylsulfones (Scheme 1). In this reaction a variety of N-benzyloxycarbonylamino phenyl *p*-tolylsulfones were synthesized from different aromatic and aliphatic aldehydes.



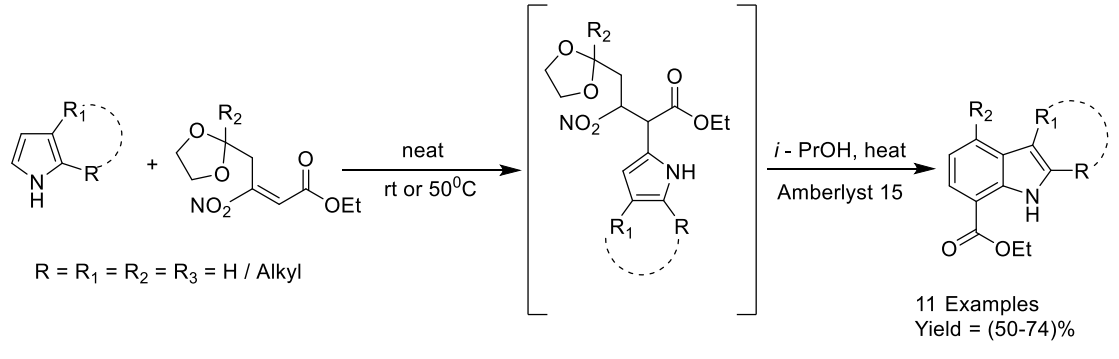
Scheme 1: Amberlyst-15-catalyzed reactions of *p*-tolylsulfones with 1, 2, 4-trimethoxy benzene

Substrates having electron donating groups in the phenyl ring were successfully converted to the corresponding diarylsulfones (Scheme 2) with high yields but aromatic ring substituted with deactivating NO_2– and CN– groups required longer reaction time. Electronic and steric effects of halogen substituted α-amidosulfones were also discussed in this reaction and it was found that *o*- and *m*- chlorobenzenes took more reaction time compared to *p*- substituted benzene but the yields were more or less comparable. The recycling of the solid acid resin was an important factor in this heterogeneous catalytic reaction and major advantage was its easy recovery by centrifugation or by simple filtration. The catalyst Amberlyst-15 was consecutively reused by simple filtration without any further treatment.



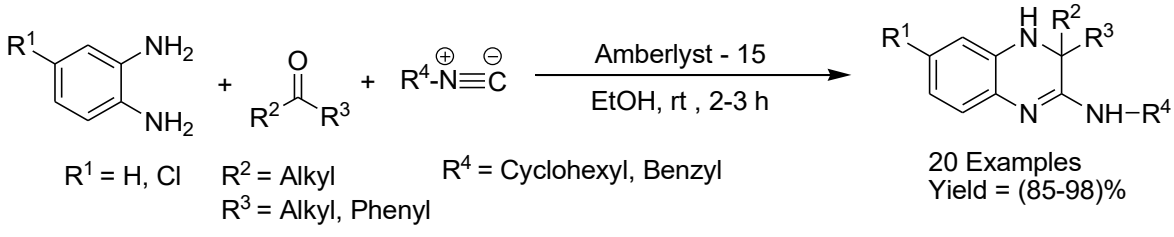
Scheme 2: Amberlyst-15 catalyzed reactions of p-tolylsulfones with electron-rich arenes

Ballini and his team reported[2] an excellent chemoselective procedure for the synthesis of polysubstituted indoles from pyrroles, under very mild conditions, affording moderate yield of the products in one-pot using Amberlyst 15. With the proper choice of starting materials, several substituents were introduced in both the indole and the phenyl rings and the products were obtained in moderate to high yields (Scheme 3). Moreover many important functional groups survived under this protocol. This approach was considered to be very efficient from the sustainability point of view as the reaction was done in eco-compatible solvent and solid-supported reagents where classical work-up was avoided and the crude product was directly charged on a chromatographic column, after filtration of the catalyst from the reaction mixture.



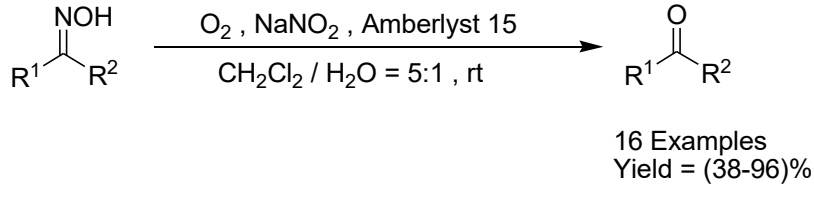
Scheme 3: General pathway for the synthesis of indole derivatives

Murugulla Adharvana Chari reported[3] synthesized a polysubstituted 3, 4-dihydroquinoxalin-2-amine derivatives using different aromatic diamines, carbonyl compounds and several isocyanides in the presence of Amberlyst-15 as a heterogeneous solid acid catalyst. A variety of structurally diverse isocyanides and ketones were used in this reaction to get the products in excellent yields (Scheme 4). He found that the catalyst worked very well with aliphatic, substituted aryl and even in cyclic ketones to afford products in excellent yields. Amberlyst-15 was highly active for the synthesis of derivatives of 3, 4-dihydroquinoxalin-2-amine using substituted ketones and the diamines in high yields and less reaction time. Amberlyst-15 being a heterogeneous and reusable catalyst made this method clean, simple, practical and also economically viable.



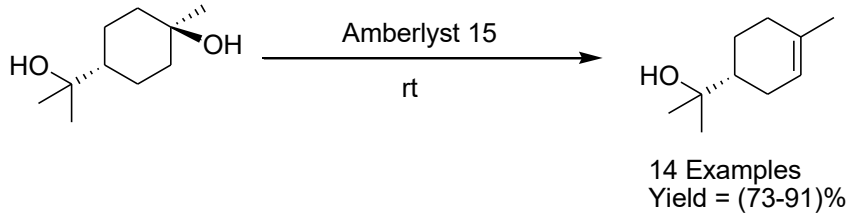
Scheme 4: Synthesis of 3, 4-dihydroquinoxalin-2-amine derivatives using Amberlyst-15 catalyst

Zhang *et al.* have developed[4] a mild, efficient and easy system using molecular oxygen as terminal oxidant, $NaNO_2$ as the catalyst and Amberlyst-15 as a reusable initiator for the oxidative cleavage of oximes to their corresponding carbonyl compounds. This protocol was considered to be the first example of an aerobic oxidative deoximation to carbonyl compounds using $NaNO_2$ as the catalyst, as shown in Scheme 5. The use of O_2 as a terminal oxidant made this transformation attractive and environmentally benign for both laboratory and industrial applications. Amberlyst-15 which acted as the initiator of $NaNO_2$ was reused without regeneration.



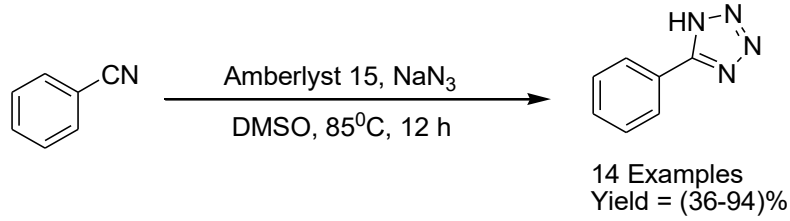
Scheme 5: Deoximation of keto- and aldoximes to carbonyl compounds catalyzed by $NaNO_2$ using O_2 as the oxidant under mild conditions

Afonso and his team have developed[5] an inexpensive and highly efficient protocol for the alteration of tertiary alcohols to their most stable alkenes under mild conditions using Amberlyst-15 as a heterogeneous catalyst (Scheme 6). In this procedure the occurrence of the rearranged and polymerization products were not observed. Some functional groups which are generally affected under acidic conditions, such NHCBz, NHBoc, OSEM, OTBDMS, OBOM and 1, 3-dioxolanemoities remained unaffected during the conditions of alcohol dehydration. Amberlyst-15 was easily recovered from the reaction medium and reused for five cycles without much decrease in the catalytic efficiency.



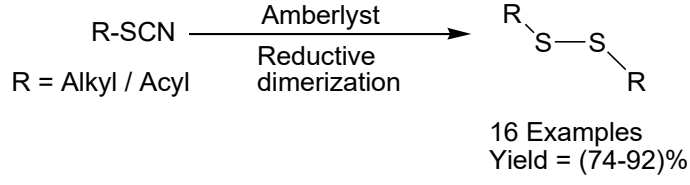
Scheme 6: Dehydration of *trans*-terpin in different solvents

Shelkar *et al.* reported[6] an efficient method for the preparation of 5-substituted 1H-tetrazole derivatives using solid acid resin Amberlyst-15 as a successful heterogeneous catalyst. This method was beneficial as the catalyst was non-toxic and stable at room temperature and gave the products in high yield employing a simple work-up procedure (Scheme 7). In aromatic nitriles, electron-donating or electron-withdrawing property of the substituent played a significant role on the yield of the product. The experimental results demonstrated that the electron-donating substituent at the 4-position furnished the product in excellent yields. The heteroaromatic nitriles gave their corresponding tetrazole in moderate yields but upon exploring the reactions of aliphatic nitriles with sodium azide under same reaction conditions it was exhibited that the catalyst had low activity for aliphatic nitriles compared to aromatic nitriles. The catalyst could be recovered from the reaction mixture by simple filtration, after that it was washed with diethyl ether followed by 0.1 N HCl and dried at 60^0C for one hour. The recovered catalyst was reused for three cycles with negligible loss of activity. As the most probable reason for the catalytic activity they suggested that the catalyst has physical properties like high H^+ exchange capacity and large surface area which made it superior to other existing catalysts.



Scheme 7: Reaction of benzonitrile and sodium azide with Amberlyst-15

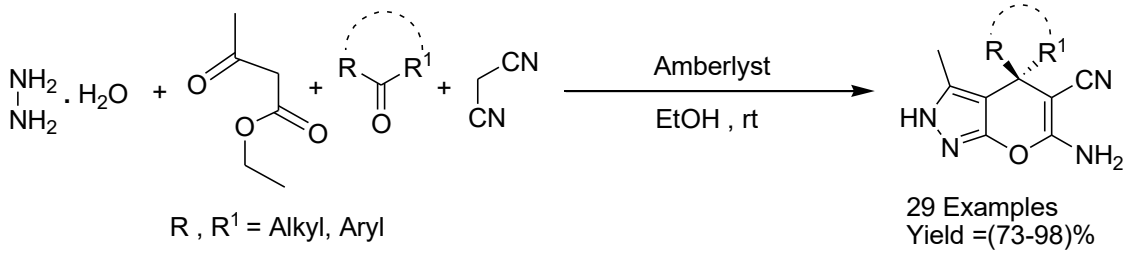
Basu and his team[7] came up with an excellent and eco-friendly protocol to form disulfide bond (S–S linkage) from alkyl and acyl methyl thiocyanates, making their corresponding disulfides in moderate to high yields under metal-free conditions (Scheme 8). This protocol further established the advantage of Amberlyst as a heterogeneous catalyst over existing homogeneous catalysts. Some distinguished features of this reaction included the possibility of carrying out the reaction in water. Even cross-over experiments were performed to reveal that the procedure was very effective for the preparation of unsymmetrical disulfides also. The mechanistic study of the reaction suggested that the S–S linkage was formed in a step-wise manner and not in a concerted mechanism.



Scheme 8: Synthesis of various organic disulfides using Amberlyst in water

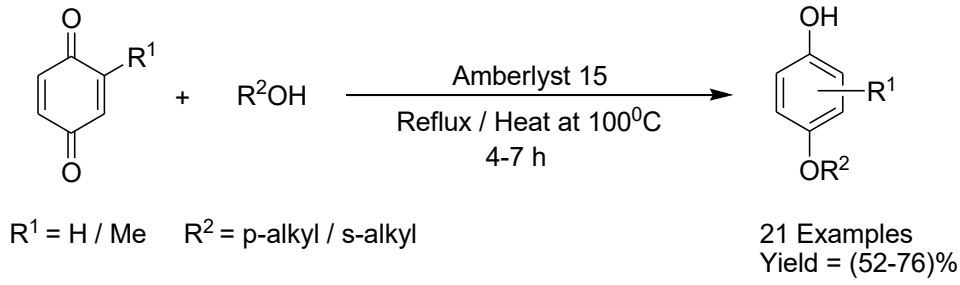
Bihani *et al*. employed[8] Amberlyst as an exceptionally efficient catalyst for the synthesis of a number of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano [2, 3-c] pyrazole-carbonitriles with the help of a four-component reaction using a mixture of hydrazine hydrate, ethyl acetoacetate, aldehyde and malononitrile in ethanol at room temperature (Scheme 9). The catalytic activity of Amberlyst was compared with other resins in order to confirm the best catalyst for the aforesaid conversion. It was noted that the protocol did not give good yield for aliphatic aldehydes. After thorough investigation, it was observed that formation of the Knoevenagel product from the reaction of aliphatic aldehydes with malononitrile were very slow at room temperature.

Upon increasing the temperature the formation of aldol products were also observed in addition to the required Knoevenagel product. But Amberlyst was found to work really well for acyclic/cyclic ketones to give their corresponding dihydropyrano[2, 3-c]pyrazoles or the spirocyclic variants. Some extraordinary attributes of the reaction include easy recovery of the catalyst, reusability of the catalyst at room temperature, short reaction time, mild reaction conditions avoiding environmentally hazardous solvents and no requirement of further chromatographic purification which made this procedure very useful for both academic and industrial purpose.



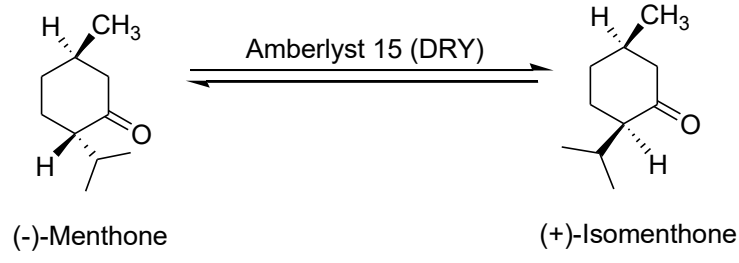
Scheme 9: Synthesis of dihydropyrano [2, 3-c] pyrazole

Asok K. Mallik and his team reported[9] a proficient method for the conversion of *p*-benzoquinones to *p*-alkoxyphenols where primary or secondary alcohols acted as reducing agents at an intermediate stage (Scheme 10). It is a growing trend now-a-days to explore the reducing property of alcohols for the conversion of various organic substrates and this process came out as one of the pioneering examples in this field. For symmetrical benzoquinones the process went quite well, but when unsymmetrical *p*-benzoquinones were used as substrate it was observed that both isomeric products were formed approximately in the ratio of 15:1, which could not be separated by column chromatography using silica gel. The isolation of the major product was successful by fractional crystallization only in cases where the products were obtained by using methanol. The mechanistic studies based on this reaction suggested that the protonated quinone was first methylated and then the forming product was reduced with protonated quinol thus setting up a chain process which went continuously to the end.



Scheme 10: Conversion of *p*-benzoquinones to *p*-alkoxyphenols

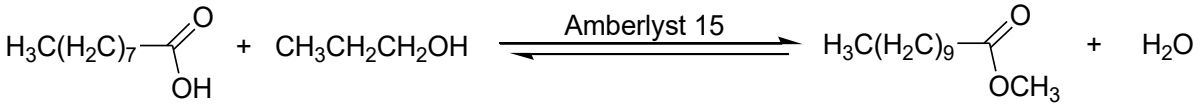
Hampton and his team developed[10] a novel organic reaction involving the acid catalysed isomerisation of (−) menthone to (+) isomenthone (Scheme 11). This method replaced the traditional mineral acid catalyst with an acidic ion-exchange resin, Amberlyst-15. This modification dramatically reduced the amount of generated waste, decreased the hazards caused by concentrated acid and allowed the isomer ratio to be recorded as a function of time. The instructive impact of the conducted experiment was significantly improved through the examination of effect of the catalysts to the position of equilibrium and to the kinetics of reaction.



Scheme 11: The Isomerization of (-) Menthone to (+) Isomenthone

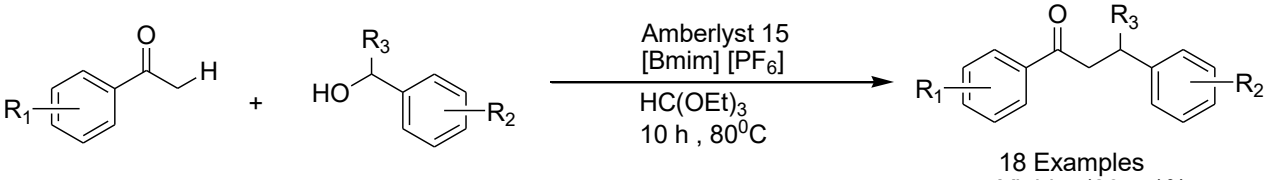
Another broad kinetic investigation of the esterification of nonanoic acid with 1-propanol in liquid phase was carried out[11] by Sharma *et al.* using Amberlyst 15 resin (Scheme 12). Kinetic experiments were also conducted using a batch reactor system over the temperature range of 323.15 to 363.15 K. It was found that both internal and external diffusion limitations did not influence the overall reaction rate. The conversion of nonanoic acid got improved with increasing temperature and catalyst loading. The model predicted the kinetic activities of the studied system reasonably well while water was found to be highly adsorbed than other species present in the system.

After studying the influence of carbon chain length in the alcohol and their effects on reaction kinetics, it was observed that activation energy increased with the increase in chain lengths of alcohols.



Scheme 12: Esterification of nonanoic acid with 1-propanol

Bhanage and his team have developed[12] an inexpensive, metal-free and relevant method for the direct α-alkylation of acetophenones with benzhydrols and also 1-phenylethanols using resin Amberlyst-15 and ionic liquid (Scheme 13). The reaction protocol was governed in an atom- and step-economic way to construct a C−C bond where water is the only by-product. It was noted that sterically bulky benhydrols also worked well providing the corresponding products in good yield. 1-Phenylethanol and their derivatives with electron donating groups and halogen substituents also furnished the required products in high yields. They examined the reaction also with aliphatic ketones which provided the product in comparatively low yield and the reaction with cyclohexanone provided the corresponding product in very less amount. Moreover, the reaction with ketones having electron withdrawing groups and aliphatic as well as allylic alcohols failed to produce the desired products under the optimized reaction condition. In addition to this, the catalytic system had moisture-stability, greater substrate compatibility, functional group tolerability, advantages in the form of high yield of products, mild conditions, operational simplicity and reusability of the catalyst. It was found that the catalyst was utilized for upto four times with negligible loss in catalytic activity.



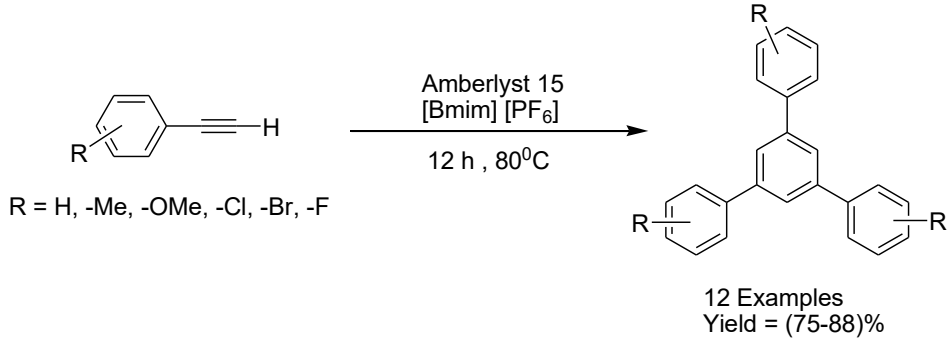
R_1 = H, -Me, -OMe, -Cl, -$N(CH_3)_2$

R_2 = H, -Me, -OMe, -Cl, -Br

R_3 = -Ph, -Me

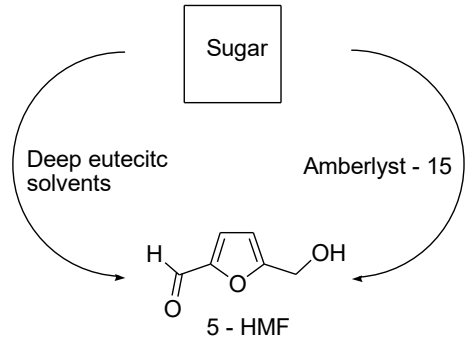
Scheme 13: Direct α-alkylation reactions of ketones

Synthesis of C_3-symmetric triarylbenzenes via cyclotrimerization of alkynes was also developed[13] using Amberlyst-15 / [Bmim] [PF_6] as a reusable catalytic system (Scheme 14). This method provided an easy, compatible and effective method for the construction of 1, 3, 5-triarylbenzene derivatives with greater yields. Their studies revealed that the alkynes having halo substituents at *ortho*, -*meta*, and -*para* positions also gave the required 1, 3, 5-trihaloarenes in very high yields under the optimized conditions. Moreover, the reaction also worked well with disubstituted, bulky, and internal alkynes providing the respective triaryl benzenes in high yields. This method came out as an extremely effective one employing simple experimental procedure, short reaction time, hazardous solvent and transition metal-free mild reaction conditions to make it a 'green' approach. The reused catalyst made this process waste-free and suitable for scaling-up.



Scheme 14: Synthesis of C_3 symmetric triarylbenzenes via cyclotrimerization of alkynes

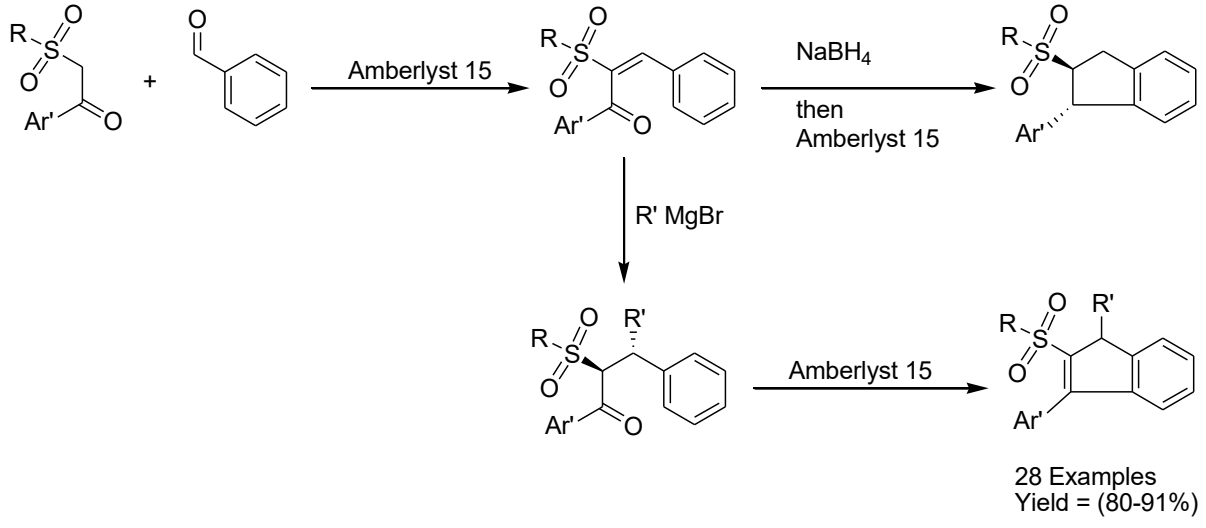
Marullo*et al*. came up[14] with a sustainable approach for the dehydration of sucrose and fructose in deep eutectic solvent using Amberlyst 15 as a heterogeneous catalyst (Scheme 15). This catalytic system was checked with different initial amount of substrates and the catalyst was reused and recycled for upto 5 cycles with marginal loss of catalytic activity. They carried out the dehydration of fructose obtaining a conversion to 5-HMF in 71% yield, which is equivalent to that observed under silent conditions.



Scheme 15: Dehydration of sucrose and fructose in deep eutectic solvent using Amberlyst-15

Another novel method utilising Amberlyst 15 for the synthesis of 2-sulfonylindenes and 2-sulfonylindanes was implemented[15] by Chang and his team. This high-yield and facile synthetic route provided the possibility for intramolecular Friedel-Crafts annulations in toluene under reflux through the formation of two carbon-carbon (C-C) bonds (Scheme 16).

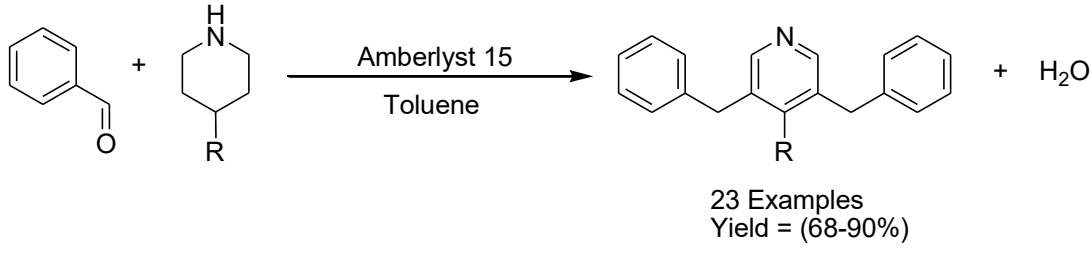
The team also demonstrated the DFT calculations to explain the regioselectivity of the addition reaction. This process provided a convenient route for the synthesis of two carbon−carbon (C−C) bonds. They also took the initiative to explore synthetic applications of the newly developed method towards the formation of quinoline, indanone, isoquinoline, chroman and flavanone skeletons.



Scheme 16: Synthesis of 2-sulfonyl indenes and indanes using Amberlyst 15

Amberlyst 15 was also implemented[16] in the model Prins-Ritter reaction of (-) isopulegol with benzaldehyde and MeCN generating 4-amido derivatives of octahydro-2H-chromenes. It was shown that a little amount of water added prior to the catalyst affected the selectivity to a large extent. Without addition of water or when its amount is less, (*S*)-amide is formed from the more stable ion, but with an increase in amount of water, an increase in selectivity towards (*R*)-amide was observed, strongly suggesting a kinetically controlled formation of the preferred enantiomer which was confirmed by performing the quantum-mechanical calculations. Thus simply the addition of water turned this method into a very simple yet effective one for controlling both the selectivity and yield of the products coming out from the Prins-Ritter reaction.

Chang *et al*. reported[17] a solid support-controlled reaction pathway forming 3, 5-diarylmethylpyridines via one-pot easy intermolecular cyclo-condensation of substituted piperidines with several aryl-aldehydes under refluxing condition using toluene as the solvent in satisfactory yields (Scheme 17). This process provided a cascade like pathway for making two carbon−carbon bonds.



Scheme 17: Synthesis of 3, 5-diarylmethylpyridines using Amberlyst 15

Thus, a concise overview for the usage of solid acid resin Amberlyst with different examples has been presented to account for the significant applications of the catalyst we have utilised to validate several schemes in the following sections.

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CHAPTER-II; SECTION-2

C-N bond formation in wet acetonitrile using Amberlyst®-15(H) as a recyclable catalyst

CHAPTER-II; SECTION-2

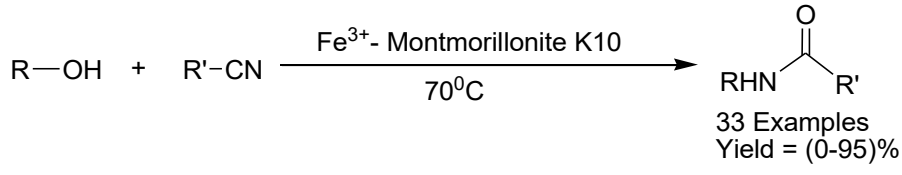
II.2. C-N bond formation in wet acetonitrile using Amberlyst®-15(H) as a recyclable catalyst

II.2.1. Introduction:

Formation of C-N bond in aliphatic skeletons, especially from alkanols, is a difficult but formidable synthetic operation. Ritter reaction of nitriles with substituted alkenes or alcohols using concentrated sulphuric acid in glacial acetic acid is often used for this purpose through the formation of substituted amides.

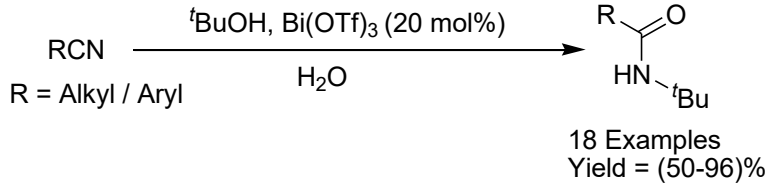
II.2.2. C-N bond formation in organic skeleton: A Review

In order to avoid the involvement of such a strong mineral acid, several modifications have been proposed. Lakouraj and his team were among the pioneers in this field. They suggested[1] an effective method for the preparation of secondary amides by reaction of alcohols with nitriles using a catalytic amount of Fe^{3+}-montmorillonite K10 (Scheme 18).



Scheme 18: Synthesis of secondary amides from alcohols using Fe^{3+}-montmorillonite K10

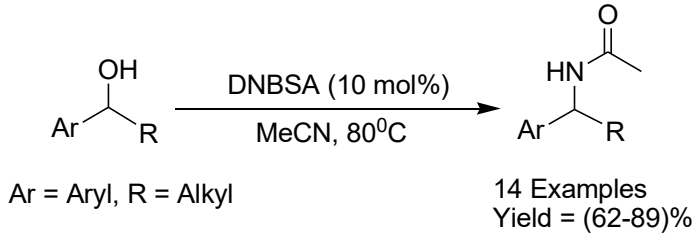
Callens *et al*. reported[2] a general procedure for the transformation of nitriles into amides using catalytic amount of bismuth triflate avoiding the use of any other corrosive acids as shown in Scheme 19.



Scheme 19: Synthesis of amides from nitriles using Bismuth triflate

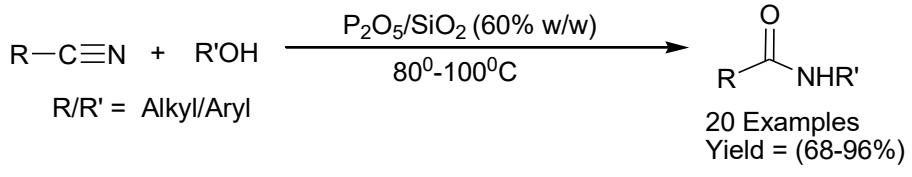
Simple organic acids like 2, 4-dinitrobenzenesulfonic acid (DNBSA) was also used[3] to catalyse the amidation of secondary benzylic alcohols.

This metal-free protocol represented a clean and environmentally compatible alternative to the use of Brønsted acids and transition metals as catalysts (Scheme 20). In this reaction a different pathway involving a formal dimerization reaction took place with tertiary α, α-dimethylbenzylic alcohols under the acid-catalytic conditions.



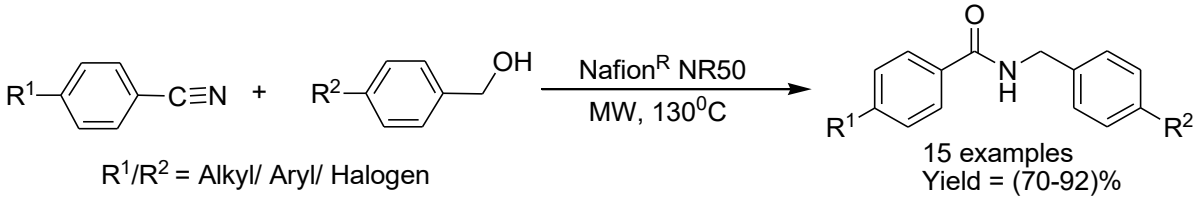
Scheme 20: Synthesis of amides from alcohols using DNBSA

Another efficient P_2O_5/SiO_2-catalyzed Ritter reaction presented[4] several advantages including clean reaction conditions, easy work up, scale up and improved yields (Scheme 21). Furthermore, the chemoselectivity of the reaction was also evaluated via the competitive Ritter reaction of benzyl alcohol.



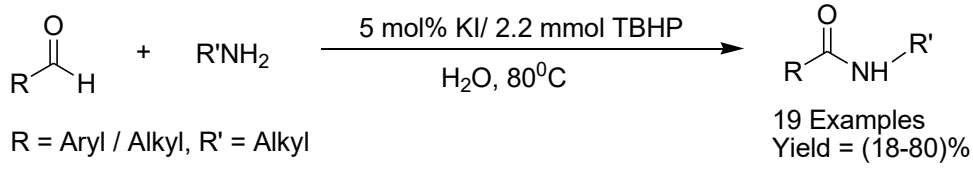
Scheme 21: Synthesis of amides from alcohols and nitriles using P_2O_5/SiO_2

An atom-economic and environment friendly method was demonstrated[5] using inexpensive, relatively low toxic and solid-supported Nafion®NR50 as a catalyst in solvent-free reaction conditions (Scheme 22). The significant feature of this procedure was the ease of handling the catalyst, as it involved simple addition of solid Nafion beads in the reaction container, which can be removed by forceps after the reaction got completed.



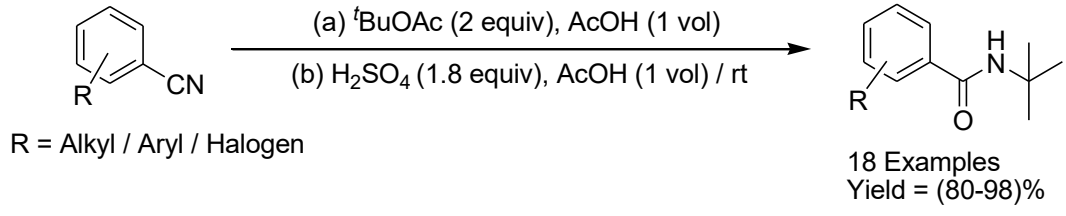
Scheme 22: Synthesis of amides from nitriles and alcohols using Nafion®NR50

Reddy *et al*. developed[6] a straightforward method for the synthesis of several amides through oxidative coupling of an aldehyde or an alcohol with an amine using TBHP (Scheme 23).This protocol eliminated the necessity of any other external base or additive. Moreover, this methodology was extended to chiral amino acid derivatives also which have important uses as intermediates in pharmaceuticals and synthetic organic chemistry.



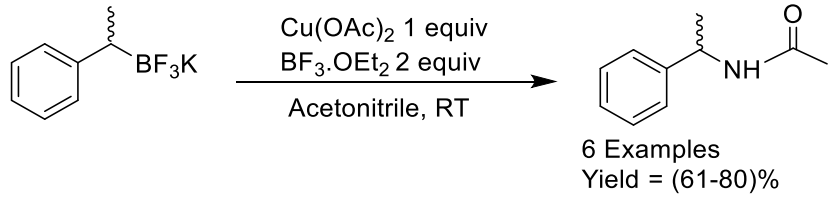
Scheme 23: Synthesis of amides from amine and alcohols using TBHP

A safe and robust method was introduced[7] to perform the Ritter reaction using *tert*-butyl acetate in combination with acetic acid (Scheme 24). The method had broad scope for aromatic, alkyl, and α, β-unsaturated nitriles.



Scheme 24: Synthesis of amides from nitriles using ^{t}BuOAc/AcOH

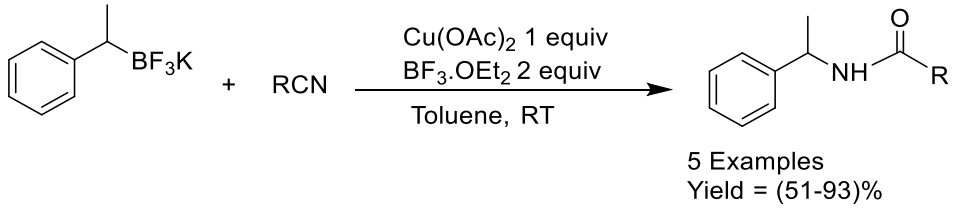
Lemaire and his team introduced[8] a mild and efficient protocol for the preparation of amides from the reaction of nitriles and trifluoroborate potassium salt derivatives catalysed by copper acetate and boron trifluoride (Scheme 25 and Scheme 26).



Scheme 25: Synthesis of amides using $Cu(OAc)_2$ and $BF_3.OEt_2$ in acetonitrile (1)

This method was conducted at room temperature without any necessity of dry and inert atmosphere as well as any of the additional metal-ligand complex.

They proposed that the coupling involved an oxidative nucleophilic substitution followed by the attack of the nitrile as nucleophile as shown in the mechanism (Figure 1).



Scheme 26: Synthesis of amides using $Cu(OAc)_2$ and $BF_3.OEt_2$ in acetonitrile (2)

They proposed that the combination of boron trifluoride and copper acetate gave rise to an oxidative complex having the capability to reverse the polarity of the C–B bond, creating a carbocation which reacted subsequently with the nucleophilic nitrogen atom of the nitrile.

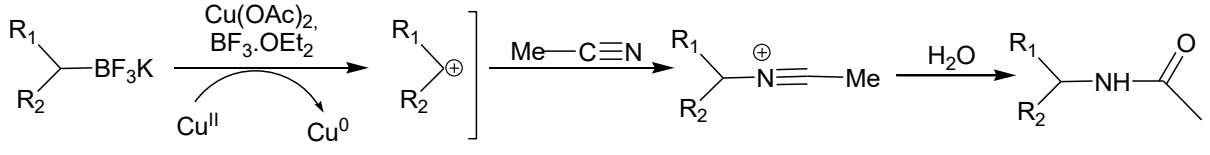
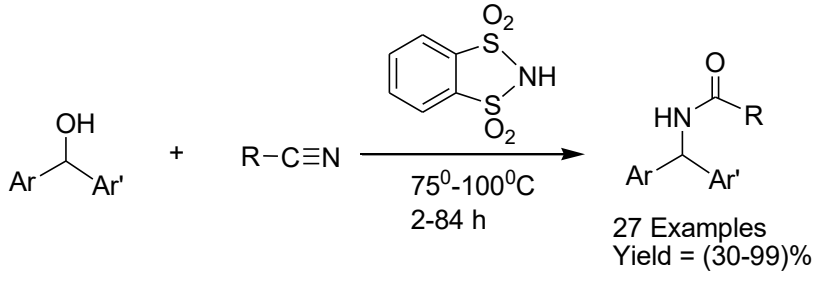


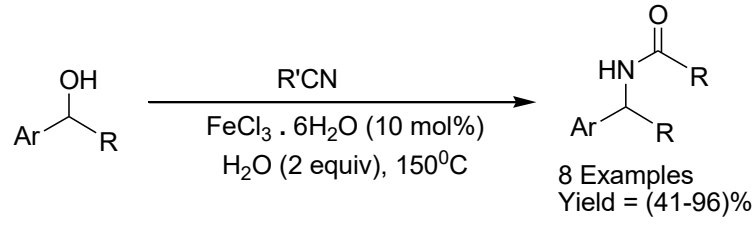
Figure 1: Mechanism for the synthesis of amides using $Cu(OAc)_2$ and $BF_3.OEt_2$

The usefulness of *o*-benzenedisulfonimide as a catalyst in Ritter-type reactions was demonstrated[9] by Barbero *et al*. where the products were obtained in moderate to excellent yields. Moreover, this method turned out to be a safe, non-toxic, and non-corrosive one in comparison those where strong liquid or solid Brønsted acids are used (Scheme 27). The catalyst was easy to recover and can be reused without any loss of catalytic activity contributing a lot towards ecological and economic advantages.



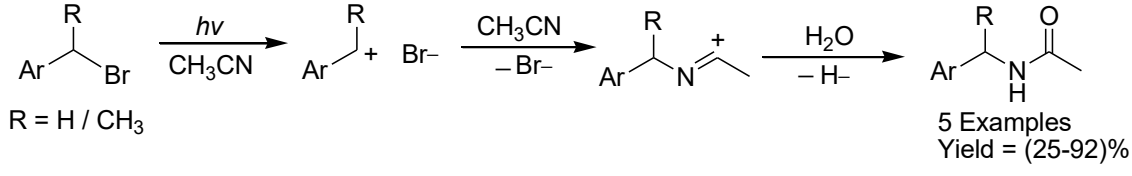
Scheme 27: Synthesis of amides using from alcohols and nitriles using *o*-benzenedisulfonimide

Some important works in this field demonstrated that $FeCl_3$ is highly capable of activating benzylic alcohols for producing carbocation intermediates, Cossy and his team proposed[10] a unique method to synthesize amides from benzylic alcohols or *t*-butyl acetate using Ritter reaction catalyzed by $FeCl_3$-$6H_2O$. The reaction pathway utilised nitriles with benzylic alcohols as well as ^{t}BuOAc generating a vast range of benzylic amides and *t*-butyl protected primary amides (Scheme 28). This process was an example of inexpensive and eco-friendly protocol allowing the preparation of several amides in good to high yields.



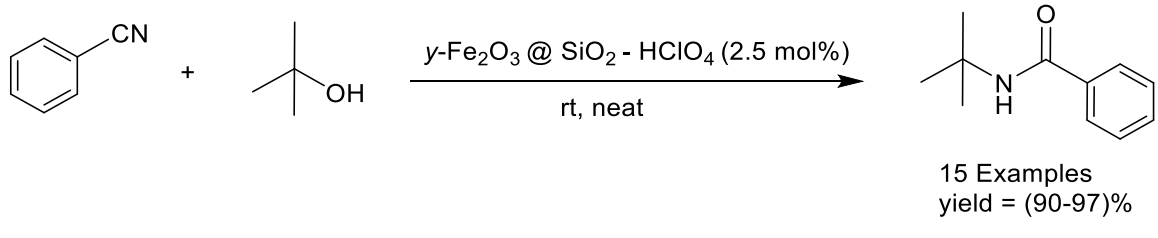
Scheme 28: Synthesis of amides using from alcohols using $FeCl_3$-$6H_2O$

The photo-Ritter reaction[11] was one of the most promising alternative methods that overcame some of the disadvantages existing in the previous methods allowing a more 'green' synthetic approach (Scheme 29).



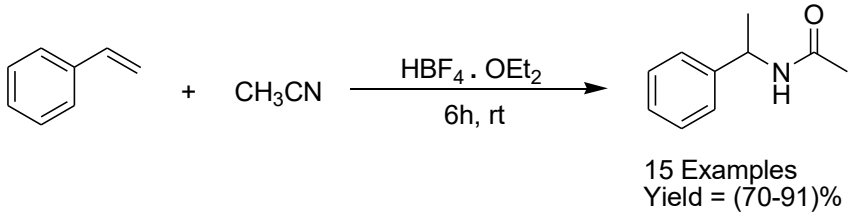
Scheme 29: Synthesis of amides by photo-Ritter reaction

Heydari and his team developed[12] a convenient and efficient magnetically recoverable nanocomposite catalyst for the preparation of different amides from alcohols and nitriles using [γ-Fe_2O_3@SiO_2-$HClO_4$] (Scheme 30). Some important aspects of this work included the involvement of a mild, cost-effective, efficient, easily applicable and reusable catalytic system for the modified Ritter reaction.



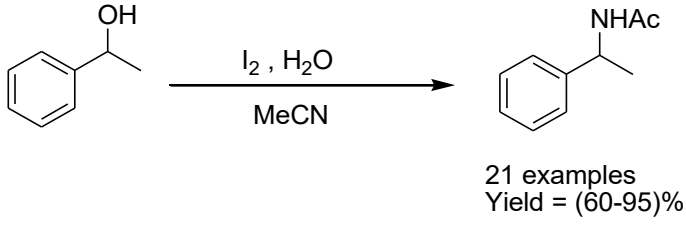
Scheme 30: Synthesis of amides using [γ-Fe_2O_3@SiO_2-$HClO_4$]

Reddy *et al*. suggested[13] a very efficient method where a variety of alkenes underwent smooth amidation with nitriles in the presence of HBF_4-OEt_2 at room temperature and mild reaction conditions affording the corresponding secondary amides in good to excellent yields (Scheme 31). The use of easily available and mild reagent HBF_4-OEt_2 made this method simple, suitable and practical.



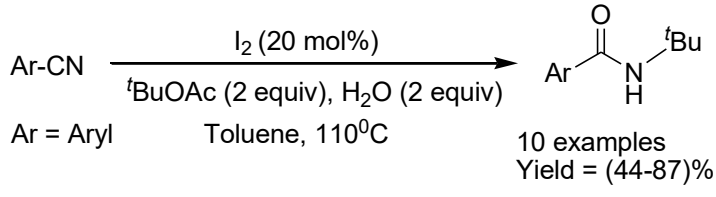
Scheme 31: Synthesis of amides using HBF_4-OEt_2

Another simple but very proficient method was developed[14] for the synthesis of amides (Scheme 32) and N-*tert*-butyl amides (Scheme 33) from alcohols, nitriles and *tert*-butyl acetate.



Scheme 32: Synthesis of amides using I_2

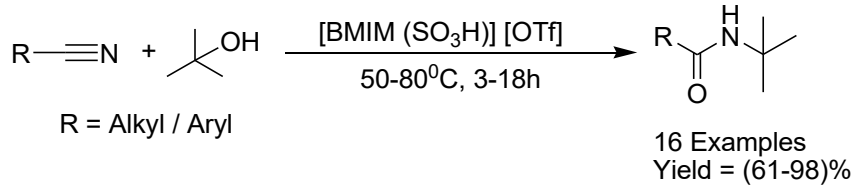
This process was an excellent implementation of Ritter reaction using catalytic amount of molecular iodine in a sealed tube making it an inexpensive and eco-friendly process.



Scheme 33: Synthesis of *tert*butyl amides using I_2

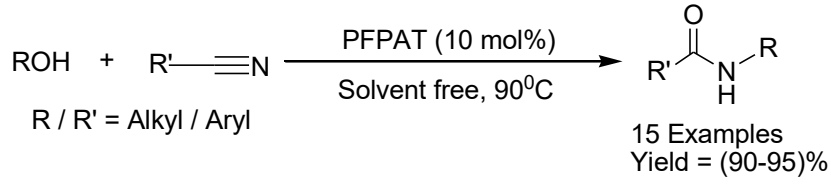
Laali and his team had demonstrated[15] the utility of Brønsted-acid imidazolium ionic liquid [BMIM(SO_3H)][OTf] as a catalyst for the synthesis of a wide variety of amides in high yield under mild conditions via the Ritter reaction of alcohols with nitriles (Scheme 34).

They also illustrated the utility of $NOPF_6$ immobilized in $[BMIM][PF_6]$ for the reaction of bromides with nitriles and for the preparation of adamantyl amides from adamantane and nitriles.



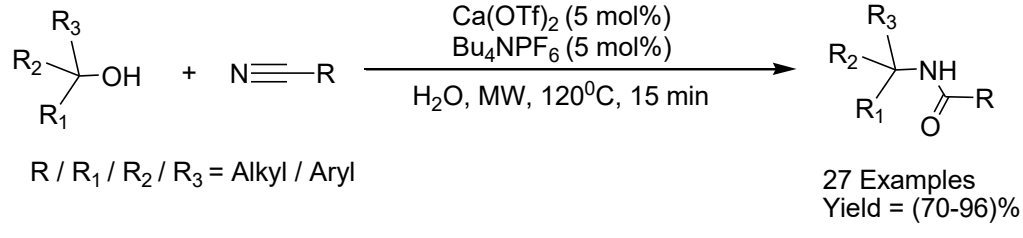
Scheme 34: Synthesis of *tert* butyl amides using $[BMIM(SO_3H)][OTf]$

Another brilliant chemoselective and metal-free methodology was executed[16] for a modified Ritter reaction using pentafluorophenylammoniumtriflate (PFPAT) as an organocatalyst (Scheme 35). PFPAT was easily prepared from commercially available pentafluoroaniline and triflic acid at low cost and the product isolation in this case was also very easy.



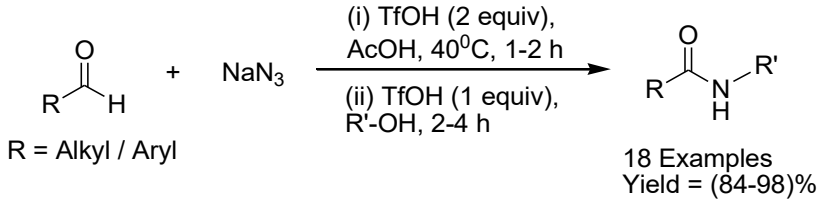
Scheme 35: Synthesis of amides using PFPAT

Yaragorla and his team came up[17] with a solvent-free synthetic protocol for Ca(II)-promoted Ritter reaction to provide various primary amides from alcohols and nitriles (Scheme 36). This methodology enabled the synthesis of a wide range of important amides and gathered much attention due to the simple and environmentally benign reaction conditions.



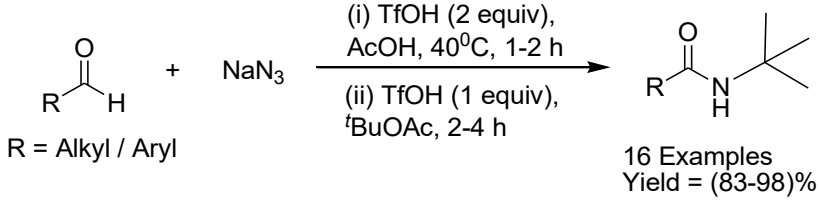
Scheme 36: Synthesis of amides using $Ca(OTf)_2$

A one-pot protocol for Schmidt–Ritter reaction was developed[18] using easily available aldehydes, alcohols (and acetates) and sodium azide with TfOH. This reaction pathway enabled the synthesis of N-acylimides (Scheme 37and Scheme 38) through facile Schmidt reaction.



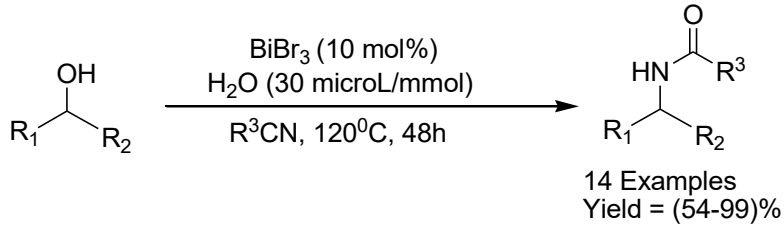
Scheme 37: Synthesis of amides using TfOH/AcOH (1)

The proposed synthetic route showed that the imides are the intermediates in Ritter reaction to form the amides ensuring wide substrate scope with excellent yields.



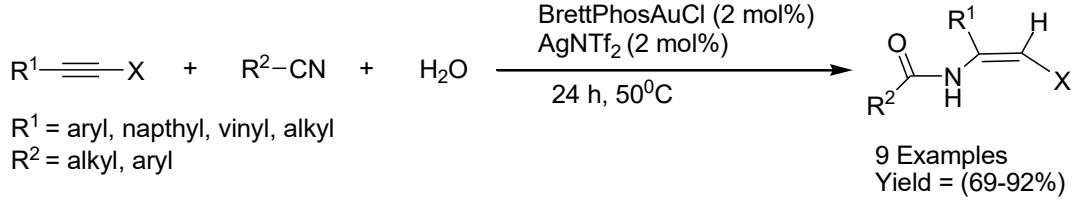
Scheme 38: Synthesis of amides using TfOH/AcOH (2)

Ueno *et al*. developed[19] an environmentally benign process for the amidation using alcohols and nitriles with commercially available bismuth salt as an effective catalyst (Scheme 39). This reaction procedure revealed that utilization of the ether came out as by-product was the key for optimizing this reaction. This observation revealed the significance of using bismuth salt as a catalyst, which is inexpensive, could be easily removed using aqueous hydrochloric acid and purified by washing and drying without any organic solvent.



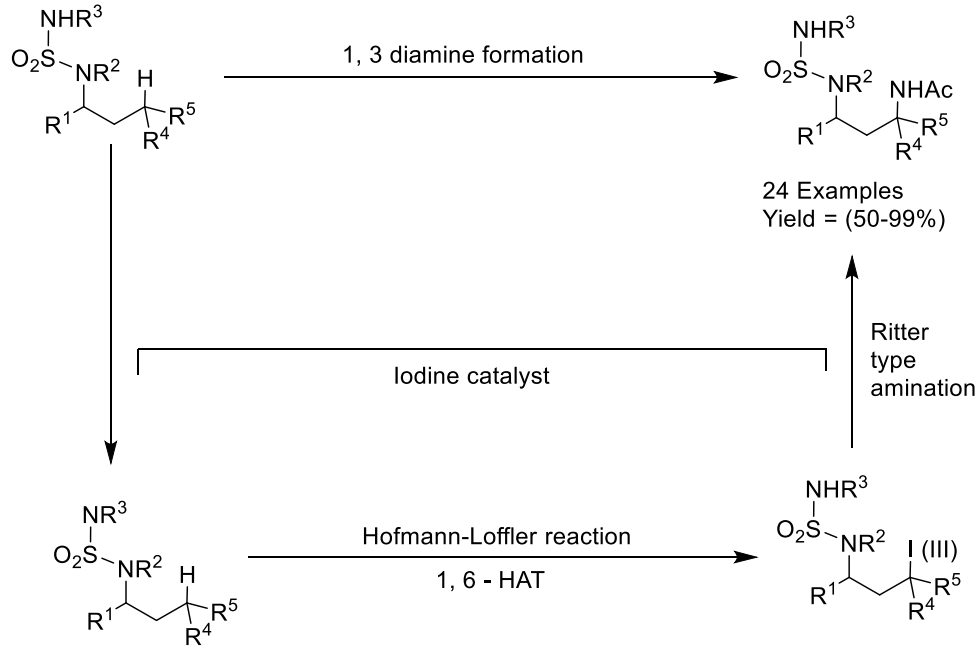
Scheme 39: Synthesis of amides using $BiBr_3$

Yang *et al*. reported[20] an efficient as well as stereoselective method for the preparation of (*Z*)-β-halogenated enamide by gold catalysed Ritter reaction. The team used 2 mol% BrettPhosAuCl and 2 mol% $AgNTf_2$ for a broad range of nitriles which underwent the Ritter reaction smoothly with vinylic, aliphatic, aromatic and halogen containing alkynes to provide structurally varied (*Z*)-β-halogenated enamides in satisfactory yields (Scheme 40). Taking into consideration that other nitriles are not as easy to avail as acetonitrile, they implemented 1, 2-dichloroethane (DCE) as solvent to decrease the amount of nitrile; where it was shown that most of the nitriles reacted to give rise to the corresponding (*Z*)-*β*-chlorogenated enamides with good yields.



Scheme 40: Synthesis of (*Z*)-β-halogenated enamide using Ritter reaction

Another iodine catalysed Ritter-type amidation reaction of non-activated C-H bonds was presented[21] *via* the formation of 1, 3-α-tertiary diamines where a sulfamidyl radical served the purpose of a promoter towards tertiary C-H bond to iodination via an exclusive 1, 6-hydrogen atom transfer (HAT) process (Scheme 41).

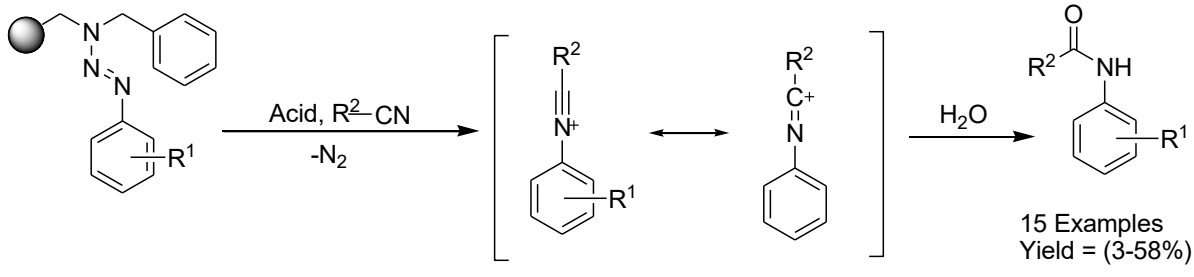


Scheme 41: Synthesis of 1, 3 diamine derivatives using Iodine as a catalyst

Iodine in is high oxidation state often has the role of a promoter towards nucleophilic substitution, but here no cyclization by the sulfamide was observed interrupting the usual Hofmann−Loffler pathway. This successive Ritter reaction furnishing C-N bonds was one of the pioneer concepts for catalyst turnover in iodine redox reaction. The method had the advantages of providing broad range of 1, 3 diamine derivatives with 42 to 99% yields.

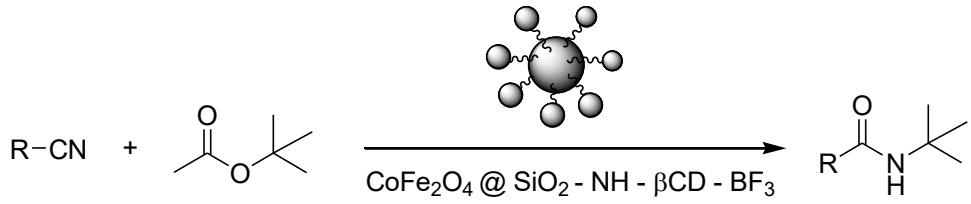
N-Arylamides were obtained[22] via a novel route utilising the cleavage of aryltriazenes with aryl or alkyl nitriles. A different type of Ritter reaction was thus developed allowing the use of acetonitrile as solvent as well as reagent using solid-supported precursors (Scheme 42). The optimised reaction produced a diverse range of N-arylacetamides using aryltriazenes as building blocks. Moreover, synthesis of arylboronic ester substituted triazenes was also demonstrated in the report. This method was expanded further to validate the use of other commercially available nitriles as the suitable reagents for the Ritter type reaction.

To examine the potential of the described protocol for the synthesis of novel compounds, the cleavage via Ritter-type conversion was successfully merged with further on-bead modifications. The application of this protocol offered immense opportunities to synthesize several amides and initiate greater use of the Ritter reaction using triazenes in solution phase.



Scheme 42: Synthesis of N-arylacetamides using Ritter type reaction

Hamadi and his team described[23] the synthesis of BF_3-functionalised β-CD grafted magnetic nanoparticles as a magnetically recoverable catalyst. They found the $CoFe_2O_4$@SiO_2-NH-βCD-BF_3 catalyst in solvent-free condition gave excellent catalytic activities and performed the required reaction with yields up to 95%, in low reaction time and high reusability (Scheme 43). This unique catalyst bearing super acidic sites generated by immobilised BF_3 was then successfully used in the modified Ritter reaction and reused at least upto 6 times without any significant loss in catalytic activity.



Scheme 43: Synthesis and use of BF_3-functionalised β-CD grafted magnetic nanoparticles

A vivid overview of recently developed protocols for C-N bond formation with several substrates and catalysts has been demonstrated to account for the relevance and importance of the investigation going to be described afterwards.

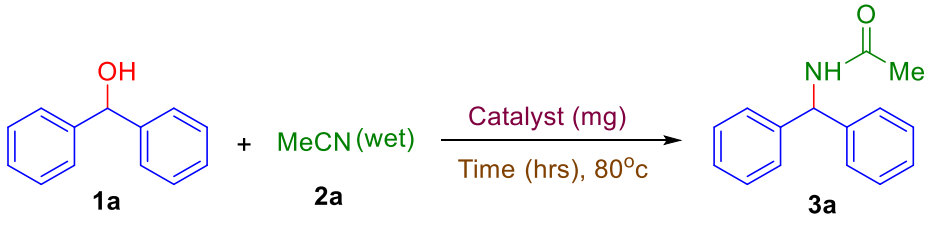
II.2.3. Present investigation:

II.2.3.1. Background of the investigation:

Many of the aforesaid methods for C-N bond formation suffer from several disadvantages such as use of corrosive acid catalysts,[7, 18] toxic and moisture-sensitive reagents,[7] use of expensive compounds and materials,[20] elevated reaction temperatures,[4, 5, 9, 10, 14, 17, 19] prolonged reaction time,[19, 20] susceptibility with acid-labile and bulky functional groups and concomitant formation of several by-products arising out of different side reactions including rearrangement. But the main drawback of most of the existing methods is the decomposition of the catalysts during aqueous work-up leading to tedious protocols for isolation, separation and recovery of the products. Recyclable resins bearing acidic sites offer the advantages not only due to their subtle catalytic attributes but also from the standpoint of reusability along with physical and chemical stability. Further advantages are associated with their heterogeneous nature in terms of their facile separation from the reaction mixture and easier isolation of the products. Keeping in mind the aforesaid attributes, we report herein an admirable catalytic application of Amberlyst®-15(H) for the formation of C–N bond in wet acetonitrile.

II.2.3.2. Results and Discussion:

To check the applicability of Amberlyst®-15(H) in this reaction, the reaction was carried out with benzhydrol (**1a**, 1 mmol), wet MeCN (**2a**, 1 mmol) in the presence of various catalysts along with different solvent systems at 80^{0}C to produce N-benzhydrylacetamide (**3a**) (Scheme 44), as presented in Table 1.



Scheme 44: Reaction of benzhydrol (**1a**) using different catalysts and reaction medium

Table 1: Optimization of the reaction conditions[a] using different catalysts and solvents

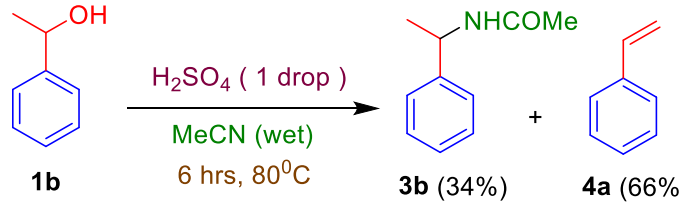
Entry	Catalyst	Amount (mg)	Solvent	Time (h)	Yield of 3a(%)[b]
1	Dowex-50	40	Toluene	6	--
2	Dowex-50	50	DMF	8	- -
3	Dowex-50	50	Acetonitrile	8	32
4	Amberlite (IR-45)	40	Toluene	6	24
5	Amberlite (IR-45)	50	DMF	8	- -
6	Amberlyst®-15(H)	40	Toluene	6	40
7	Amberlyst®-15(H)	50	Toluene	6	46
8	**Amberlyst®-15(H)**	**50**	**Wet Acetonitrile (0.1% of water)**	**6**	**88**
9	Amberlyst®-15(H)	50	Acetonitrile (Anhydrous)	8	- -
10	Amberlyst®-15(H)	50	DMF	8	- -
11	Urea nitrate	80	Toluene	8	20
12	Alumina (acidic)	60	Acetonitrile	6	--
13	Ni- Alumina	60	Acetonitrile	6	--

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1 mmol), catalyst and time (as indicated), solvent (3 ml)

[b]Yield of the isolated product.

From the results shown in Table 1, we standardized the reaction following the condition as specified in entry 8 which afforded 88% of the corresponding amide **3a**. The reactions did neither occur in anhydrous acetonitrile (entry 9) nor in water alone; wet acetonitrile was chosen as the suitable reaction medium where the amount of water was very crucial for optimum performance (0.1-0.3%). Best result was obtained with commercially available acetonitrile containing 0.1% of water. Use of toluene as a solvent in place of acetonitrile led to inferior results (entries 6 and 7). DMF was found not at all suitable as the solvent in this present protocol (entry 10). Before going to Amberlyst®-15(H), the same reaction was attempted with another well-known resin Dowex-50 where no conversion took place in toluene and DMF (entries 1 and 2) and only 32% of **3a** was obtained in acetonitrile solvent (entry 3). Similarly Amberlite (IR-45) produced only 24% of the required product in toluene

(Entry 4) and no reaction occurred in DMF (entry 5) leading to exclusive recovery of the substrate. In order to look for another potential alternative of Amberlyst®-15(H), the reaction was carried out with urea nitrate where the product was obtained only in trace amount (entry 11). Even the other well-known acidic supports such as acidic alumina and Ni-alumina also failed in this case to provide the desired product **3a** (entries 12 and 13). The reaction was also carried out with 1-phenylethanol (**1b**) under optimised reaction condition using 1 drop of conc. H_2SO_4 as the catalyst in place of Amberlyst®-15(H) and a mixture of **3b** and styrene (**4a**) was obtained in 1:1.9 ratio (Scheme 45), but **3b** was obtained exclusively from **1b** using Amberlyst®-15(H).



Scheme 45: Reaction of 1-phenylethanol with 1 drop H_2SO_4 under optimised condition

In this way the essentiality, efficacy and applicability of Amberlyst®-15(H) as a solid acid resin was firmly established for such kind of organic transformation. The present study led to the advent of a utilitarian and eco-compatible protocol for C-N bond formation using easily accessible substrates and catalyst. Moreover the same amide **3a** was obtained when methyl and ethyl ethers of **1a** were used as the substrates in place of **1a**. Thus, the aforesaid reaction evolved as an effective method for converting secondary alcohols to their corresponding N-acyl derivatives with high yields.

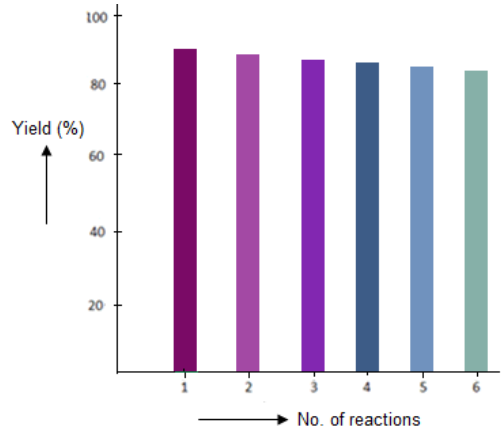
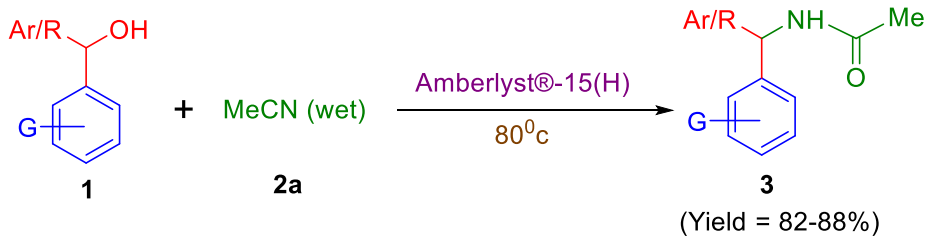


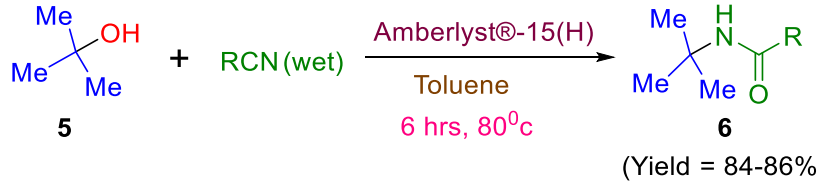
Figure 2: Recycling of Amberlyst®-15(H) using **1a** in moist acetonitrile at 80°C for 6 hours; % of yield was the isolated yield of **3a**

The catalyst i.e. Amberlyst®-15(H) was recovered by filtration, repeatedly washed with ethyl acetate, dried and further reused consecutively with marginal loss of its catalytic activity (Figure 2).



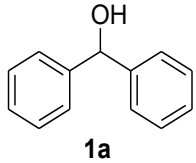
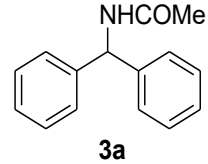
Scheme 46: Reaction of substituted secondary benzylic alcohols with wet acetonitirle under optimised condition

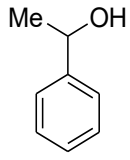
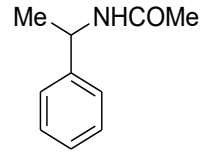
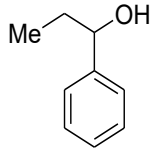
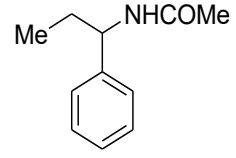
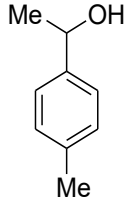
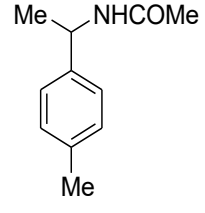
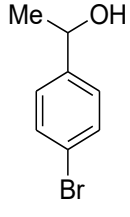
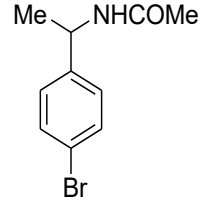
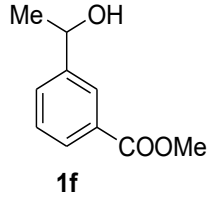
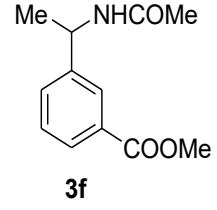
This protocol was further extended to substituted secondary (Scheme 46) and tertiary alcohols (Scheme 47) where a good number of substituted amides were obtained with satisfactory yield (Tables 2 and 3 respectively).

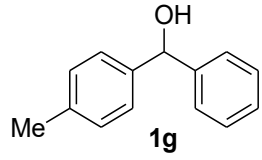
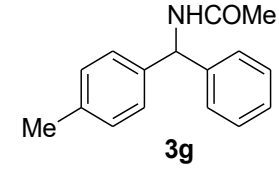
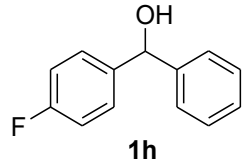
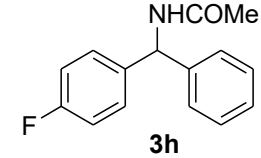
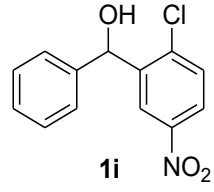
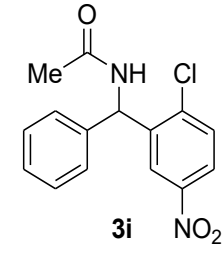
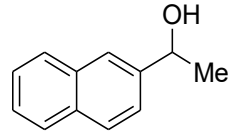
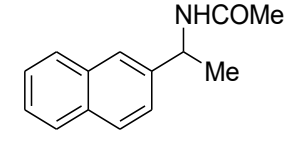
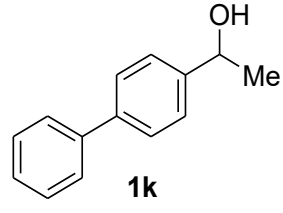
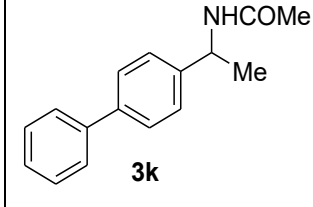
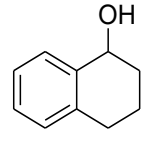
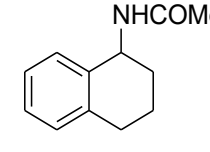


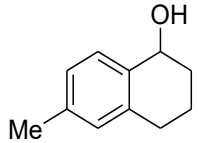
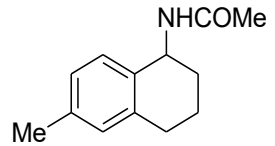
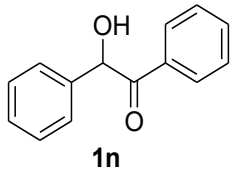
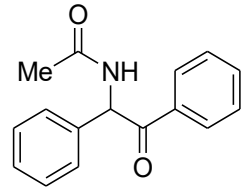
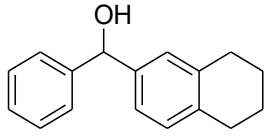
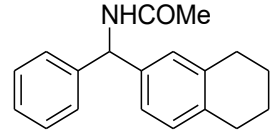
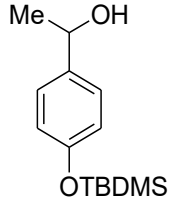
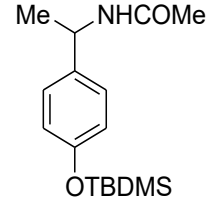
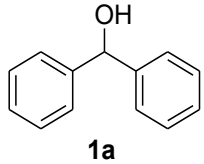
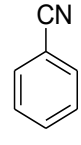
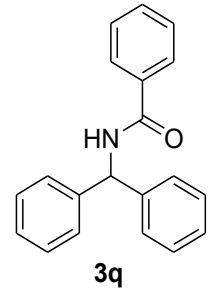
Scheme 47: Reaction of *t*-butanol with alkyl/aryl nitriles

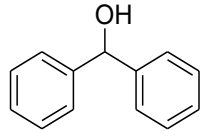
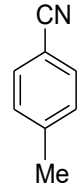
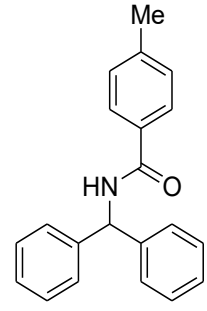
Table 2: Reaction of different secondary alcohols with acetonitrile under optimized reaction conditions using Amberlyst®-15(H) as a catalyst (According to Scheme 46)

Entry	Secondary alcohols (1)	Nitriles (2)	Amides (3)	Time (h)	Yield (%)
1	 **1a**	MeCN **2a**	 **3a**	6	88

2	 **1b**	MeCN **2a**	 **3b**	4.5	88
3	 **1c**	MeCN **2a**	 **3c**	5	86
4	 **1d**	MeCN **2a**	 **3d**	5	86
5	 **1e**	MeCN **2a**	 **3e**	5	87
6	 **1f**	MeCN **2a**	 **3f**	6	84

7	 **1g**	MeCN **2a**	 **3g**	4.5	86
8	 **1h**	MeCN **2a**	 **3h**	6	83
9	 **1i**	MeCN **2a**	 **3i**	6	82
10	 **1j**	MeCN **2a**	 **3j**	4.5	88
11	 **1k**	MeCN **2a**	 **3k**	5.5	82
12	 **1l**	MeCN **2a**	 **3l**	5	85

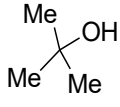
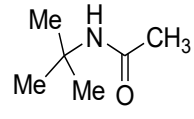
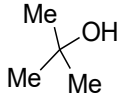
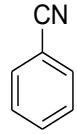
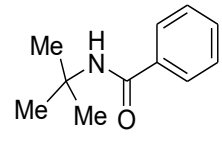
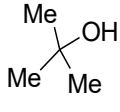
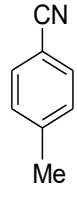
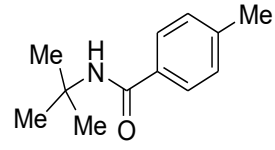
13	 **1m**	MeCN **2a**	 **3m**	5	83
14	 **1n**	MeCN **2a**	 **3n**	5.5	82
15	 **1o**	MeCN **2a**	 **3o**	5.5	84
16	 **1p**	MeCN **2a**	 **3p**	6	83
17	 **1a**	 **2b**	 **3q**	5.5	84

18	 **1a**	 **2c**	 **3r**	5.5	82

Under the optimised condition unsubstituted benzhydrol (**1a)** produced N-benzhydrylacetamide (**3a)** in satisfactory yield (yield refers to that of the isolated pure product fully characterised spectroscopically). The formation of **3a** was confirmed by generation of a new peak in ^{1}H NMR at δ 2.06 (at δ 23.1 in ^{13}C NMR) due to the –CH_3 group of acetamido-methyl moiety, which was not present in **1a** and in ^{13}C NMR there was a peak at δ 169.5 from which the presence of an amide group was justified. When an equimolar mixture of **1a** and **1b** was reacted under the present protocol both of the products **3a** and **3b** were obtained in 1:1 ratio. This condensation reaction also took place very efficiently with both ring-unsubstituted and alkyl/aryl-substituted secondary benzylic alcohols to afford **3b**, **3c**, **3d**, **3g**, **3j** and **3k** with good yield. Particularly in **3g** the presence of two methyl groups was clearly evident by two consecutive singlets at δ 2.03 (at δ 21.1 in ^{13}C NMR) and δ 2.33 (at δ 23.2 in ^{13}C NMR) where the peak at δ 2.33 (at δ 23.2 in ^{13}C NMR) was little bit deshielded due to the paramagnetic anisotropic effect of the C=O moiety of the –$NHCOCH_3$ group. In ^{13}C NMR there was a peak at δ 169.4 signifying the presence of the amide functionality. Secondary benzylic carbinols **1e** and **1h** bearing halogen substituents in the aromatic ring reacted smoothly to produce **3e** and **3h** with 87% and 83% yields respectively. Even sterically crowded benzhydrol (**1i**) having a halogen substituent (-Cl) at *ortho* position along with an electron-withdrawing group (-NO_2) at the same ring reacted efficiently to furnish **3i** in 82% yield. Hydrolysable functional group -COOMe also survived in the present protocol to produce **3f** in 84% yield. The reaction gave quite impressive results with differently substituted α-tetralol molecules forming **3l**, **3m** and **3o** with 85%, 83% and 84% yields respectively. α-hydroxyketone (**1n**) also reacted under this protocol and formed **3n** (82%) which is otherwise difficult to prepare. TBDMS group in **1p** also survived under this procedure without any O-Si bond cleavage and **3p** was obtained in 83% yield.

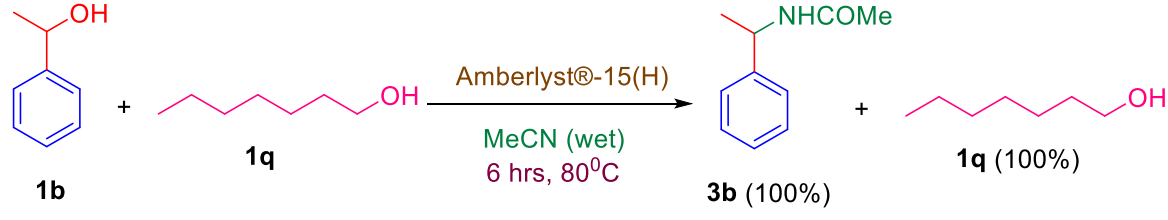
When benzhydol (**1a**) was reacted with benzonitrile and 4-methylbenzonitrile as a reagent in place of acetonitrile using toluene as a solvent, it produced **3q** and **3r** respectively with satisfactory yield. Product **3q** was identified through ^{1}H and ^{13}C NMR spectral analyses. In ^{13}C NMR there was a peak at δ 166.5 strongly suggesting the presence of an amide group. However no such reaction took place with aromatic or aliphatic primary alcohols where the unchanged substrates were recovered. Even with dialkyl secondary alcohol the reaction was inefficient to react under this protocol. Therefore this protocol is very much selective for only secondary alcohols where the aromatic ring is connected to the carbinol carbon.

Table 3: Reaction of tertiary alcohol (**5a**) with Acetonitrile under optimized reaction conditions using Amberlyst®-15(H) as a catalyst (as per Scheme 47)

Entry	Tertiary alcohols (5)	Nitriles (2)	Amides (6)	Time (h)	Yield (%)
1	 **5a**	MeCN **2a**	 **6a**	6	84
2	 **5a**	 **2b**	 **6b**	6	86
3	 **5a**	 **2c**	 **6c**	6	84

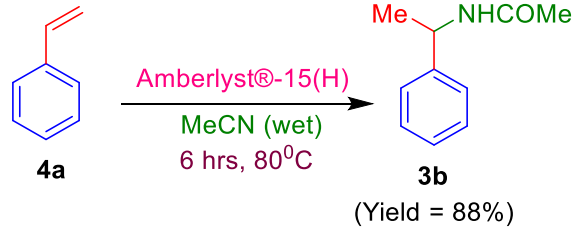
tert-Butanol (**5a**) responded efficiently under the present protocol giving N-*tert*-butyl-amides (**6a-c**) without any cleavage of any C-C bonds. In **6a** the presence of three equivalent methyl groups belonging to *t*-butyl moiety and one methyl group of acetamido moiety was evident by two consecutive singlets at δ 1.34and δ 1.91 in ^{1}H NMR in 3:1 ratio (at δ 28.8 and δ 24.5 in ^{13}C NMR respectively). The signal at δ 51.1 due the quaternary carbon atom along with the signal at δ 169.5 due to amide moiety in ^{13}C NMR confirmed the formation of the product **6a**. Similarly in **6b** the signal for three equivalent methyl groups came at δ 28.9 in ^{13}C NMR while the peak for the quaternary carbon atom appeared at δ 51.6 along with the peak at δ 166.9 in ^{13}C NMR for amide moiety.

To substantiate the selectivity between aromatic alcohol and aliphatic alcohol, the competition reaction was carried out under optimised condition taking equimolecular proportions of 1-phenylethanol (**1b**) and heptanol (**1q**) where the product **3b** was obtained as expected by the conversion of **1b**; leaving **1q** totally unaffected (Scheme 48). No occurrence of peak due to –C<u>H</u>$_2$NHCOCH$_3$ at δ 3.24 ppm in ^{1}H spectra further confirmed the fact that the aliphatic –CH$_2$OH was not transformed into –CH$_2$NHCOCH$_3$.



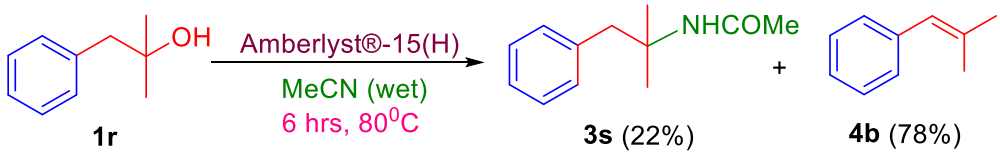
Scheme 48: Intermolecular competition experiment (1)

As a continuity of this theme, styrene (**4a**) was subjected to the optimized condition and produced N-(1-phenylethyl)-acetamide (**3b**) as the sole product (Scheme 49). This observation suggested that the reaction might proceed through a carbocationic intermediate.



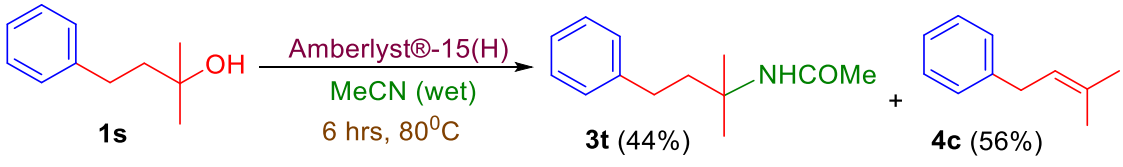
Scheme 49: Reaction of styrene with wet acetonitirle under optimised condition

This protocol was also explored with bulky tertiary alcohol **1r** keeping the phenyl ring insulated from the carbinol centre with one methylene moiety (Scheme 50). The corresponding amide **3s** was obtained as the minor product whereas the major product **4b** was obtained through the elimination reaction. Such an observation pinpoints towards the formation of a highly stabilized long-lived carbocationic intermediate.



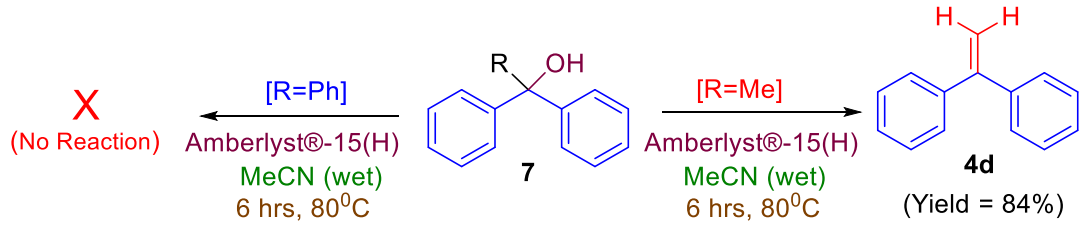
Scheme 50: Reaction of 2-methyl-1-phenyl-2-propanol (**1r**) with wet acetonitirle

When the phenyl ring was kept insulated from the carbinol centre with two successive methylene moieties in (**1s**), the relative proportion of amide (**3t**) was increased (Scheme 51) albeit the preponderance of the elimination product (**4c**).



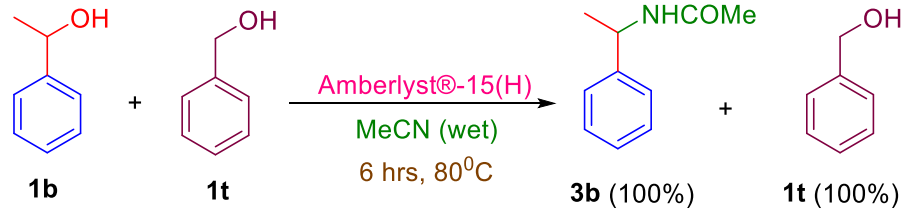
Scheme 51: Reaction of 2-methyl-4-phenylbutan-2-ol **(1s)** with wet acetonitirle

The optimised reaction protocol was then applied for highly substituted tertiary alcohols (**7**) where the generation of stable carbocation was expected. Keeping resemblance to our expectation, 1, 1-diphenylethanol produced the elimination product 1, 1-diphenylethene (**4d**) after the stipulated reaction time with 84% yield (Scheme 52). Interestingly, triphenylmethanol was recovered totally unchanged after the reaction (Scheme 52). This might be due to increased steric crowding around the reaction centre. These observations also indicated towards the formation of carbocationic intermediate during the reaction.



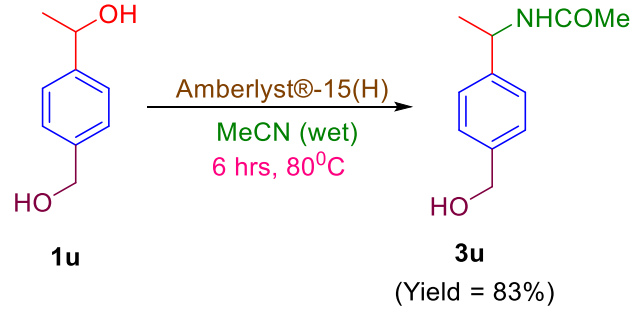
Scheme 52: Reactions of tertiary alcohols with wet acetonitirle under optimised condition

Along with this, both intermolecular as well as intramolecular selectivity studies were executed to establish further the superiority of the present protocol. When 1-phenylethanol (**1b**) was subjected to the optimized condition along with an equimolecular amount of benzyl alcohol (**1t**), the product **3b** was obtained exclusively starting from **1b** leaving behind **1t** unaffected (Scheme 53).



Scheme 53: Intermolecular competition experiment (2)

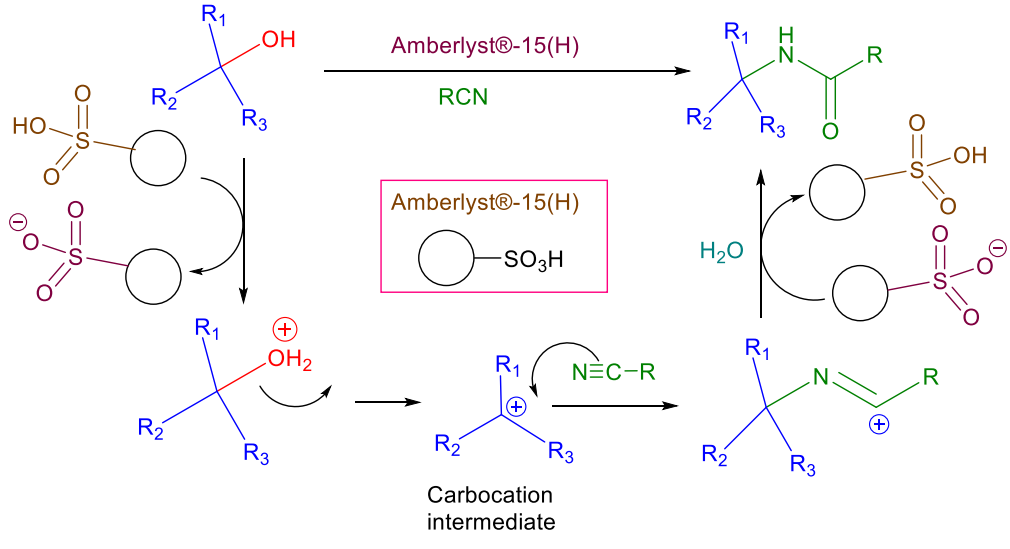
On the other hand when the substrate **1u** containing both the aromatic primary and secondary carbinol moieties in the same molecule was reacted under this protocol, the product **3u** was obtained exclusively (Scheme 54) with 83% yield. Only the aromatic secondary carbinol was converted chemoselectively to the corresponding amide without affecting the aromatic primary carbinol moiety. This study conclusively substantiated excellent and subtle chemoselectivity of the present protocol as its most important attribute.



Scheme 54: Intramolecular competition experiment

The occurrence of **3u** as the product was confirmed by both ^{1}H and ^{13}C NMR spectroscopic studies. A doublet at δ 1.46 in ^{1}H NMR (δ 21.8 in ^{13}C NMR) and a singlet at δ 1.96 in ^{1}H NMR (δ 23.6 in ^{13}C NMR) established the presence of one alkyl methyl along with one acetamino-methyl moities respectively. A singlet at δ 4.51 in ^{1}H NMR (δ 71.9 in ^{13}C NMR) corroborated the presence of the hydrogens due to unperturbed benzylic primary carbinol moiety. This study conclusively established the excellence of this protocol for chemoselective conversion of the aromatic secondary alcohol group to the corresponding amide keeping the aromatic primary alcohol group intact. The aforesaid observations indicate that this subtle chemoselectivity might originate due to preferential formation of the relatively more stable carbocationic intermediate. The results obtained in the studies delineated in Schemes 50-52 also indicated towards the involvement of carbocationic intermediates. Furthermore, when the reaction was carried out using enantiopure *R*-1-phenylethanol under the optimized reaction condition, the product **3b** was obtained as a racemic mixture. This observation also supported the formation of planar carbocation during the course of the reaction which was racemized to give the optically inactive product starting from an optically active substrate.

On the basis of the above-mentioned outcomes, a plausible mechanistic scheme has been put forward (Scheme 55) involving the formation of carbocation by through acid-catalyzed dehydration of alcohol followed bynucleophilic attack by nitrile and subsequent nucleophilic attack by water to end up with the product amide. This mechanism also accounts for the catalytic role of Amberlyst®-15(H) in terms of Brønsted acidity and recyclability.



Scheme 55: Proposed mechanism for the reaction

II.2.3.3. Conclusion:

In conclusion, commercially available Amberlyst®-15(H) has been effectively utilized as an air stable and recyclable heterogeneous inexpensive solid acid catalyst for the construction of C-N bond through chemoselective formation of diversely N-substituted amides using benzylic secondary alcohols as well as aliphatic tertiary alcohols and alkyl/aryl nitriles under environmentally acceptable conditions without any necessity of anhydrous and inert environment. Use of reagents, solvents and catalyst of negligible toxicity, mild reaction conditions, tolerance of various sensitive moieties, excellent chemoselectivity, wide substrate scope, high atom economy, formation of the most innocuous by-product (namely water), procedural simplicity, good yields and recyclability of the catalyst are the outstanding features of the present study with greater applicability compared to many existing protocols.

II.2.3.4. Experimental

General:

All organic solvents used for the reaction were purchased from Merck, and were distilled before use. Melting points were recorded in open capillary on electrical bath which are uncorrected.^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker–300 (300 MHz) and Bruker–400 (400 MHz) spectrometer in $CDCl_3$ solvent with TMS as internal reference. Mass spectrums were measured on HRMS (Qtof micro YA263). Column chromatography were performed on silica gel (60–120 mesh) supplied by SRL, India. Thin layer chromatographic separations were performed on pre-coated glass plates using silica gel G for TLC (E. Merck).

(i) <u>Representative procedure for the reaction</u>:

A. To a mixture of benzhydrol (**1a**, 184 mg, 1.0 mmol) and wet MeCN (**2a**, 4 ml) the catalyst Amberlyst®-15(H) (50 mg) was added. The reaction mixture was stirred for the required period of time at 80^0C till the reaction was complete (monitored with TLC). Then the reaction mixture was cooled to room temperature, excess MeCN was removed under reduced pressure, keeping a cotton plug on a funnel the catalyst were filtered out and washed repeatedly by ethyl acetate (20 ml) to dissolve and collect the product. The organic extracts were washed with water (3×10 ml) to remove trace of MeCN and dried over anhydrous Na_2SO_4. The crude product was obtained by removal of the solvent under reduced pressure and purified by filtration chromatography on a short column of silica gel using 1-4% ethyl acetate-hexane as eluent to afford **3a** (198 mg, Yield 88%, mp 144^0C).

B. To a mixture of *tert*-butanol (**5**, 74 mg, 1.0 mmol), and PhCN (**2b**, 103 mg, 1.0 mmol) in 4 ml toluene, the catalyst Amberlyst®-15(H) (50 mg) was added. The reaction mixture was stirred for the required period of time at 80^0C till the reaction was complete (monitored with TLC). Then the reaction mixture was cooled to room temperature, excess toluene was removed under reduced pressure, keeping a cotton plug on a funnel the catalyst were filtered out and washed repeatedly by ethyl acetate (20 ml) to dissolve and collect the product.

The organic extracts were repeatedly washed with water (3×10 ml) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure furnished the product **6b** (152 mg, Yield 86%, mp 132°C) without any necessity of further purification.

(ii) <u>Spectral and analytical data of the compounds</u>:

1. **N-benzhydrylacetamide (3a)**[19]**:** White solid (Yield 88%, mp 144°C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.06 (3H, s), 6.24 (1H, d, *J* = 7.98 Hz), 7.21-7.35 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.1, 57.0, 126.6, 127.5, 128.4, 141.6, 169.5

2. **N-(1-phenylethyl)acetamide (3b)**[19]**:** White solid (Yield 88%, mp 102°C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.47 (3H, d, *J* = 6.39 Hz), 1.96 (3H, s), 5.10-5.12 (1H, m), 7.31 (5H, bs); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.8, 23.4, 48.8, 126.2, 127.3, 128.6, 143.3, 169.2

3. **N-(1-phenylpropyl)acetamide (3c)**[19]**:** White solid (Yield 86%, mp 104°C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.88 (3H, t, *J* = 7.29 Hz), 1.98 (2H, q), 4.86-4.91 (1H, m), 7.26-7.34 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.7, 23.4, 29.1, 54.9, 126.6, 127.3, 128.6, 142.2, 169.4

4. **N-(1-p-tolylethyl)acetamide (3d)**[24]**:** White semisolid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.47 (3H, d, *J* = 6.74 Hz), 1.89 (3H, s), 2.34 (3H, s), 5.06-5.11 (1H, m), 7.13-7.22 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 20.7, 22.8, 23.4, 48.3, 125.2, 127.8, 135.3, 139.5, 169.4

5. **N-(1-(4-bromophenyl)ethyl)acetamide (3e)**[25]**:** Yellowish solid (Yield 87%, mp 100°C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.44 (3H, d, *J* = 6.87 Hz), 1.96 (3H, s), 5.02-5.07 (1H, m), 7.17 (2H, d, *J* = 8.28 Hz), 7.44 (2H, d, *J* = 8.34 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.7, 23.3, 48.3, 121.2, 127.9, 131.7, 142.4, 169.2

6. **Methyl 3-(1-acetamidoethyl)benzoate (3f)**[26]**:** Yellowish semisolid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.48 (3H, d, *J* = 2.57 Hz), 1.98 (3H, s), 3.91 (3H, s), 5.12-5.17 (1H, m), 7.28-7.31 (2H, m), 7.91-7.98 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.3, 23.4, 48.8, 50.5, 128.2, 130.4, 131.2, 142.7, 165.4, 169.6

7. **N-(phenyl(p-tolyl)methyl)acetamide (3g)**[27]**:** White semisolid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.03 (3H, s), 2.33 (3H, s), 6.16-6.22 (1H, m), 7.09-7.15 (4H, m), 7.21-7.34 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.1, 23.2, 56.7, 126.6, 128.4, 129.1, 137.1, 138.7, 141.8, 169.4

8. **N-((4-fluorophenyl)(phenyl)methyl)acetamide (3h)**[27]**:** White semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.03 (3H, s), 6.24 (1H, m), 6.98-7.04 (2H, m), 7.17-7.22 (2H, m), 7.32-7.35 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.1, 56.4, 115.6, 127.5, 128.6, 129.1, 138.1, 141.9, 160.6, 169.6

9. **N-((2-chloro-5-nitrophenyl)(phenyl)methyl)acetamide (3i):** Yellowish semisolid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.99 (3H, s), 6.19 (1H, d, *J* = 12 Hz), 7.25-7.48 (5H, m), 8.06-8.21 (1H, m), 8.40-8.41 (1H, m), 8.65-8.69 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.2, 55.0, 121.9, 123.6, 125.2, 127.6, 128.5, 129.9, 139.2, 141.4, 142.9, 147.0, 169.3

10. **N-(1-(naphthalen-6-yl)ethyl)acetamide (3j)**[28]**:** White solid (Yield 86%, mp 156^{o}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.55 (3H, d, *J* = 6.85 Hz), 1.98 (3H, s), 5.25-5.28 (1H, m), 7.41-7.47 (3H, m), 7.73-7.81 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.6, 23.4, 48.9, 124.5, 125.9, 126.2, 127.8, 128.5, 132.7, 133.3, 140.6, 169.3

11. **N-(1-biphenyl-4-yl-ethyl)-acetamide (3k)**[29]**:** White semisolid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.52 (3H, d, *J* = 6.78Hz), 2.22 (3H, s), 5.18-5.19 (1H, m), 7.26-7.40 (5H, m), 7.20-7.58 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.7, 23.5, 48.5, 125.8, 126.9, 127.3, 128.8, 136.4, 140.7, 142.2, 169.2

12. **N-(1, 2, 3, 4-tetrahydronaphthalen-4-yl)acetamide (3l)**[30]**:** Yellow semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.86-1.88 (1H, m), 2.02-2.07 (1H, m), 2.32-2.38 (3H, m), 2.81-2.86 (1H, m), 5.19-5.21 (1H, m), 7.03-7.09 (2H, m), 7.14-7.21 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 19.9, 23.4, 29.3, 30.2, 47.5, 125.9, 128.6, 135.5, 137.6, 169.4

13. **N-(1, 2, 3, 4-tetrahydro-6-methylnaphthalen-1-yl)acetamide (3m):** Yellow semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.84 (1H, bs), 2.34 (3H, s), 2.77-2.83 (1H, m), 5.98-6.06 (1H, m), 6.46-6.49 (1H, m), 6.88-7.25 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 19.4, 21.3, 23.4, 29.6, 30.3, 53.5, 125.9, 128.8, 132.5, 136.6, 169.3

14. **N-(2-oxo-1, 2-diphenylethyl)acetamide (3n)**[31]**:** White semisolid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.98 (3H, s), 5.95 (1H, s), 7.26-7.53 (8H, m), 7.90 (2H, d, *J* = 7.53Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 22.8, 61.7, 126.4, 128.2, 132.7, 136.3, 169.3, 184.6

15. **N-((1, 2, 3, 4-tetrahydronaphthalen-6-yl)(phenyl)methyl)acetamide (3o):** Yellow semisolid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.69-1.77 (4H, m), 2.04 (3H, s), 2.73 (4H, bs), 6.16-6.18 (1H, m), 6.93-7.03 (3H, m), 7.22-7.38 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.1, 23.4, 29.5, 56.8, 124.5, 127.3, 128.4, 129.1, 129.4, 136.5, 137.5, 138.7, 141.8, 169.1

16. **N-{1-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-ethyl}-acetamide (3p):** White semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.01-0.11 (6H, m), 0.86-0.97 (9H, m), 1.96 (3H, s), 6.76-6.78 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ -3.71, -2.96, 17.9, 25.5, 25.6, 25.7, 120.1, 127.4, 135.7, 154.8, 169.8

17. **N-benzhydrylbenzamide (3q)**[19]**:** White semisolid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.44-6.46 (1H, m), 7.26-7.42 (10H, m), 7.44-7.49 (3H, m), 7.81-7.83 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 57.4, 127.1, 127.5, 127.6, 128.6, 128.7, 131.7, 134.2, 141.4, 166.5

18. **N-benzhydryl-4-methylbenzamide (3r)**[27]**:** White semisolid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.39 (3H, s), 6.43-6.46 (1H, m), 7.12-7.34 (12H, m), 7.72 (2H, d, J = 7.96 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.7, 60.8, 126.2, 127.2, 128.1, 129.3, 130.4, 140.6, 141.7, 166.4

19. **N-tert-butylacetamide (6a)**[32]**:** White solid (Yield 84%, mp 96^{o}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.34 (9H, s), 1.91 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$): δ 24.5, 28.8, 51.1, 169.5

20. **N-tert-butyl-benzamide (6b)**[33]**:** White solid (Yield 86%, mp 132^{o}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.47-1.77 (9H, m), 5.94 (1H, s), 7.38-7.47 (3H, m), 7.70-7.72 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 28.9, 51.6, 126.7, 128.5, 131.0, 135.9, 166.9

21. **N-tert-Butyl-4-methyl-benzamide (6c)**[34]**:** White solid (Yield 84%, mp 116^{o}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.46 (6H, s), 1.58 (3H, s), 2.38 (3H, s), 7.19-7.22 (2H, m), 7.60-7.63 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.2, 31.4, 49.1, 128.4, 129.7, 132.7, 142.5, 168.4

22. **N-(1,1-dimethyl-2-phenyl-ethyl)-acetamide (3s)**[35]**:** White solid (Yield 22%, mp 92^{o}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.33 (6H, s), 1.92 (3H, s), 3.07 (2H, S), 5.09 (1H, s), 7.15-7.17 (3H, m), 7.23-7.32 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 24.5, 27.4, 44.6, 54.0, 126.3, 127.9, 130.5, 138.1, 169.8

23. **N-(2-methyl-4-phenylbutan-2-yl)-acetamide (3t)**[36]**:** White semisolid (Yield 44%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.36 (6H, s), 1.88 (3H, s), 2.03-2.07 (2H, m), 2.58-2.61 (2H, m), 5.27 (1H, s), 7.14-7.29 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 24.4, 27.1, 30.8, 41.7, 53.7, 125.7, 128.4, 142.2, 169.4

24. **(2-methyl-propenyl)-benzene (4b)**[37]**:** Yellow semisolid (Yield 78%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.90 (3H, s), 1.95 (3H, s), 6.31 (1H, s), 7.20-7.28 (3H, m),

7.33-7.36 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 18.4, 26.1, 126.2, 127.8, 129.2, 130.5, 136.7, 138.8

25. **(3-methyl-but-2-enyl)-benzene (4c)**[38]**:** Yellow semisolid (Yield 56%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.74-1.77 (6H, m), 3.35-3.38 (2H, m), 5.33-5.38 (1H, m), 7.19-7.35 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 20.2, 24.8, 41.7, 124.2, 127.1, 130.4, 133.2, 138.4

26. **1, 1 diphenylethylene (4d)**[39]**:** Yellow liquid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.44 (2H, s), 7.12-7.32 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 113.9, 114.5, 126.0, 127.1, 127.9, 128.2, 128.3, 128.4, 128.8, 130.2, 141.3, 141.7, 142.1, 150.3

27. **N-[1-(4-hydroxymethyl-phenyl)-ethyl]-acetamide (3u):** Yellow semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.46 (3H, d, J = 6.8 Hz), 1.96 (3H, s), 4.51 (2H, s), 5.06-5.14 (1H, m), 5.73 (1h, bs), 7.26-7.32 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.8, 23.6, 48.7, 71.9, 126.3, 128.2, 137.5, 142.7, 169.2; HRMS (ESI-TOF): *m/z* calculated for $C_{11}H_{15}O_2N$ [M + Na^+]: 216.10035; found: 216.1022.

^{1}H NMR, ^{13}C NMR and HRMS Spectra of some representative compounds

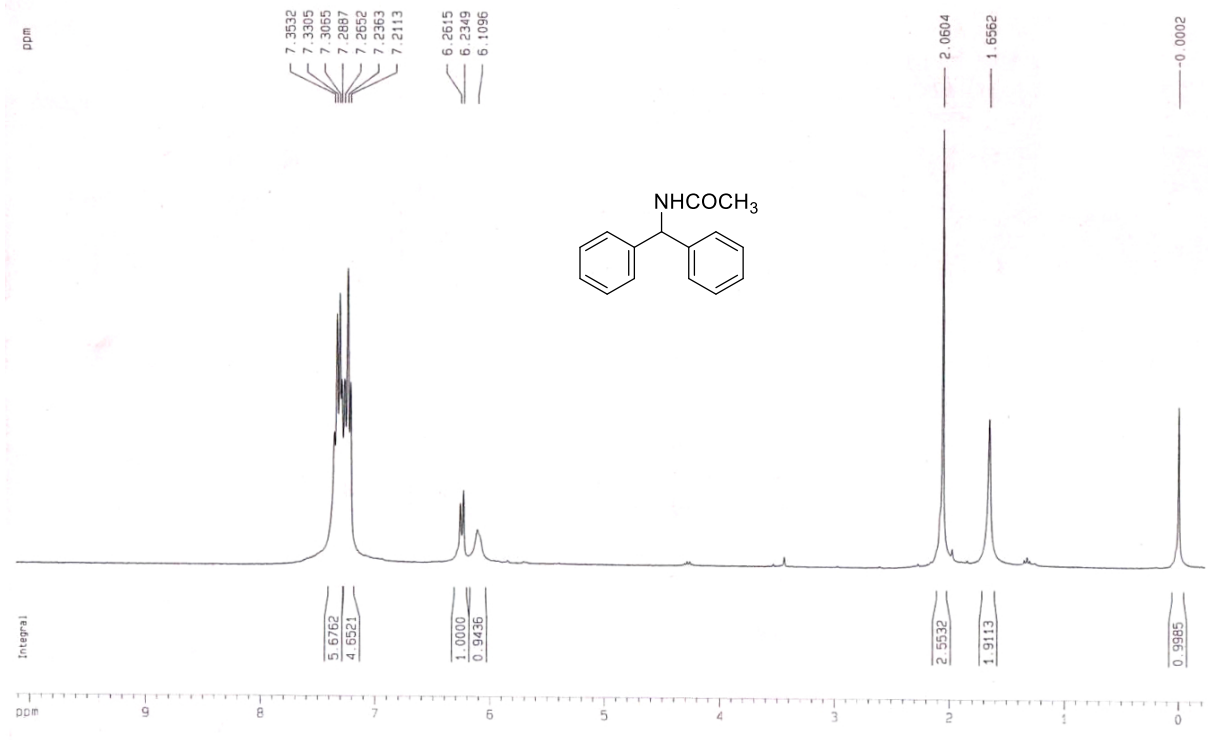


Figure 1: ^{1}H NMR of N-benzhydrylacetamide (**3a**)

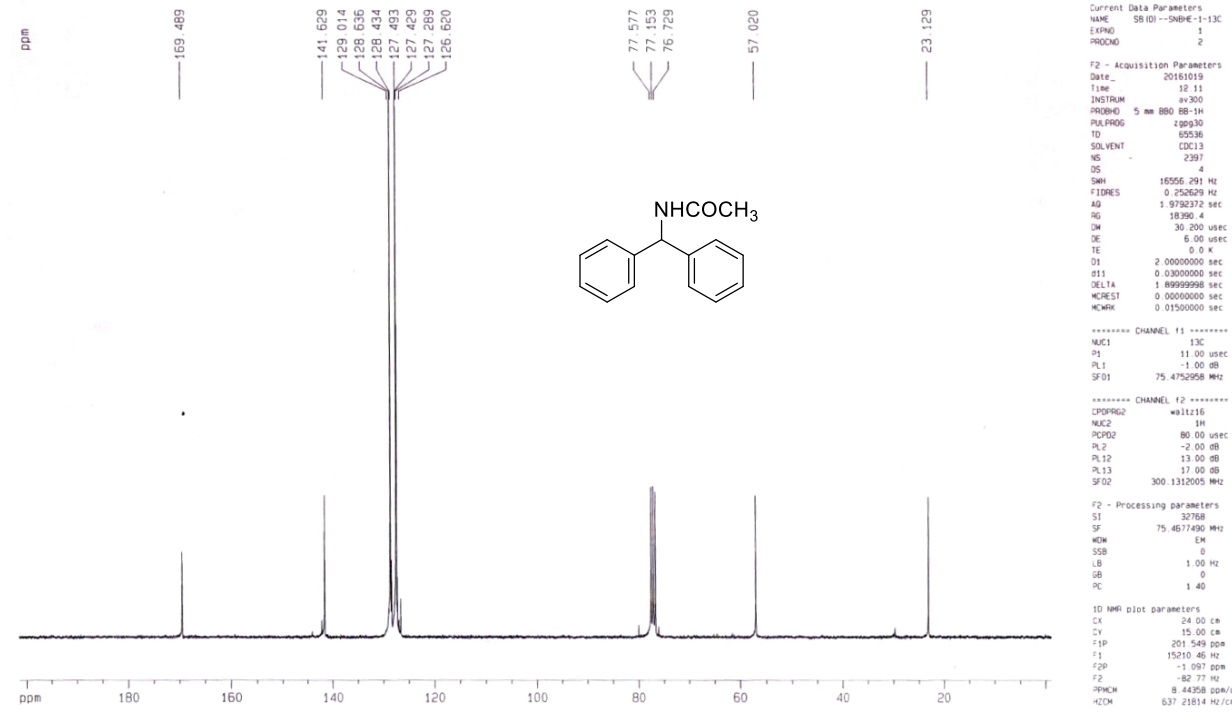


Figure 2: ^{13}C NMR of N-benzhydrylacetamide (**3a**)

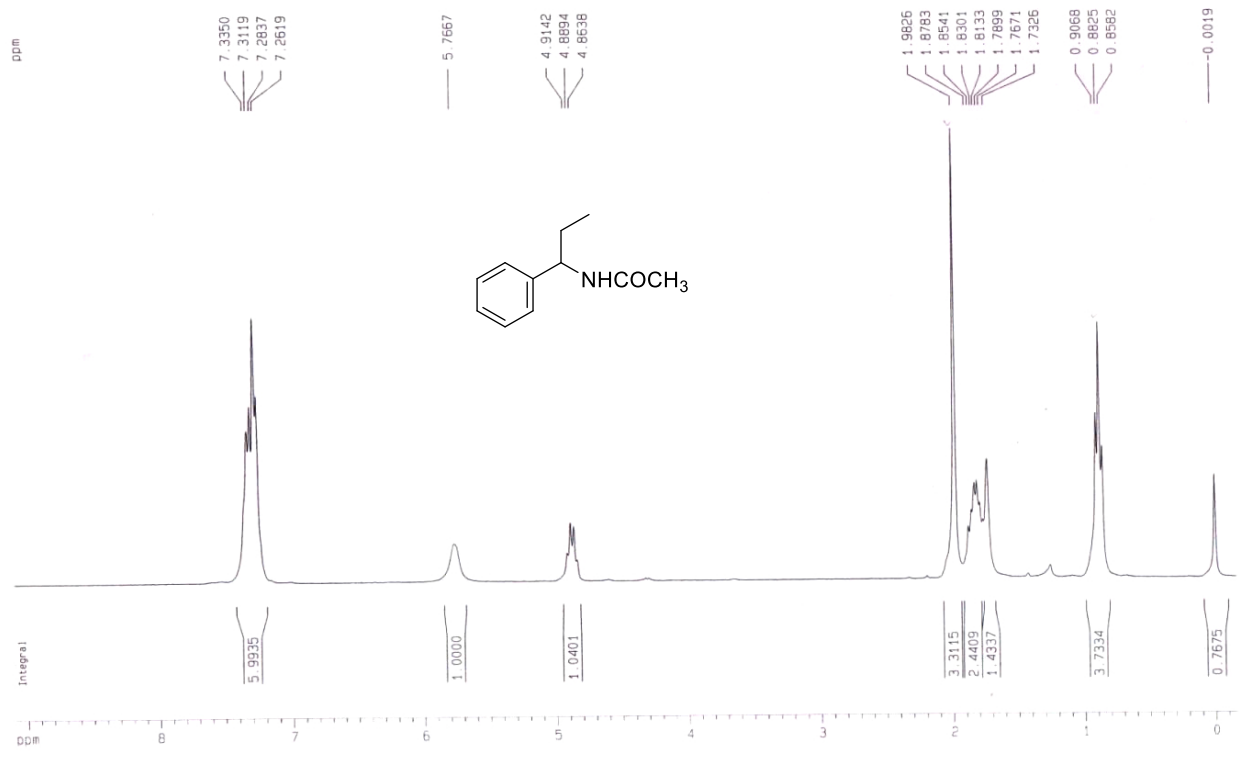


Figure 3: ^{1}H NMR of N-(1-phenylpropyl)acetamide (**3c**)

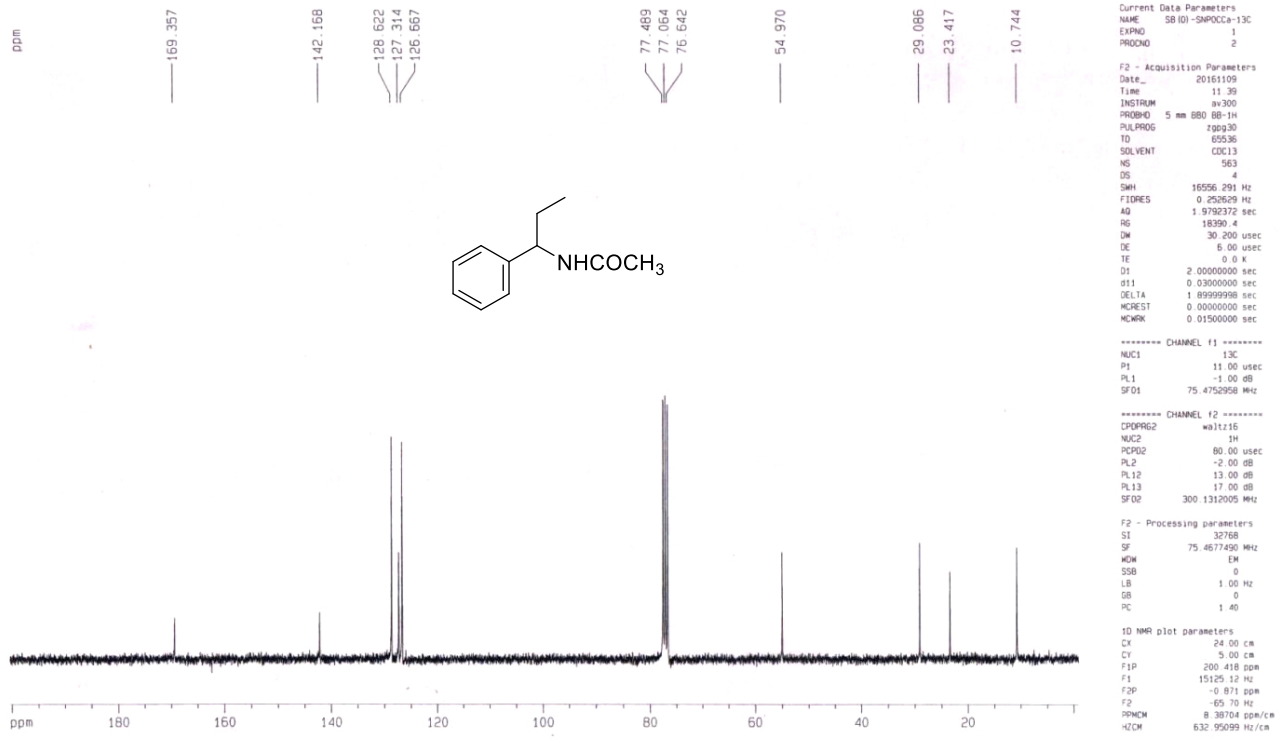


Figure 4: ^{13}C NMR of N-(1-phenylpropyl)acetamide (**3c**)

Figure 5: ^{1}H NMR of N-(1-(4-bromophenyl)ethyl)acetamide (**3e**)

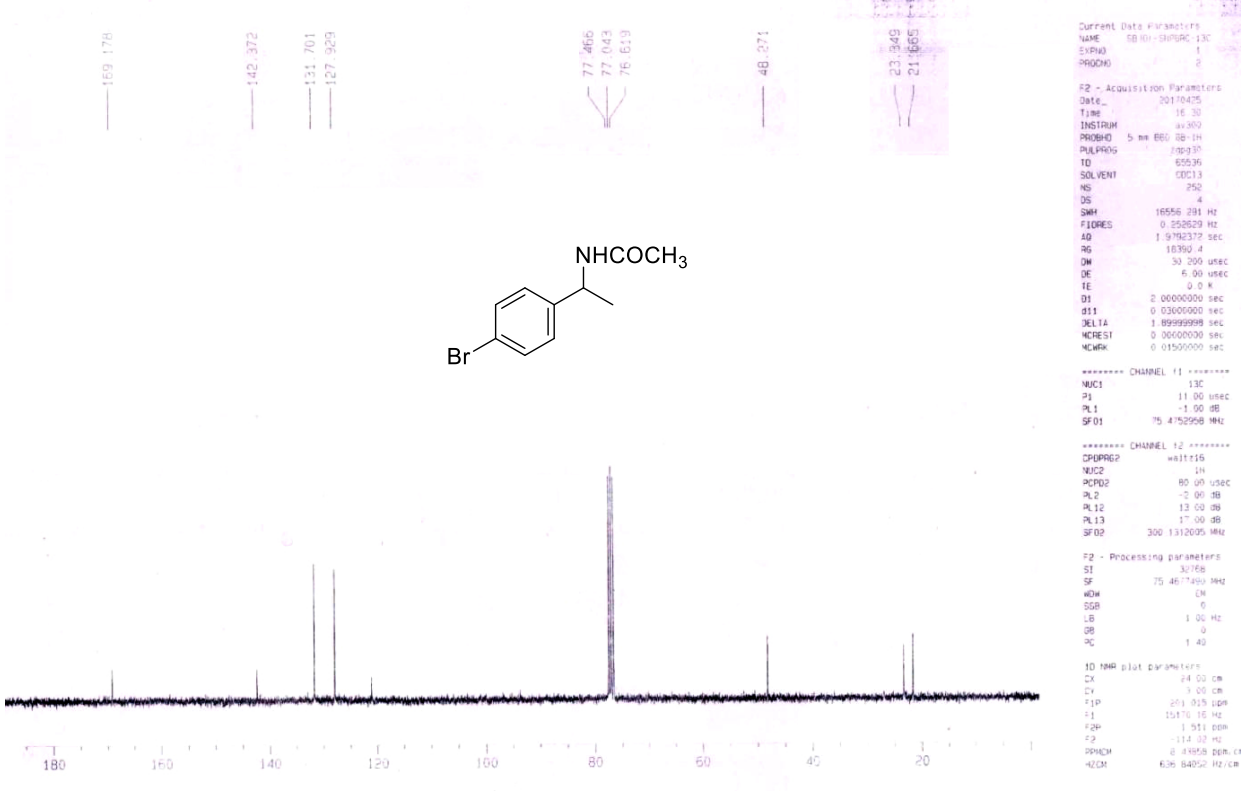


Figure 6: ^{13}C NMR of N-(1-(4-bromophenyl)ethyl)acetamide (**3e**)

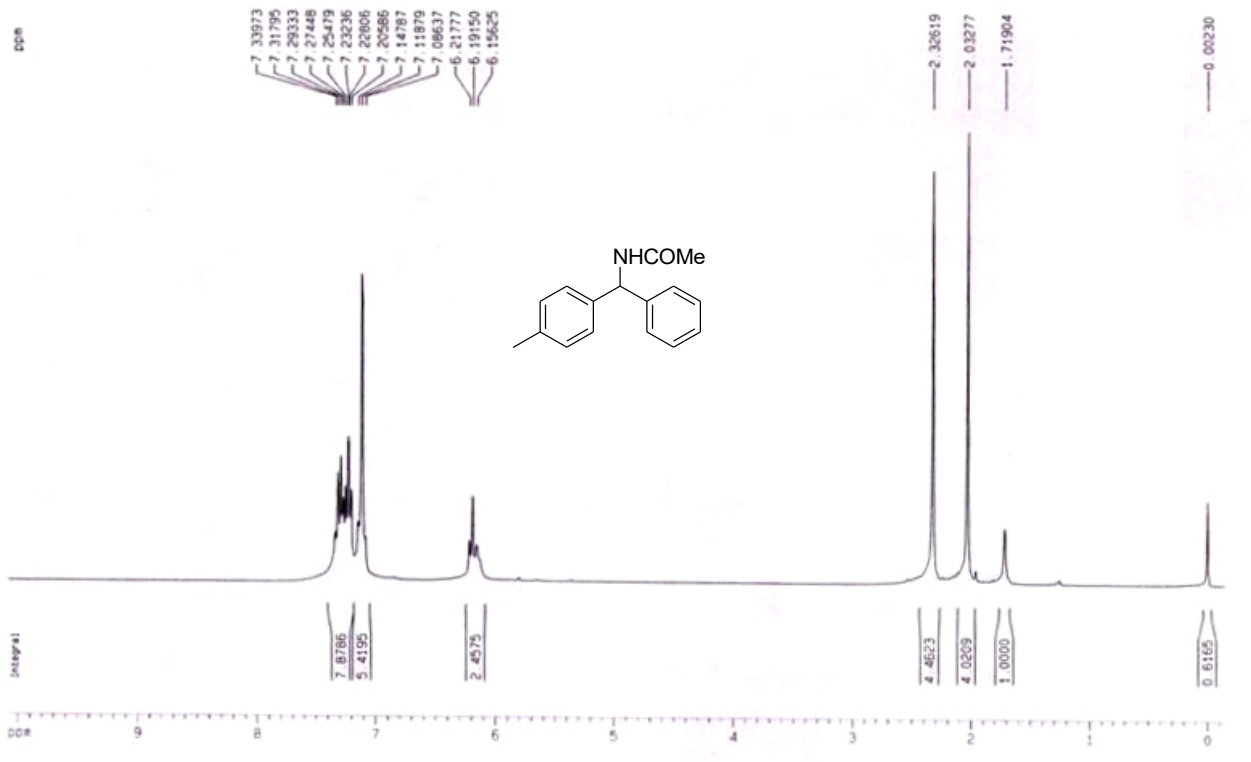


Figure 7: ^{1}H NMR of N-(phenyl(p-tolyl)methyl)acetamide (**3g**)

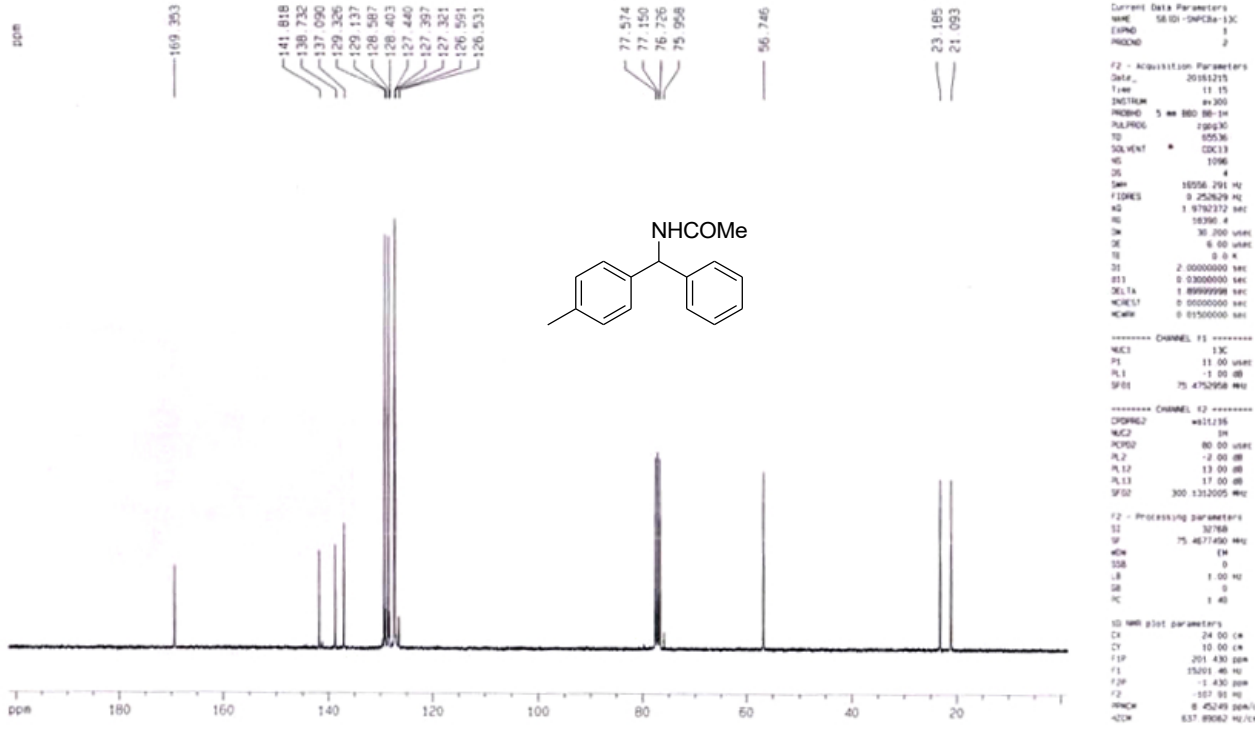


Figure 8: ^{13}C NMR of N-(phenyl(p-tolyl)methyl)acetamide (**3g**)

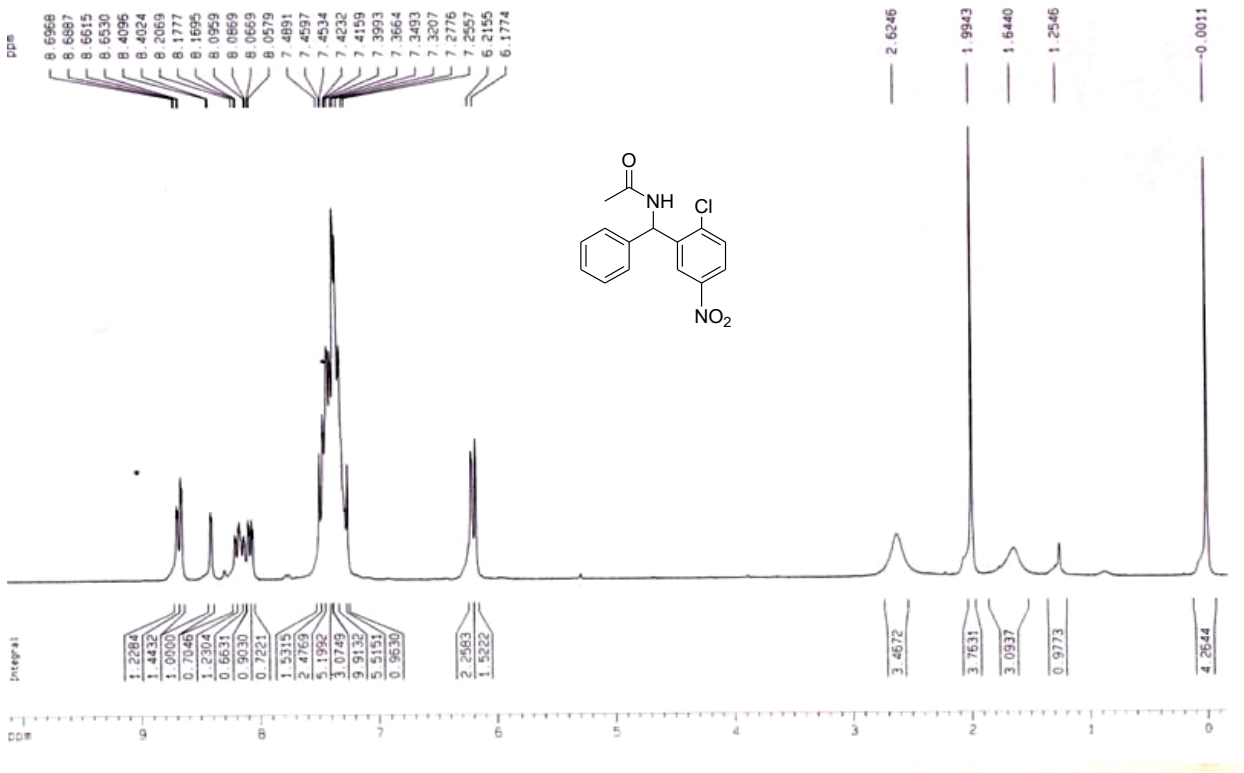


Figure 9: ^{1}H NMR of N-((2-chloro-5-nitrophenyl)(phenyl)methyl)acetamide (**3i**)

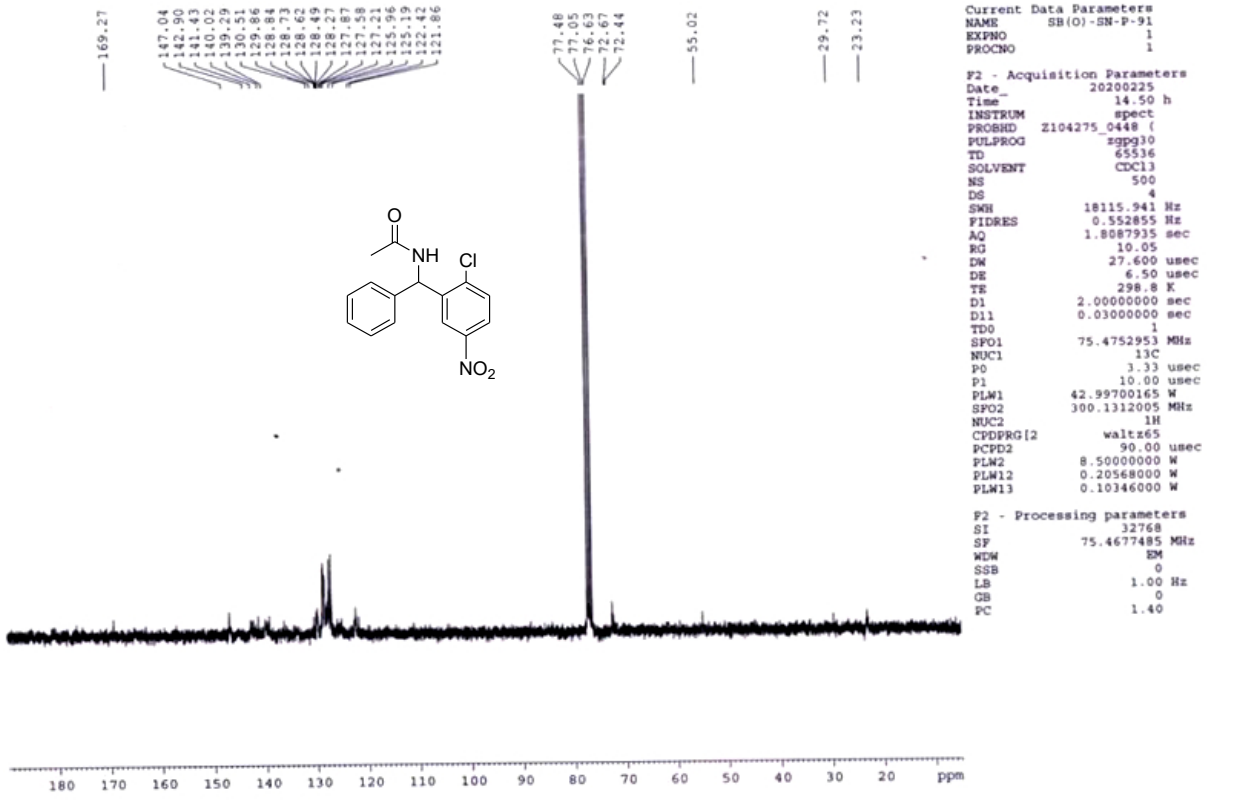


Figure 10: ^{13}C NMR of N-((2-chloro-5-nitrophenyl)(phenyl)methyl)acetamide (**3i**)

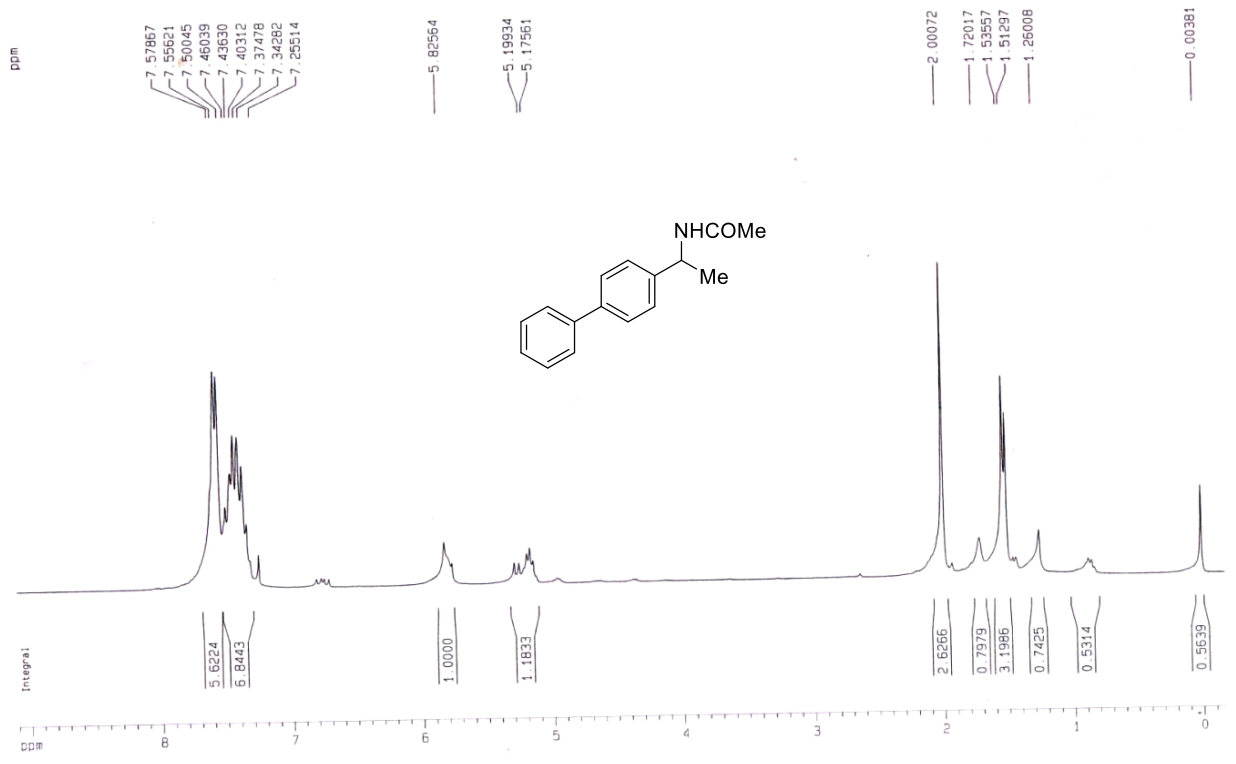


Figure 11: ^{1}H NMR of N-(1-biphenyl-4-yl-ethyl)-acetamide (**3k**)

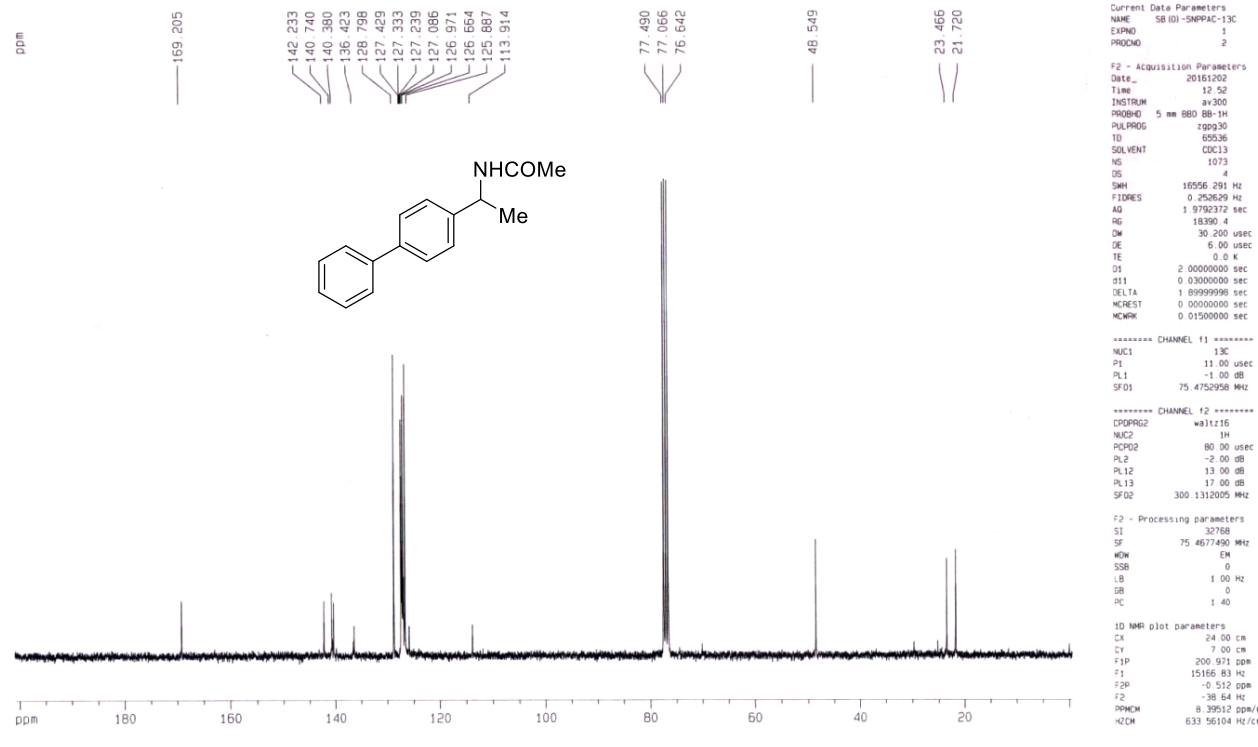


Figure 12: ^{13}C NMR of N-(1-biphenyl-4-yl-ethyl)-acetamide (**3k**)

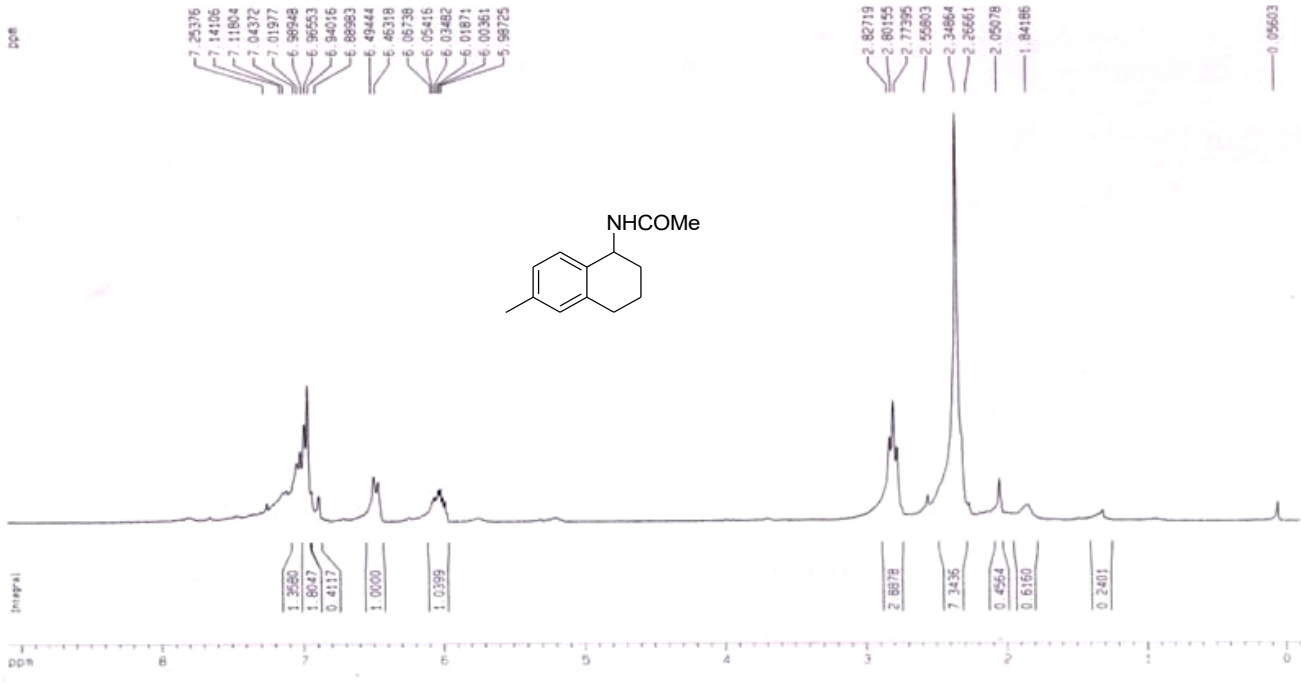


Figure 13: ^{1}H NMR of N-(1, 2, 3, 4-tetrahydro-6-methylnaphthalen-1-yl)acetamide (**3m**)

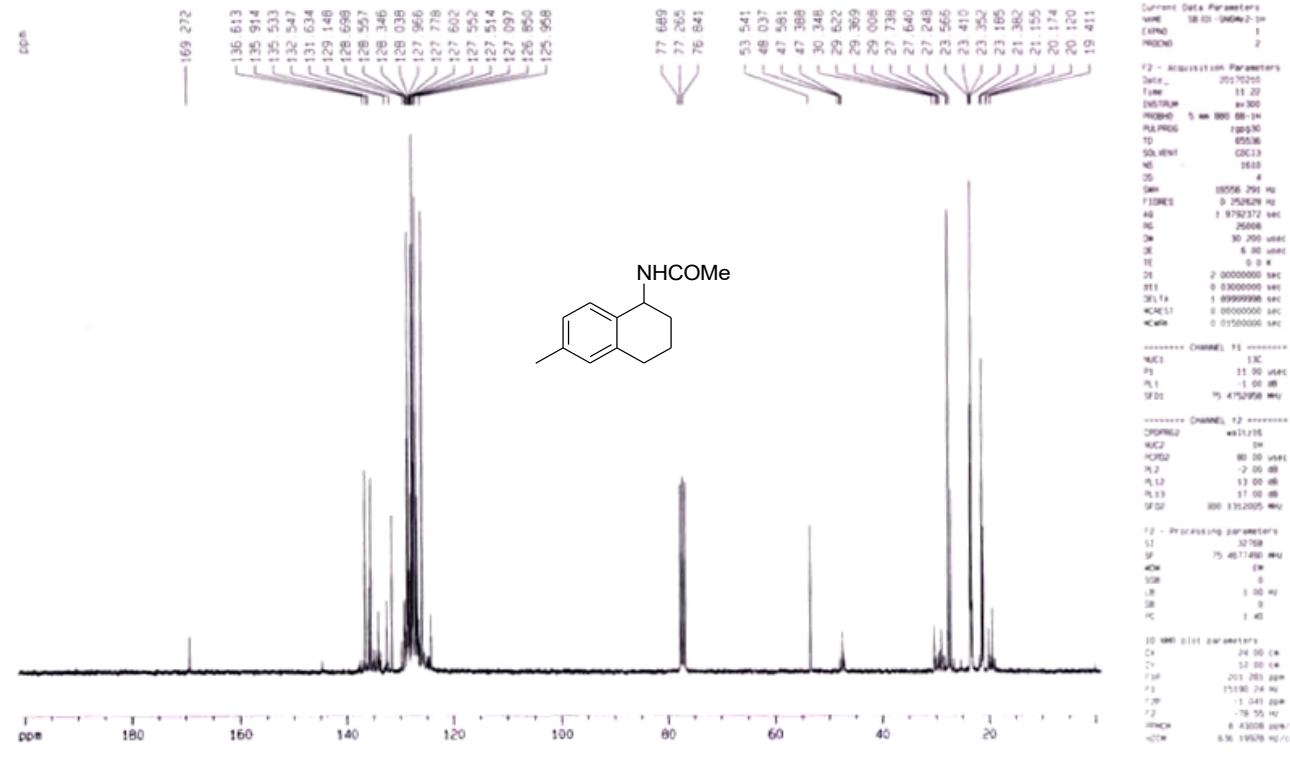


Figure 14: ^{13}C NMR of N-(1, 2, 3, 4-tetrahydro-6-methylnaphthalen-1-yl)acetamide (**3m**)

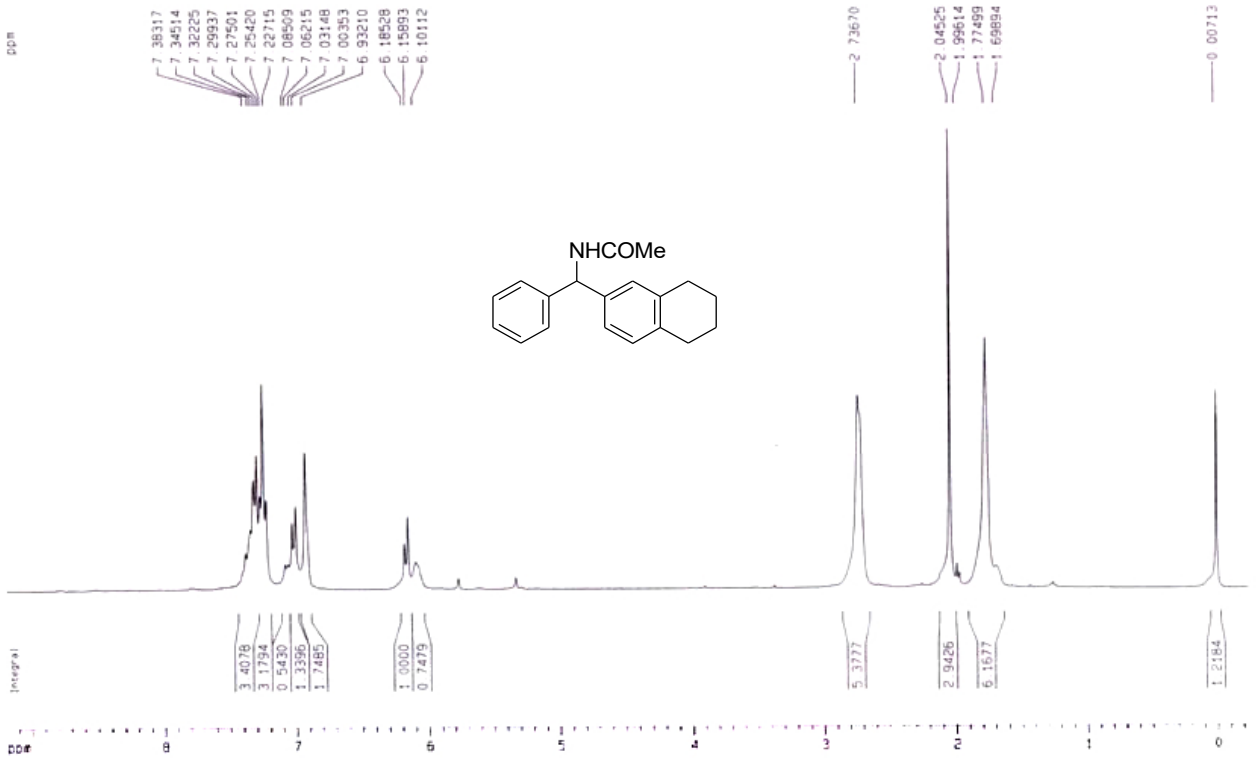


Figure 15: ^{1}H NMR of N-((1, 2, 3, 4-tetrahydronaphthalen-6-yl)(phenyl)methyl)acetamide (**3o)**

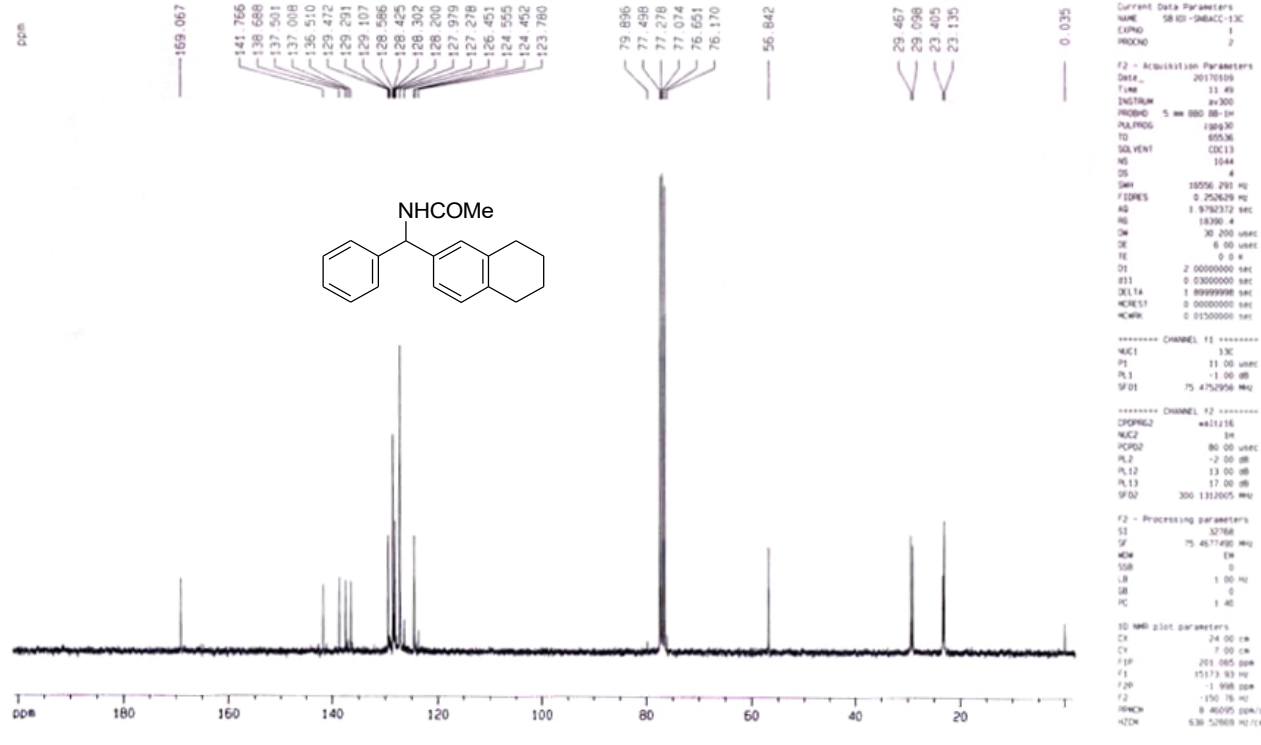


Figure 16: ^{13}C NMR of N-((1, 2, 3, 4-tetrahydronaphthalen-6-yl)(phenyl)methyl)acetamide (**3o)**

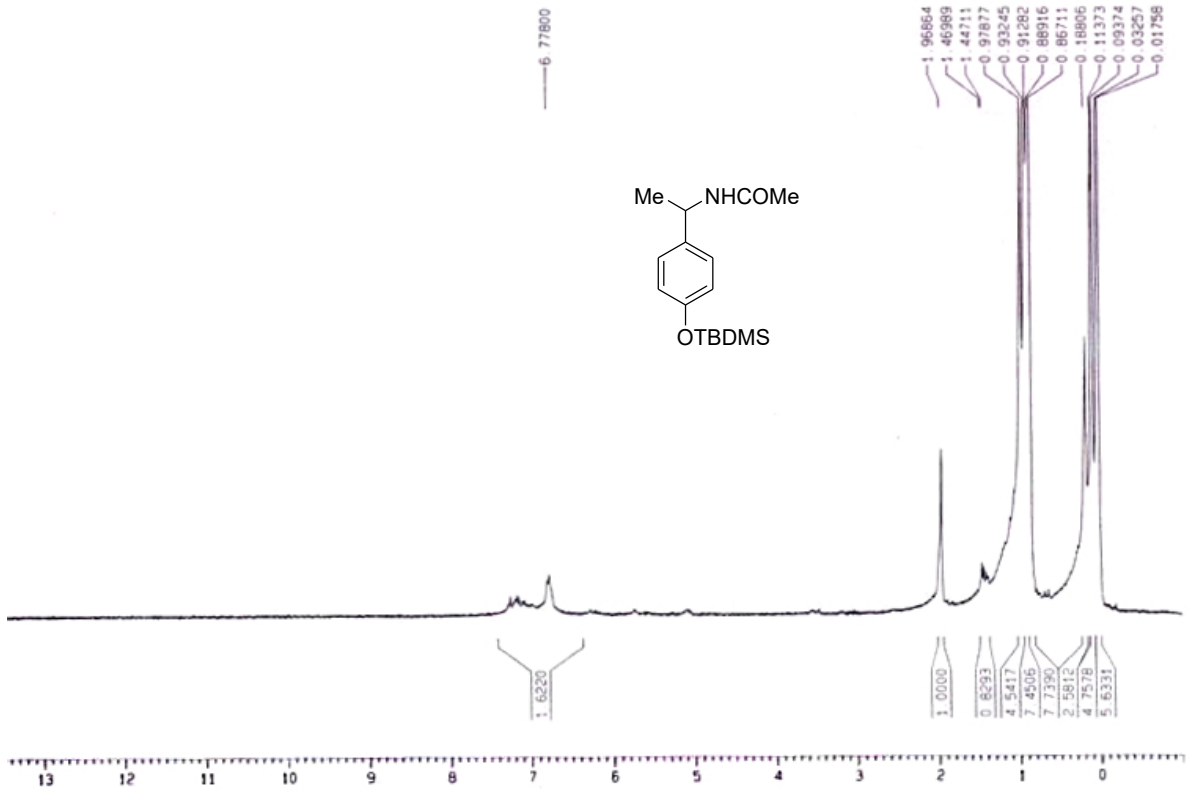


Figure 17: ^{1}H NMR of N-{1-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-ethyl}-acetamide (**3p)**

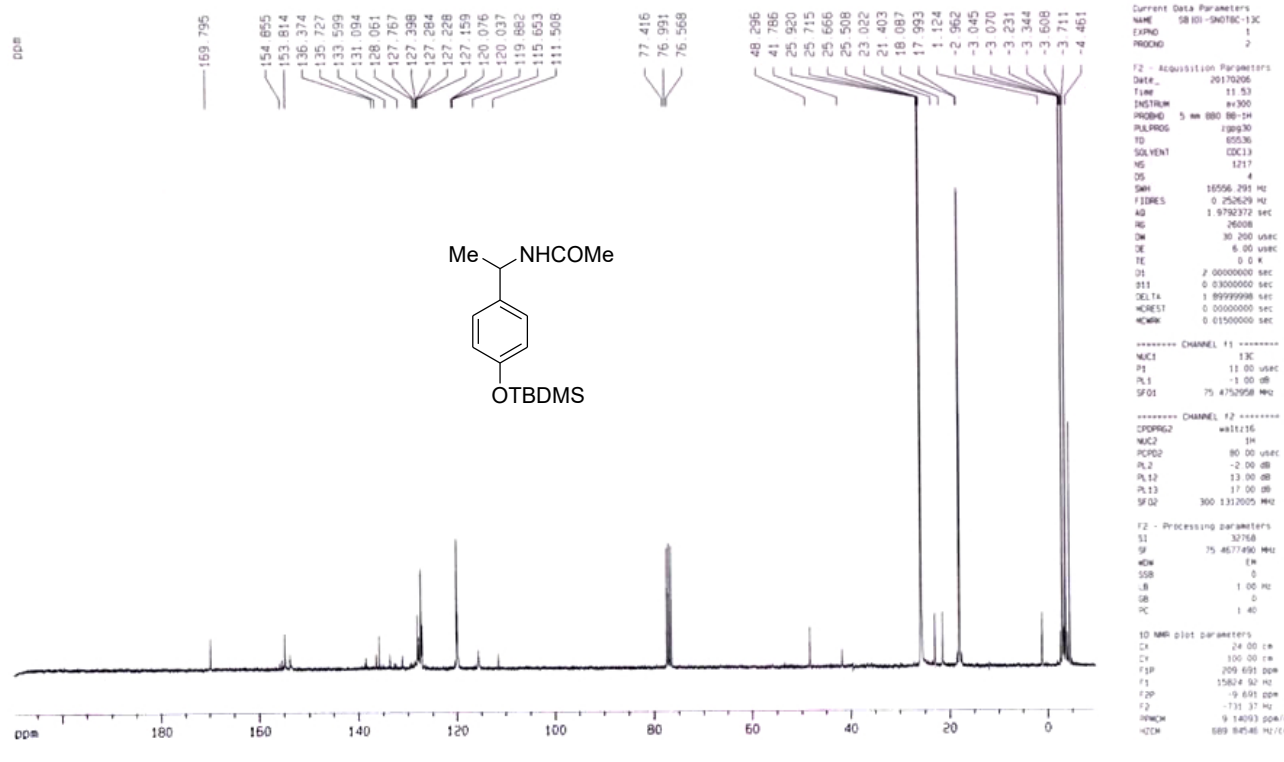


Figure 18: ^{13}C NMR of N-{1-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-ethyl}-acetamide (**3p)**

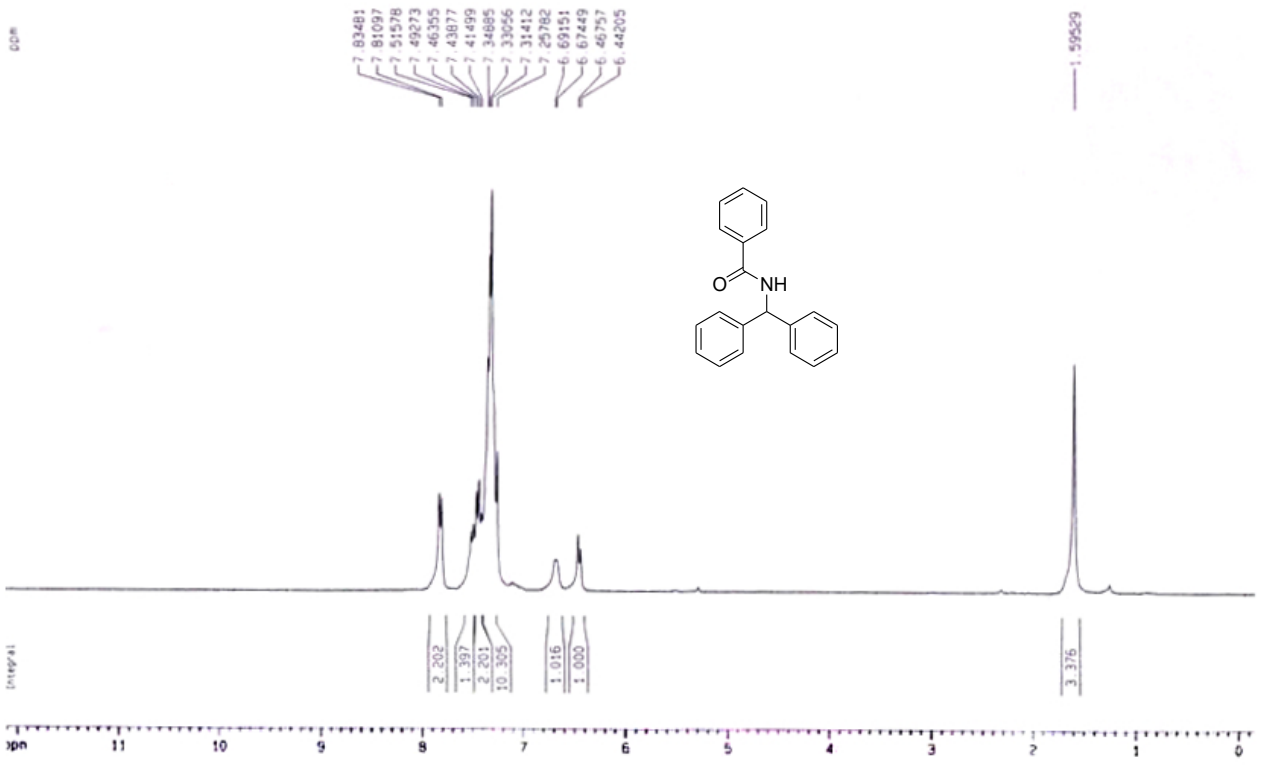


Figure 19: ^{1}H NMR of N-benzhydrylbenzamide (**3q)**

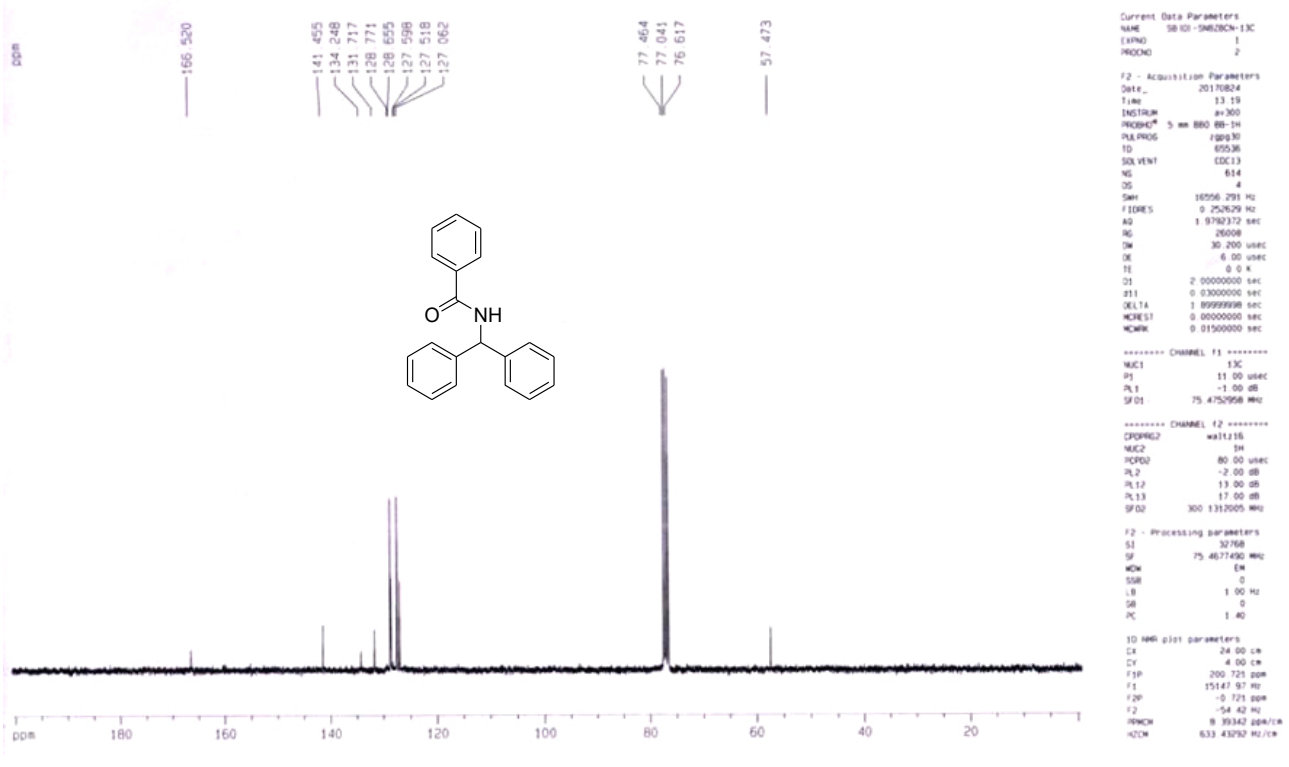


Figure 20: ^{13}C NMR of N-benzhydrylbenzamide (**3q)**

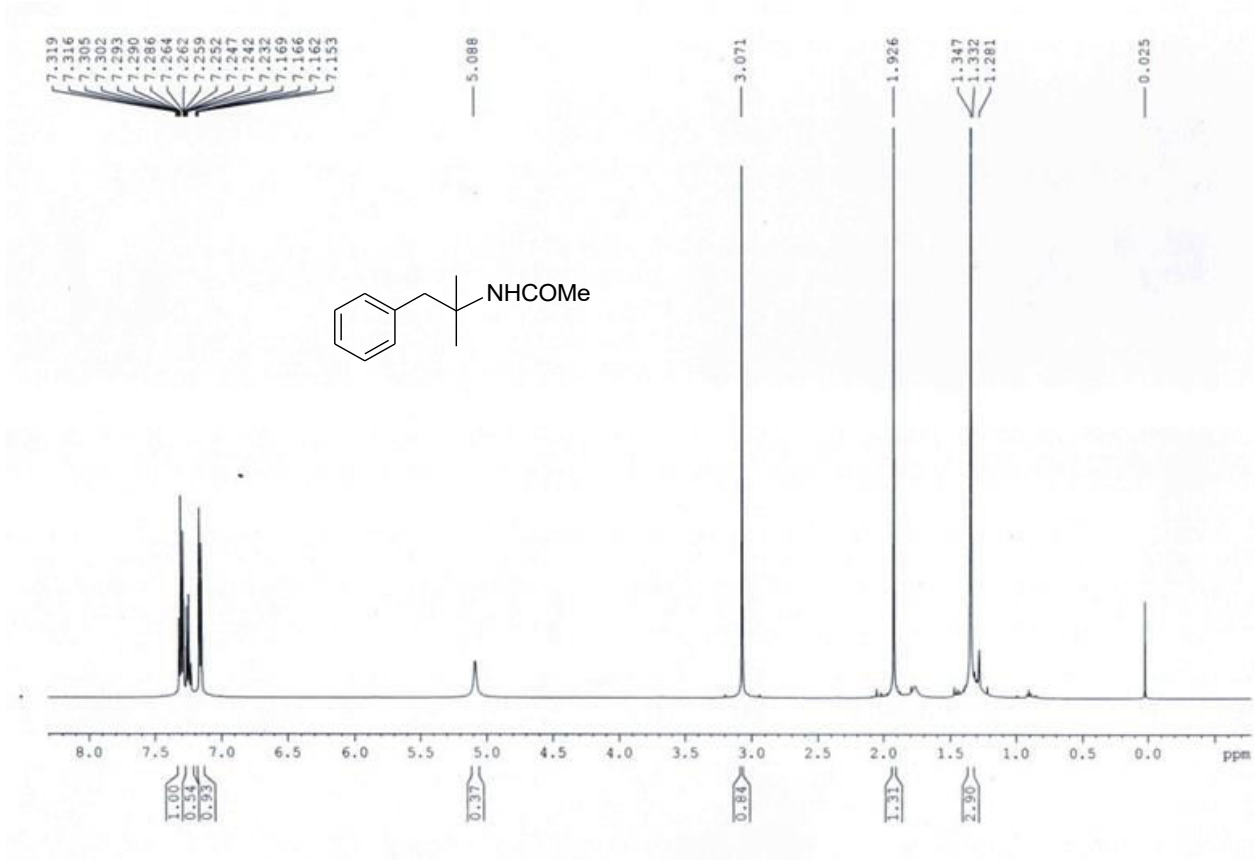


Figure 21: ^{1}H NMR of N-(1, 1-dimethyl-2-phenyl-ethyl)-acetamide (**3s)**

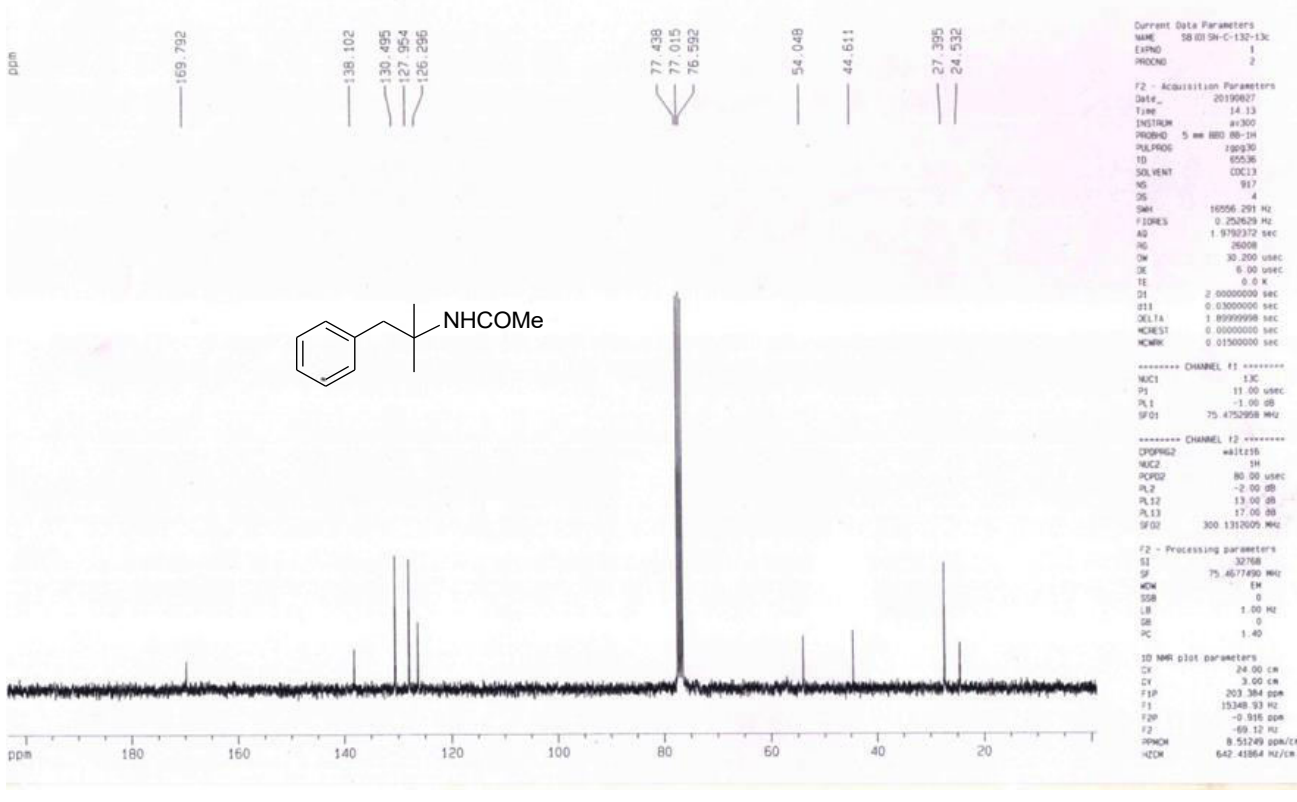


Figure 22: ^{13}C NMR of N-(1, 1-dimethyl-2-phenyl-ethyl)-acetamide (**3s)**

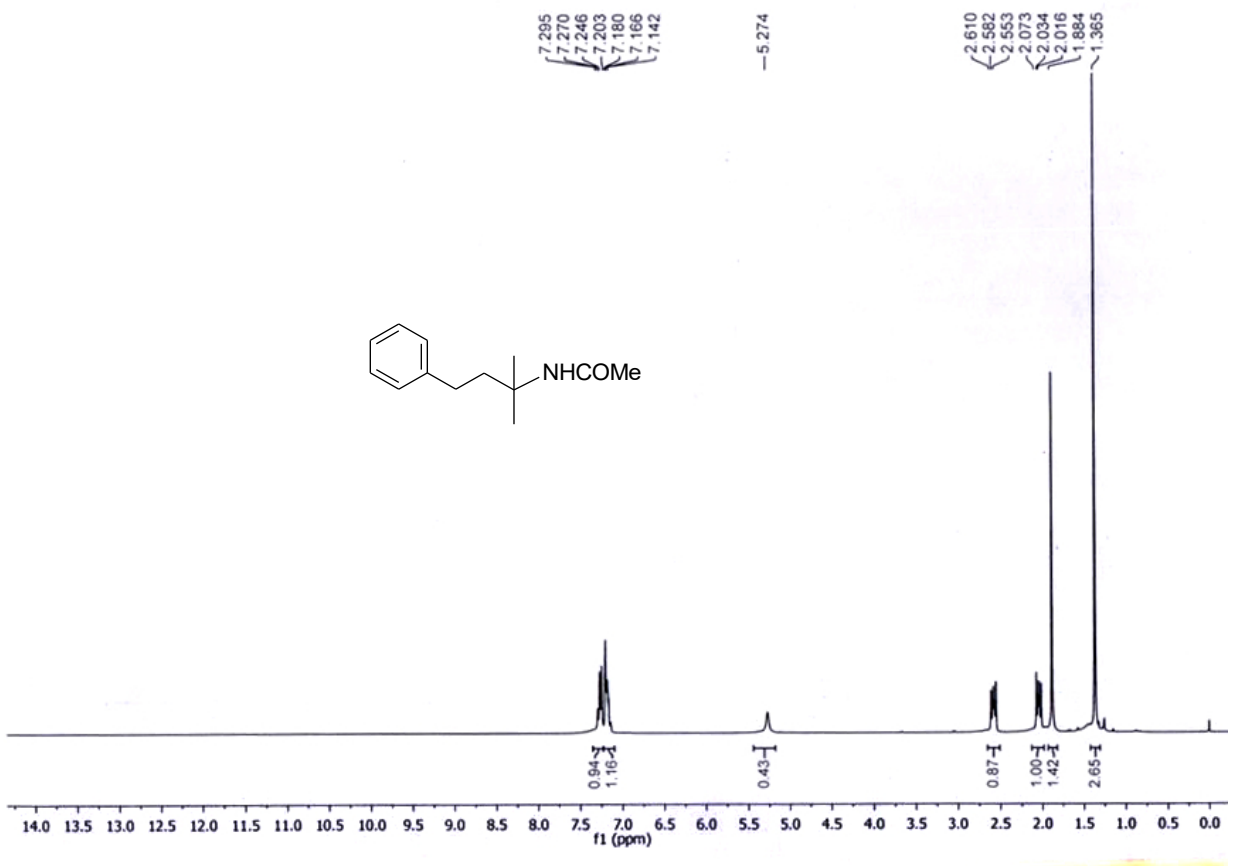


Figure 23: ^{1}H NMR of N-(2-methyl-4-phenylbutan-2-yl)-acetamide (**3t)**

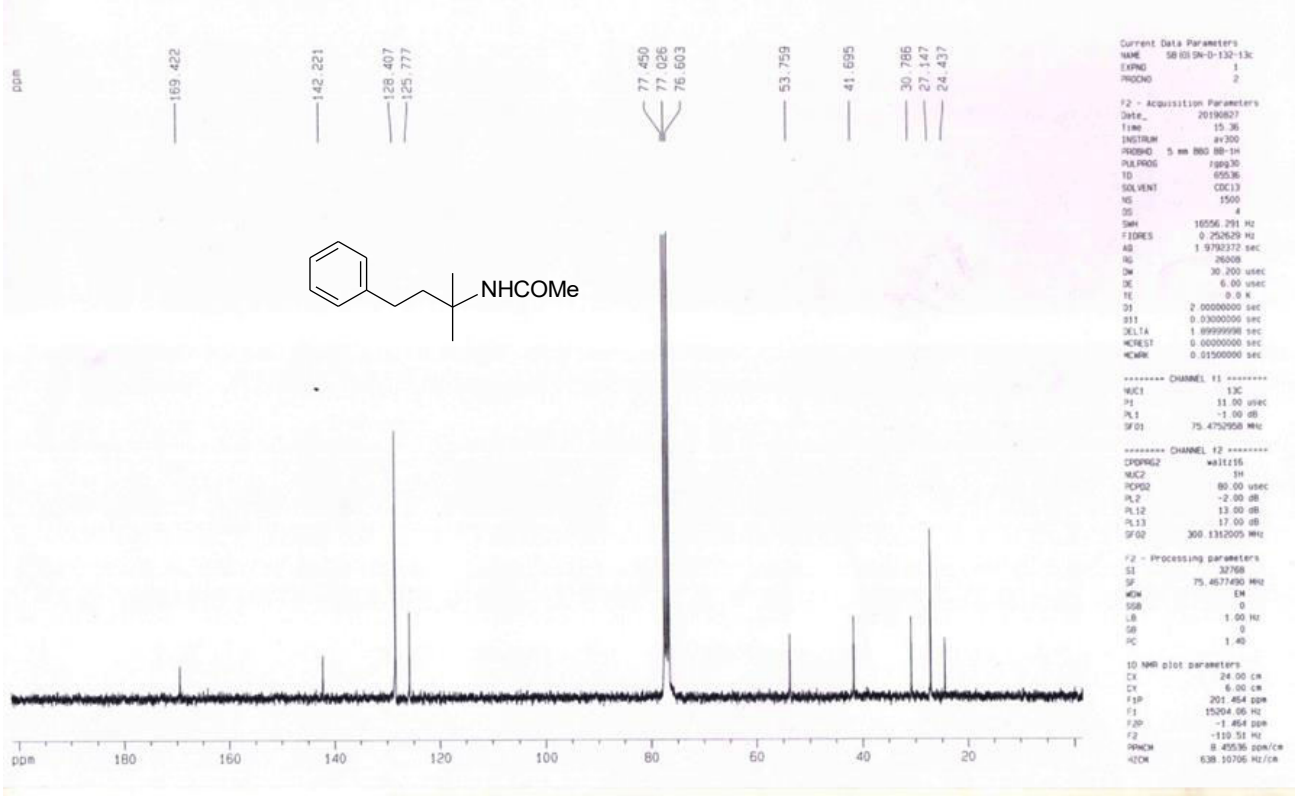


Figure 24: ^{13}C NMR of N-(2-methyl-4-phenylbutan-2-yl)-acetamide (**3t)**

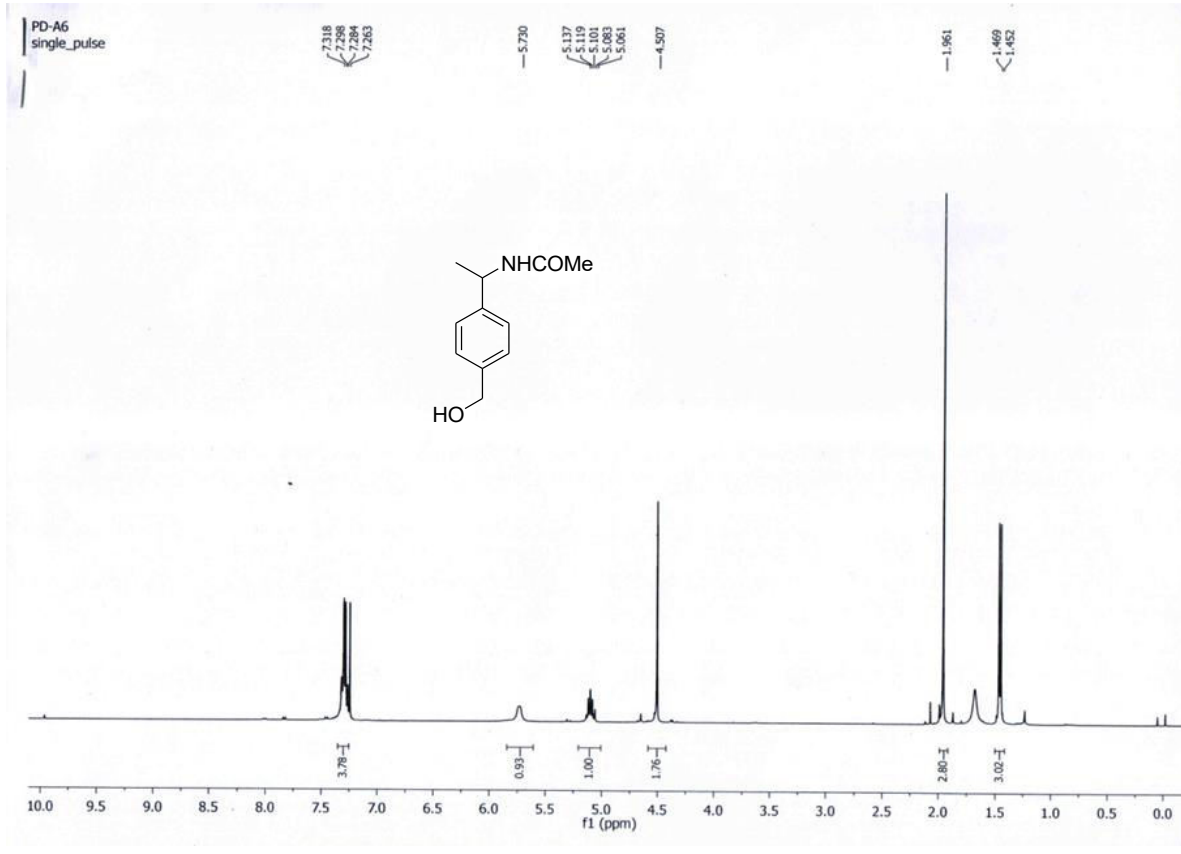


Figure 25: ^{1}H NMR of N-[1-(4-hydroxymethyl-phenyl)-ethyl]-acetamide (**3u)**

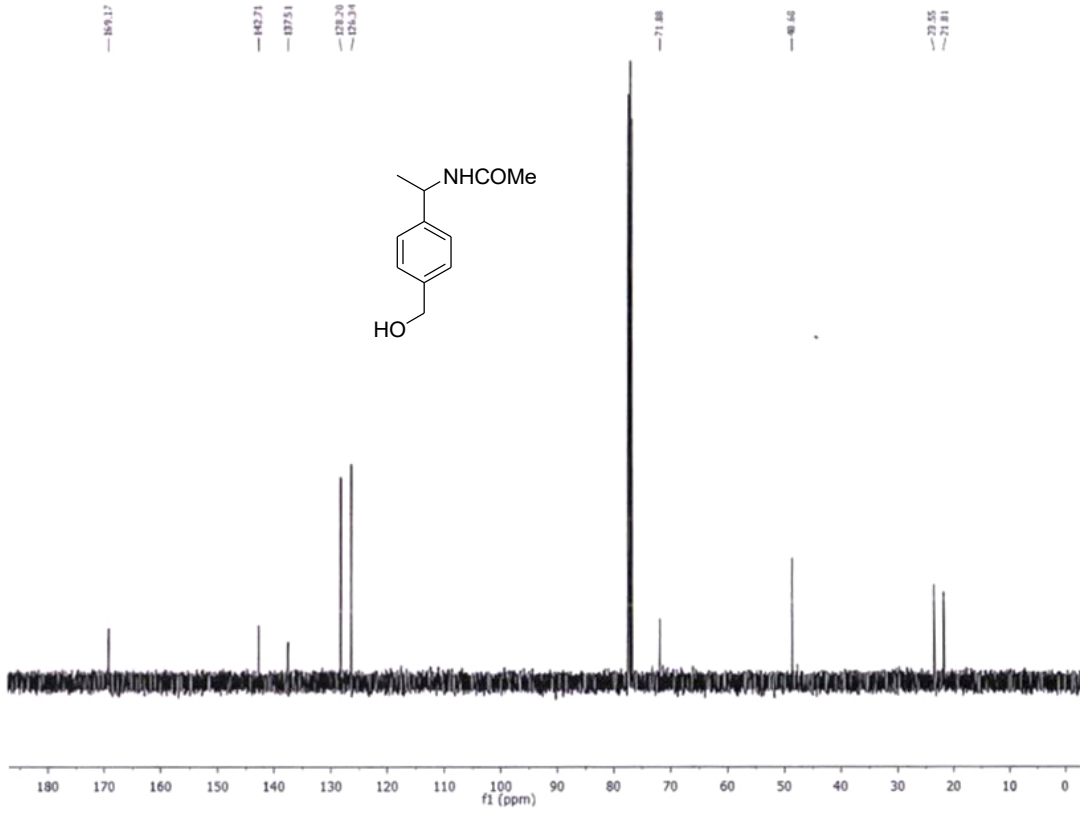


Figure 26: ^{13}C NMR of N-[1-(4-hydroxymethyl-phenyl)-ethyl]-acetamide (**3u)**

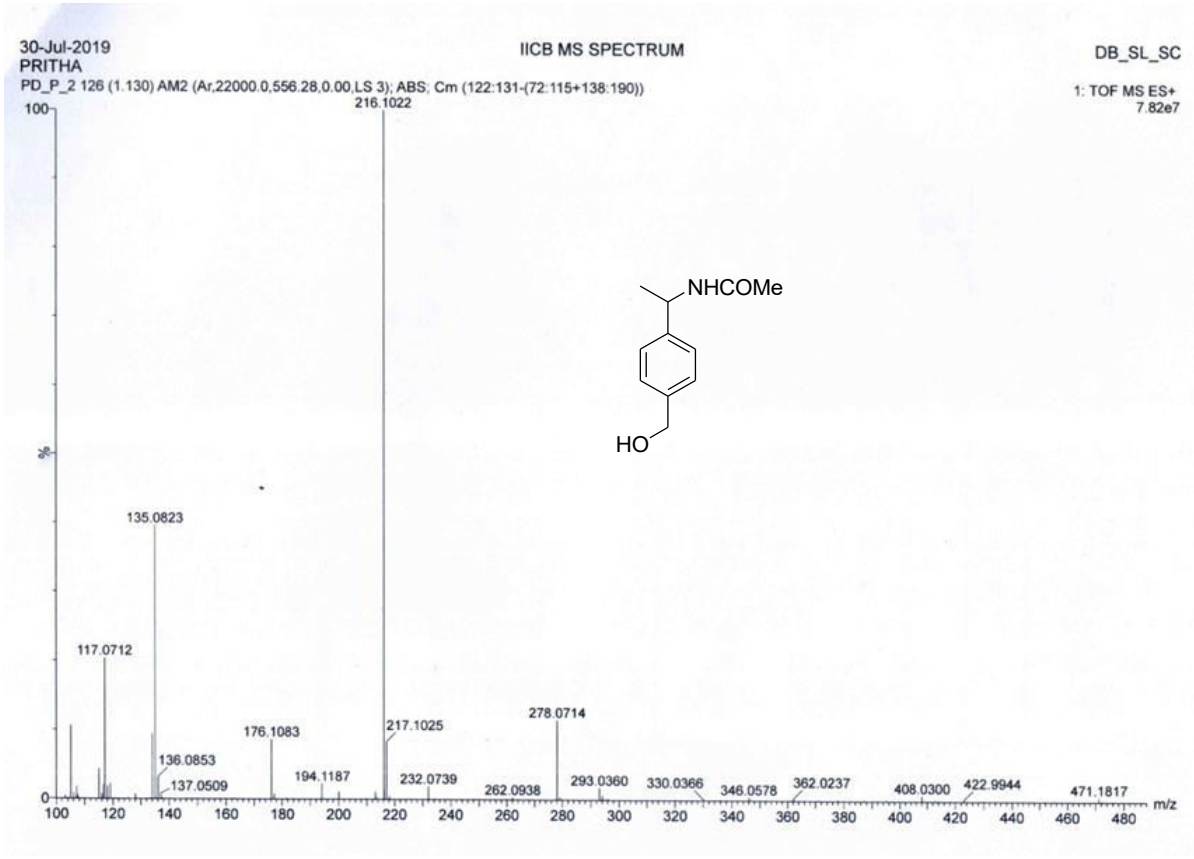


Figure 27: HRMS of N-[1-(4-hydroxymethyl-phenyl)-ethyl]-acetamide (**3u)**

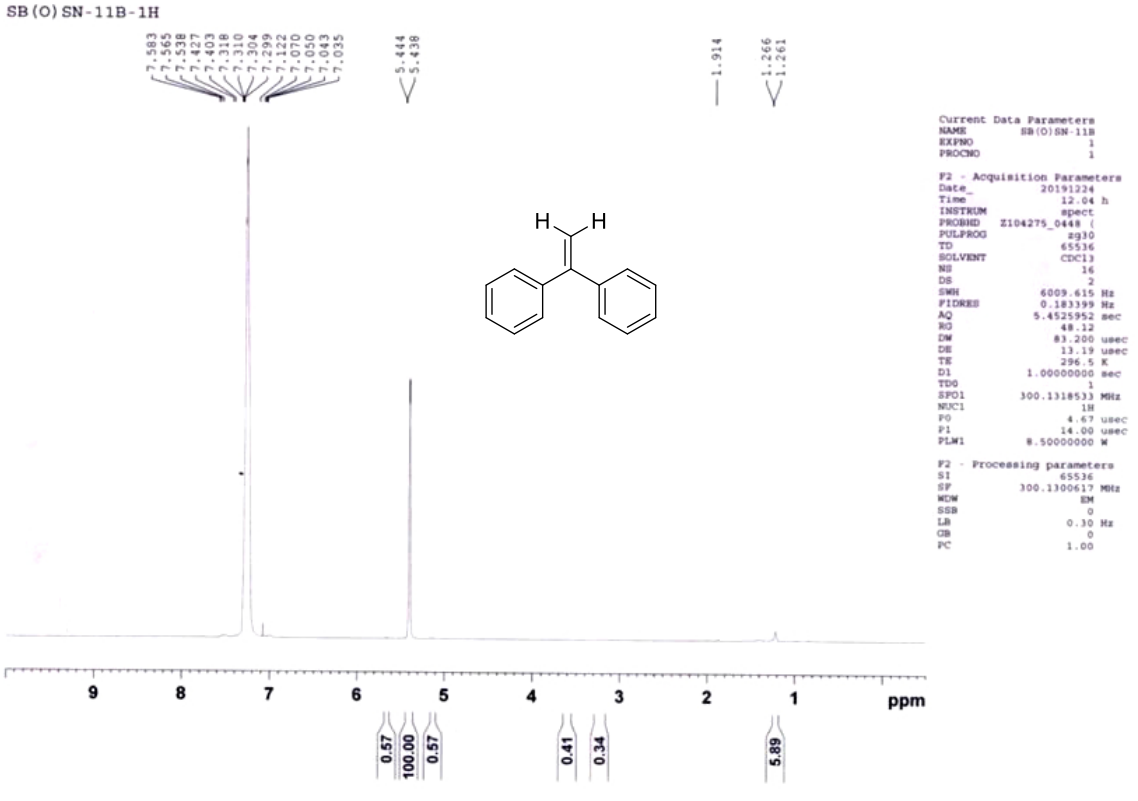


Figure 28: ^{1}H NMR of 1, 1diphenylethylene (**4d)**

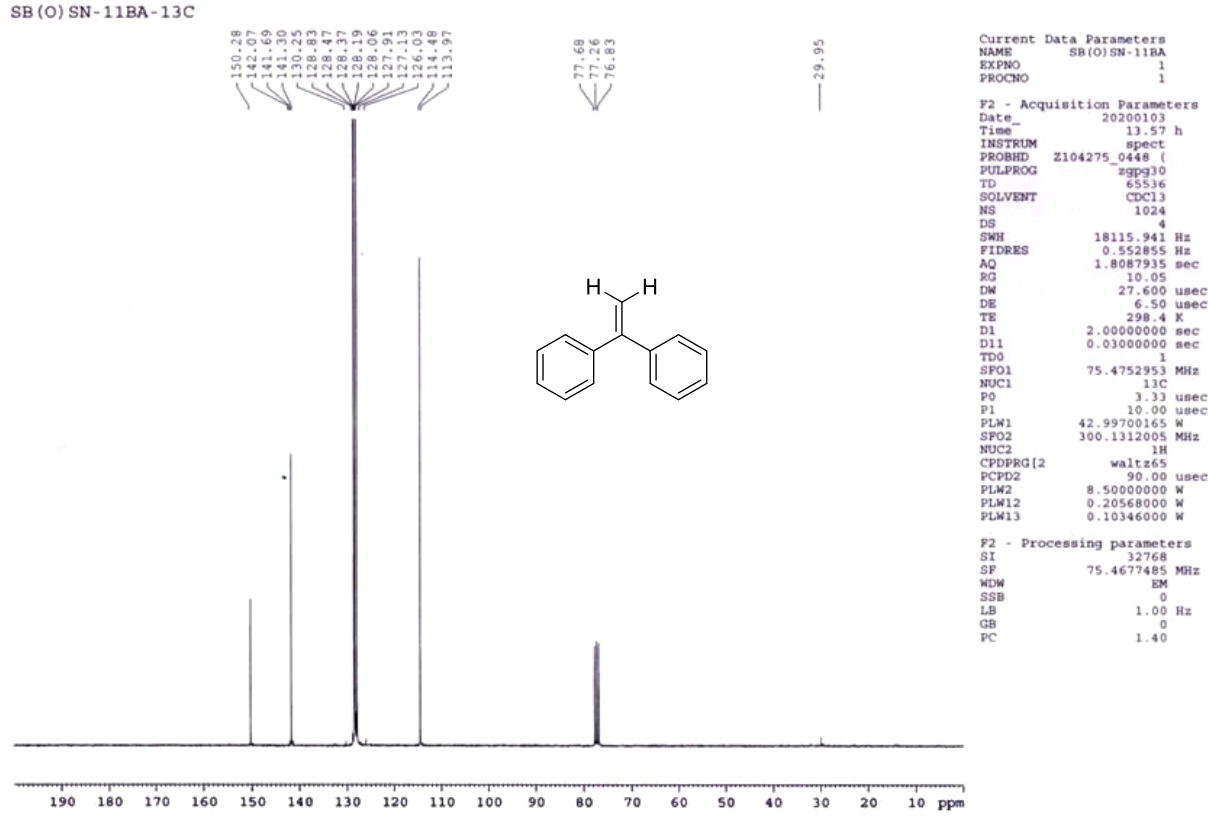


Figure 29: ^{13}C NMR of 1, 1diphenylethylene (**4d)**

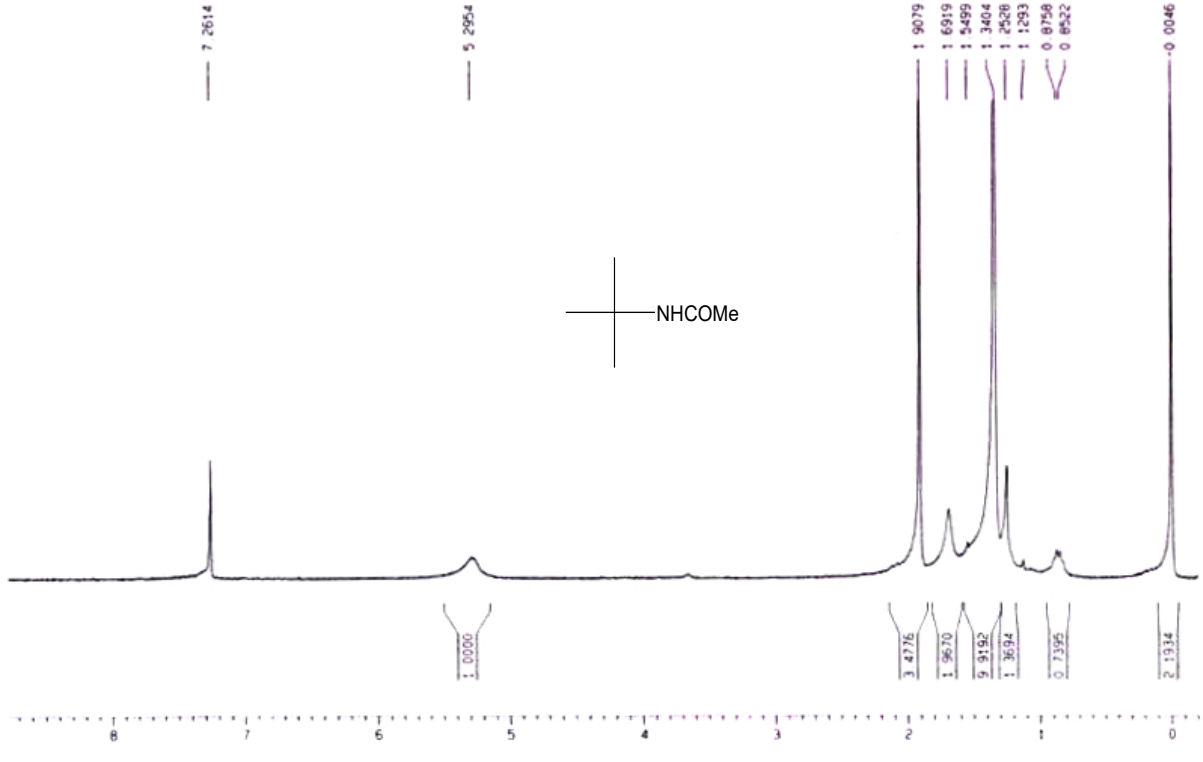


Figure 30: ^{1}H NMR of N-tert-butylacetamide (**6a)**

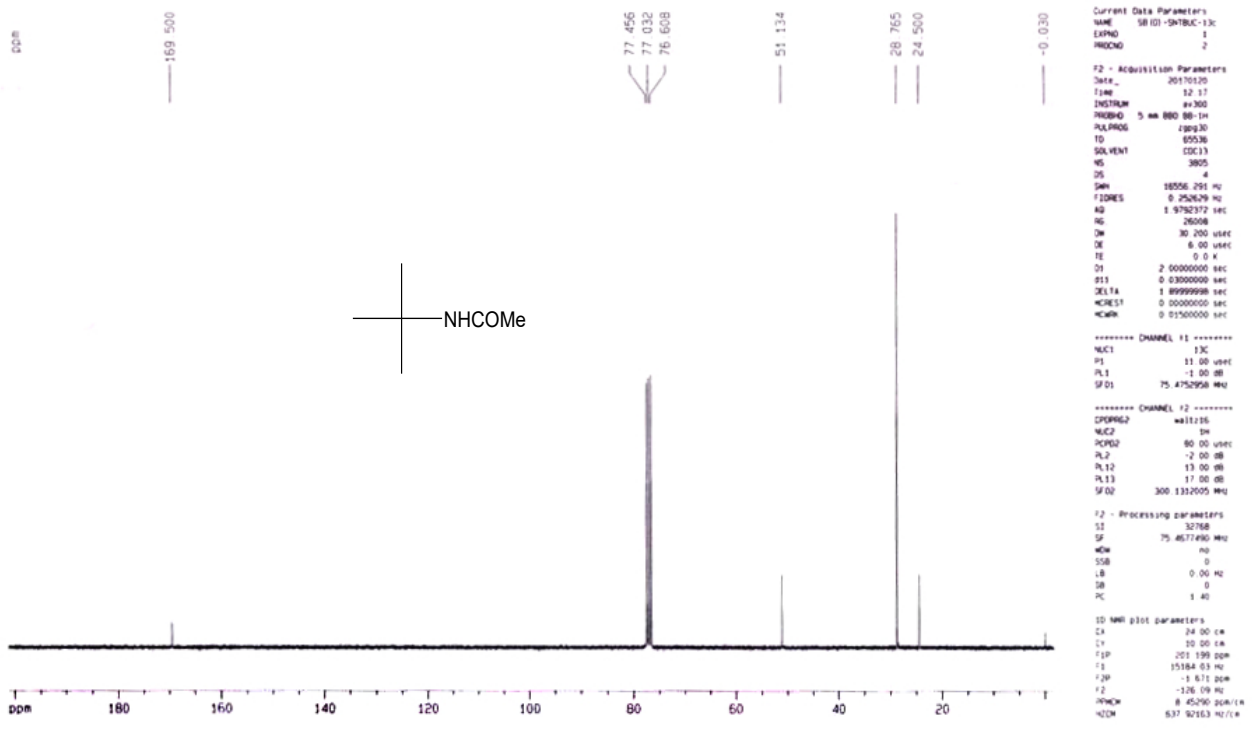


Figure 31: ^{13}C NMR of N-tert-butylacetamide (**6a)**

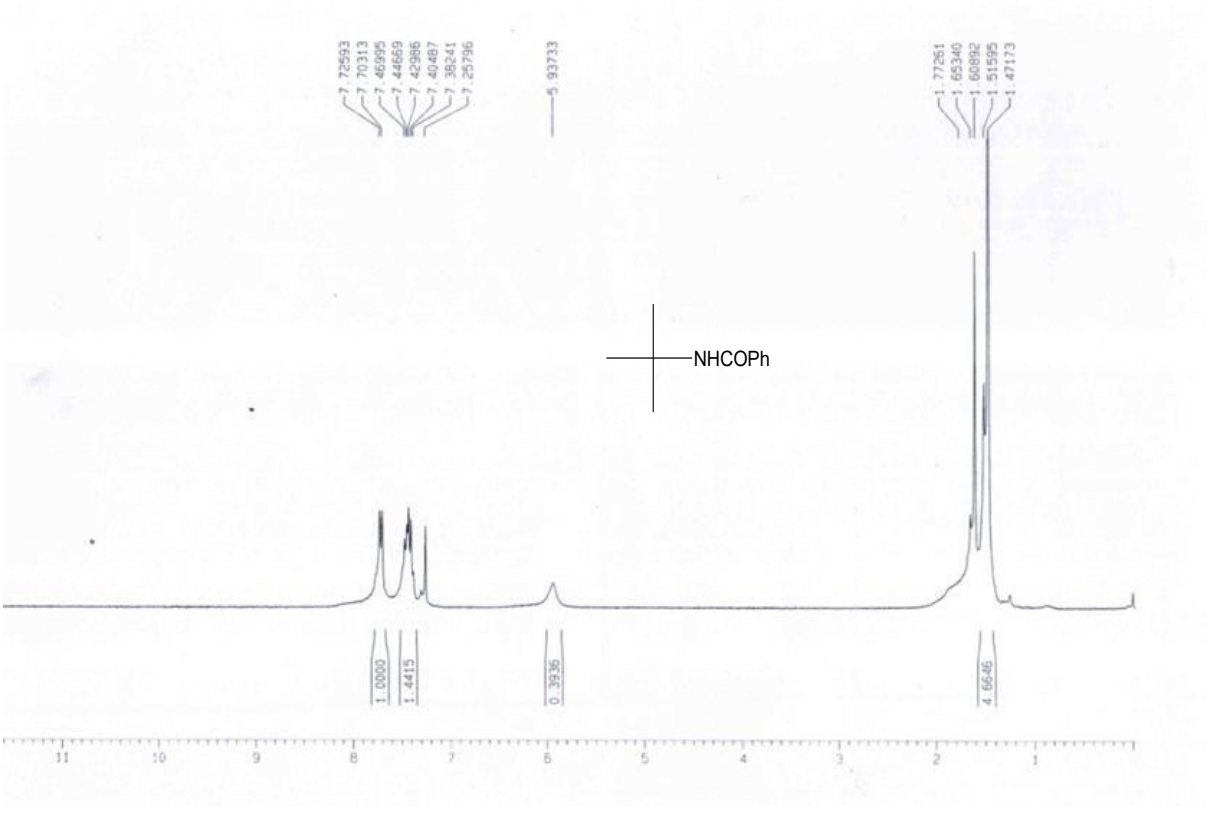


Figure 32: ^{1}H NMR of N-tert-butyl-benzamide (**6b)**

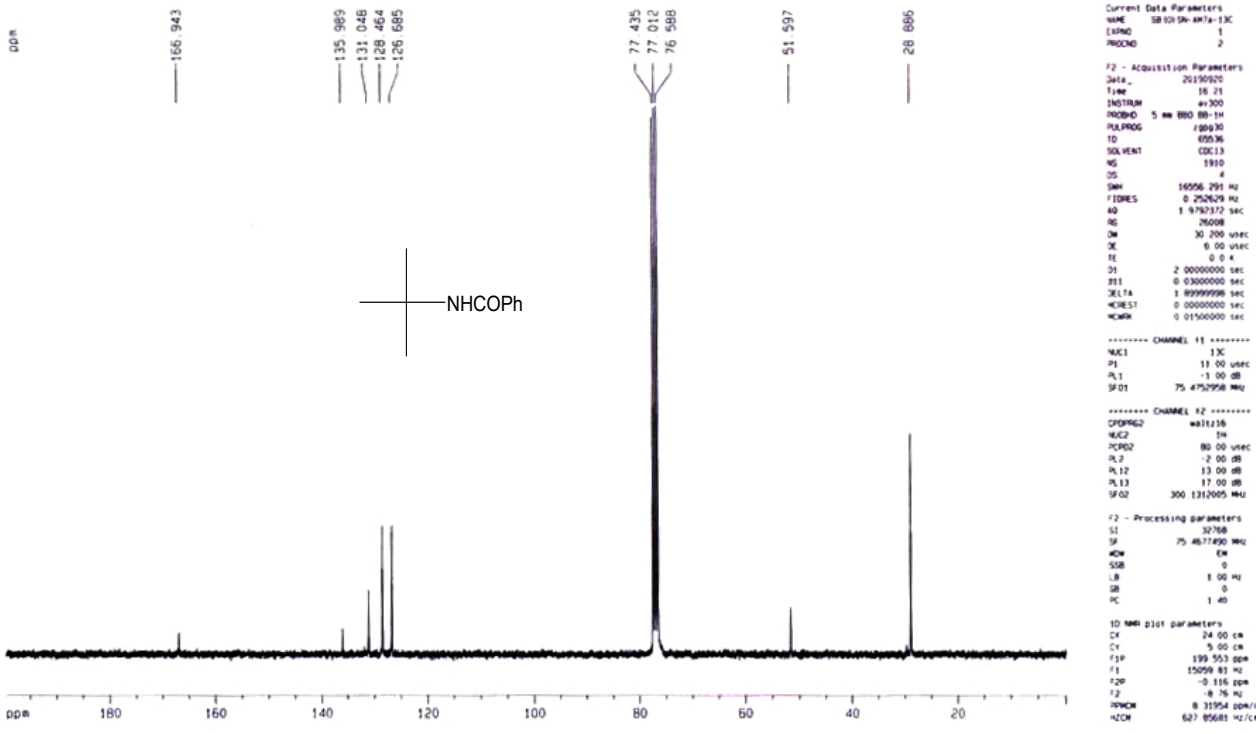


Figure 33: ^{13}C NMR of N-tert-butyl-benzamide (**6b)**

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CHAPTER-II; SECTION-3

C-O bond formation in aliphatic skeleton using Amberlyst®-15(H) as a recyclable catalyst

CHAPTER-II; SECTION-3

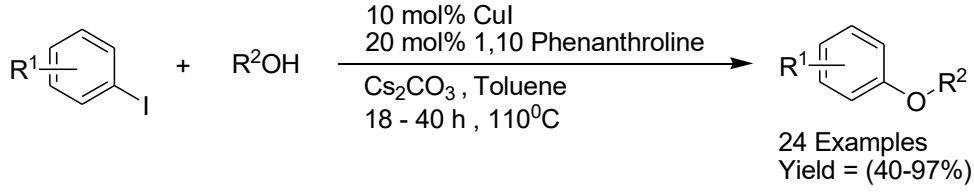
II.3. C-O bond formation in aliphatic skeleton using Amberlyst®-15(H) as a recyclable catalyst

II.3.1. Introduction:

Aryl alkyl ethers are broadly used as solvents and synthetic building blocks to prepare several kinds of cosmetics, fragrances and compounds with pharmaceutical importance. Therefore, the formation of C-O bond using metal catalysis holds its importance through years as one of the most important methods of cross-coupling reactions.

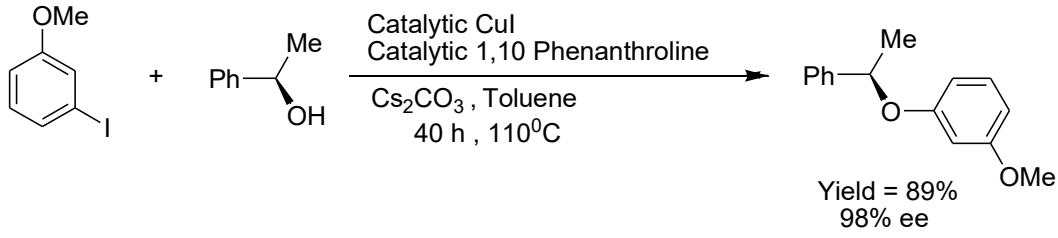
II.3.2. Recent methods for C-O bond formation: A Review

In this field significant modifications were made successively specially in Ullmann type ether synthesis. Buchwald *et al.* developed[1] an experimentally straightforward method for the convenient and efficient coupling of aryl iodides with aliphatic alcohols. This method designed for the arylation was quite cheap, performed under open atmosphere without taking any precautions to remove moisture and a series of aryl iodides were subjected to the optimised reaction conditions (Scheme 1). Primary alcohols such as methanol, butanol, heptanol and benzyl alcohol were transformed to their corresponding ethers successfully. Strong electron-donating substituents such as -OMe also gave high yields in *ortho-* , *meta-* and *para-* positions but, the electron-withdrawing substituent -CN seemed to be highly sensitive under the coupling reaction conditions.



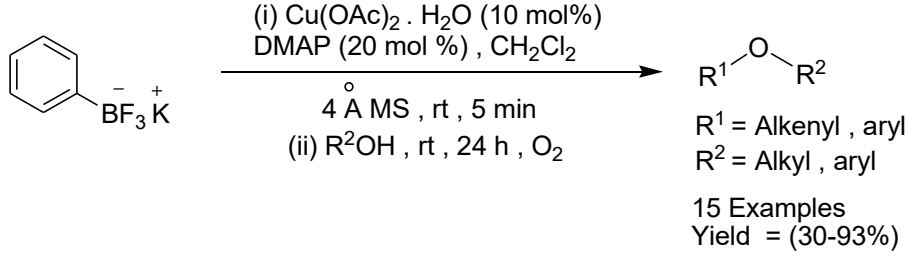
Scheme 1: Copper-catalyzed coupling of aryl iodides with primary alcohols

Secondary aryl alkyl ethers were also obtained using this method but in lower yields than their primary counterparts as *β*-hydride elimination imposed certain crucial restrictions to this method (Scheme 2).



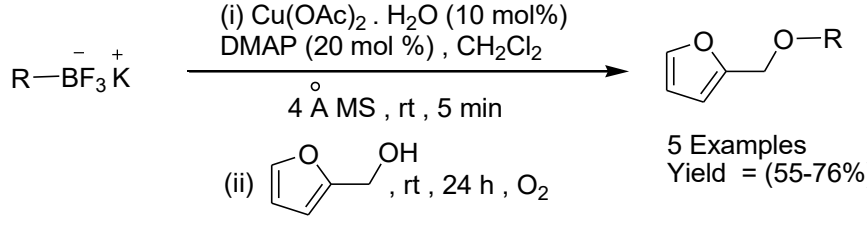
Scheme 2: Copper-catalyzed coupling of aryl iodides with secondary alcohols

Batey and his team have developed[2] a mild and highly effective neutral protocol for the formation of alkyl-aryl and alkyl-vinyl ethers through the Cu(II)-catalyzed cross-coupling using potassium organo-trifluoroborate salts with primary and secondary aliphatic alcohols (Scheme 3).



Scheme 3: Copper(II)-Catalyzed *O*-Phenylation of alcohols

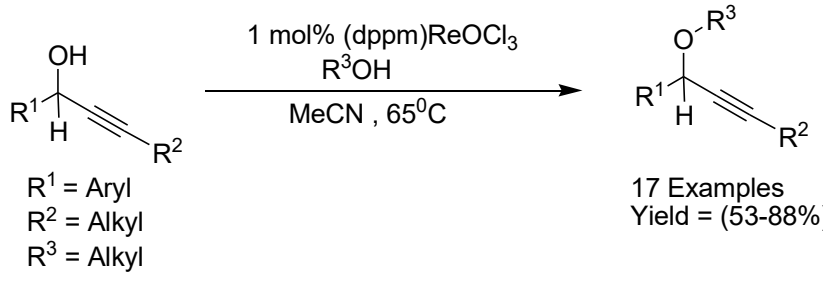
Secondary aliphatic alcohols while undergoing this cross-coupling gave lower yields than the primary alcohols. Meanwhile the reaction appeared to be quite sensitive to steric effects surrounding the hydroxyl group. Alkyltrifluoroborate derivatives were not so much effective under such conditions, because of their comparatively lower reactivity towards transmetallation with copper salts (Scheme 4).



Scheme 4: Copper(II)-Catalyzed *O*-Arylation/Alkenylation of 2-furfuryl alcohols

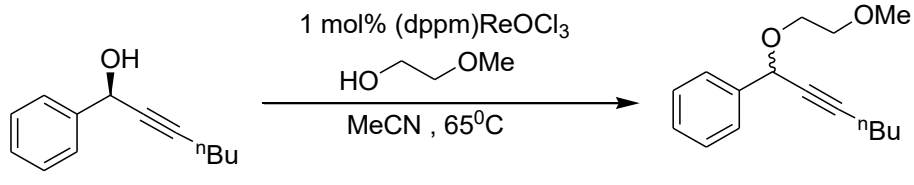
Another air and moisture-tolerant method for etherification of propargyl alcohols was reported[3] using rhenium-oxo complex as the catalyst, where the substrate scope was verified

using a broad range of functional groups including aryl halides, alkenes, α, β-unsaturated acetals and esters (Scheme 5). The transformation was regioselective with no allenic side products being observed. As no activation of the electrophilic alcohol as an ester or sulfonate was required in this current strategy, water was the only by-product formed after the reaction time. Moreover, displacement of the propargylic alcohols occurred preferably here over the reactive electrophiles as primary alkyl halides and conjugated esters.



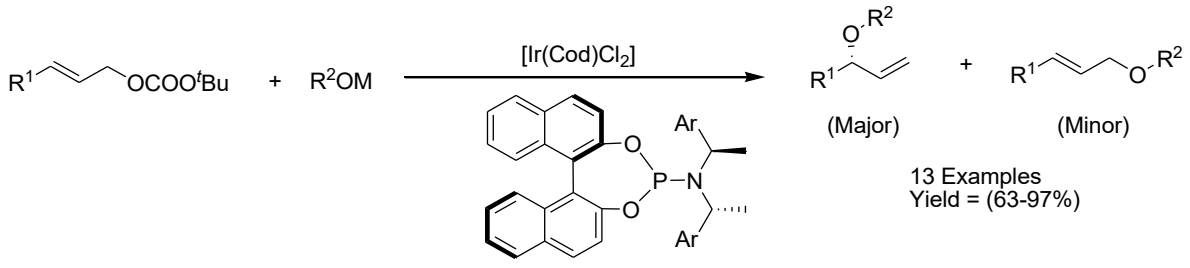
Scheme 5: Re-Oxo-catalyzed etherification of propargyl alcohols

On the basis of their proposed mechanism which seemed to proceed through a chiral allene intermediate, they anticipated that the propargylic etherification to be stereospecific, but the rhenium catalyzed reaction rather afforded racemic methyl ether starting from enantiomerically pure propargyl alcohol (Scheme 6).



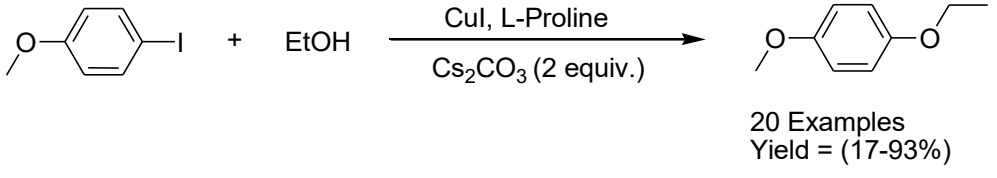
Scheme 6: Re-Oxo-catalyzed etherification of enantiomerically pure propargyl alcohol

Hartwig and his team developed[4] a simple and selective method for allylic etherification using both primary and secondary aliphatic alkoxides as substrates (Scheme 7). Tertiary alkoxides also formed the allylic ether products in satisfactory yields, but the reactions were sluggish and the enantioselectivity was lower than the case of secondary alkoxides. The catalyst was able to control the newly formed stereocenter when chiral secondary alkoxides were reacted under the optimized reaction condition.



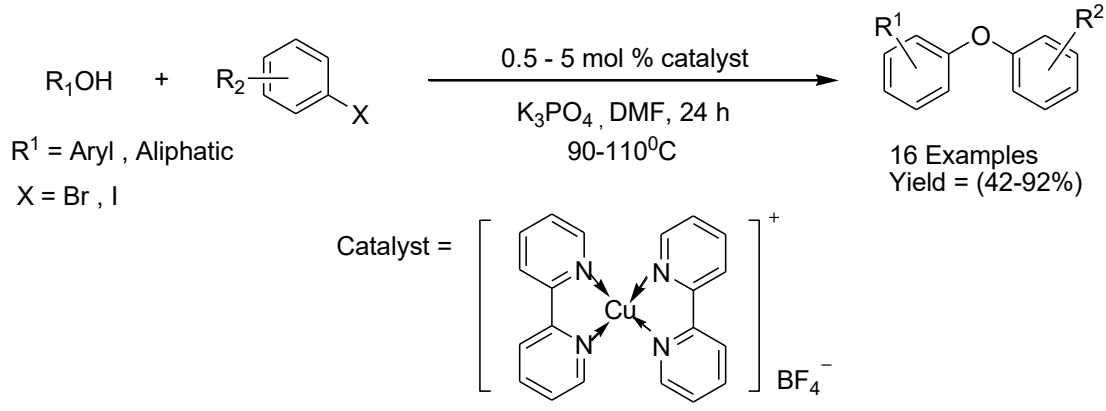
Scheme 7: The synthesis of chiral allylic ethers

Another Ullmann-type reaction demonstrated[5] that *N*, *N*-dimethylglycine is an excellent ligand for coupling of aryl iodides with aliphatic alcohols. It was found that primary alcohols such as ethanol, benzyl alcohol can be transformed successfully to their corresponding ethers under the reaction conditions (Scheme 8). The reaction proceeded very well even with aryl iodide carrying either electron-withdrawing or electron-donating groups. This reaction worked under relatively mild conditions using a simple catalytic system which was applicable for a wide variety of substrates.



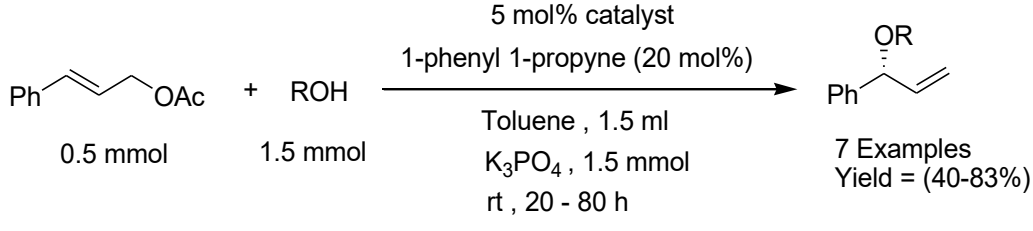
Scheme 8: CuI-catalyzed coupling reactions of aryl halides with alcohols

Niu *et al.* had described[6] the use of a new air-stable copper(I)-bipyridyl catalyst for the *O*-arylation of alcohols and phenols. Electron-neutral, rich and deficient aryl halides provided the corresponding products in moderate to excellent yields (Scheme 9). Aryl iodides or aryl bromides with electron-withdrawing groups, such as -CN, *p*-keto or *p*-nitro were proved as good substrates when coupled with phenol at lower catalyst loadings at comparatively low temperature. This method displayed increased reactivity, required less catalyst loading without any moisture-sensitive and expensive bases.



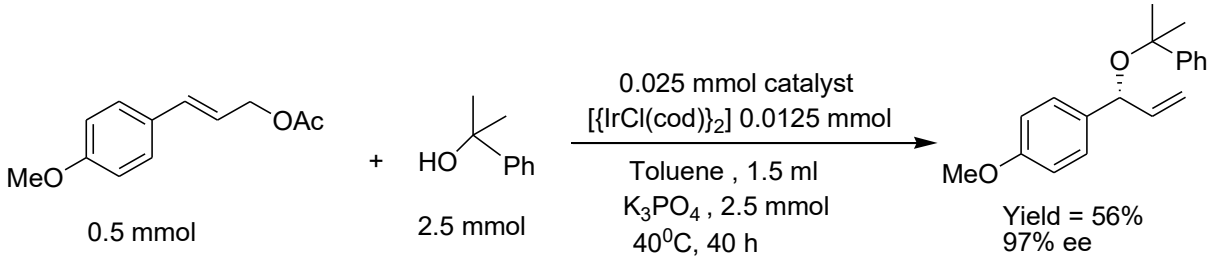
Scheme 9: The coupling reaction of unhindered aryl halides with phenols

An additional similar method demonstrated[7] that allylic asymmetric etherification including the first asymmetric allylation of a tertiary alcohol in good yield and enantioselectivity could be performed using allyl acetates in combination with alcohols and a suitable nucleophile (Scheme 10). In addition to the reactions using primary and secondary alcohols, the results showed that alkali metal alkoxides in lower concentrations can be proficient nucleophiles for allylic substitution. For high conversion, the use of powdered K_3PO_4 was necessary.

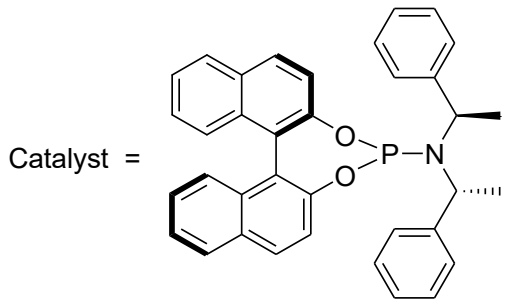


Scheme 10: Allylic etherification with various alcohols

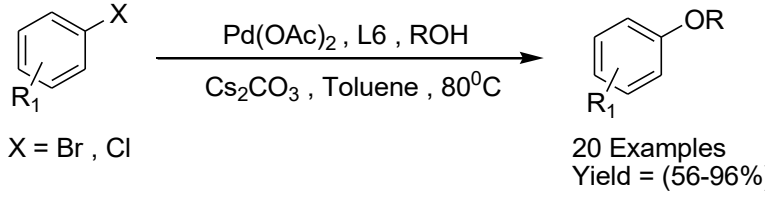
Not only aromatic but aliphatic allylic carbonates also reacted under the optimised condition to give their respective substitution products in satisfactory yields with branched site selectivity and high to excellent enantiomeric excess (Scheme 11).



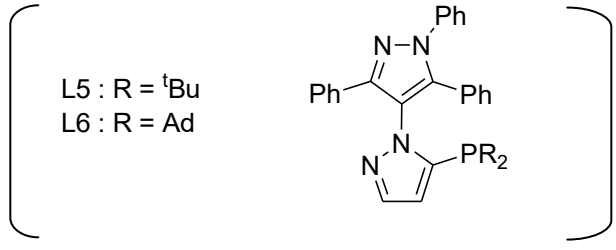
Scheme 11: Enantioselective allylic etherification with 2-phenylpropan-2-ol



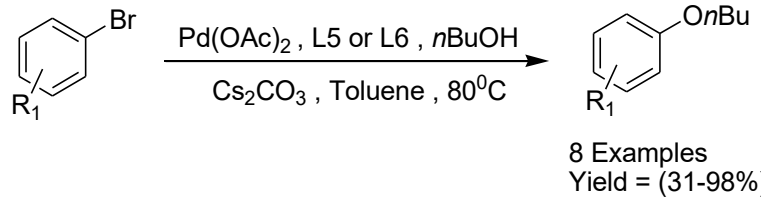
An effective procedure for palladium-catalyzed coupling[8] of heteroaryl chlorides and bromides with aliphatic primary alcohols was developed by Beller *et al*. This synthesis explored the scope for novel bulky di-1-adamantyl-substituted bipyrazolylphosphine ligand towards the reaction of arylhalides including unactivated as well as activated heteroaryl bromides and aryl chlorides with primary alcohols giving their corresponding ethers in high yield (Scheme 12 and Scheme 13).



Scheme 12: Pd-catalyzed coupling reactions of aryl halides with primary alcohols

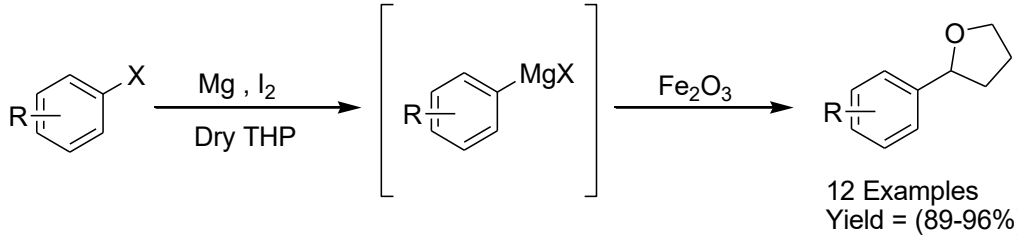


Variation of the solvent confirmed toluene as optimal and when compared to KOH and K_2CO_3, Cs_2CO_3 came out as the better base for this reaction. Functionalization of several primary alcohols in the presence of secondary and tertiary alcohols also proceeded well with excellent regioselectivity.



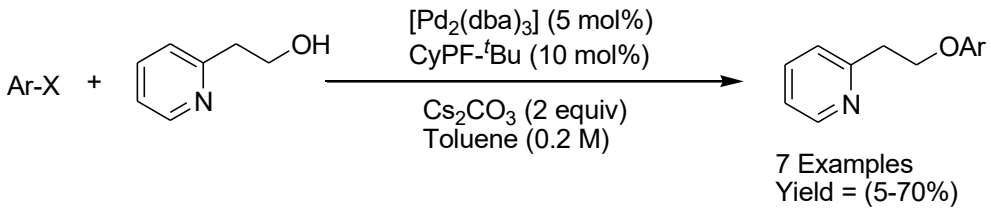
Scheme 13: Selective Pd-catalyzed arylation of functionalized alcohols

Vishwakarma and his team reported[9] a novel and efficient iron oxide catalyzed cross-coupling reaction using organolithium species, organometallic species such as alkyl/aryl magnesium halides and α-hydrogen bearing cyclic aliphatic ethers through the activation of C(sp^3)-H bond (Scheme 14). Substrates having electron-donating and electron-withdrawing groups located at the arylmagnesium halide moiety went through the cross-coupling reaction smoothly to afford their corresponding cyclic ethers in good yields. The results found in this methodology suggested that Fe_2O_3 based intermediates facilitated the generation of carbon radicals and gave d-block organometallic surfaces greater scope for further cross-coupling.



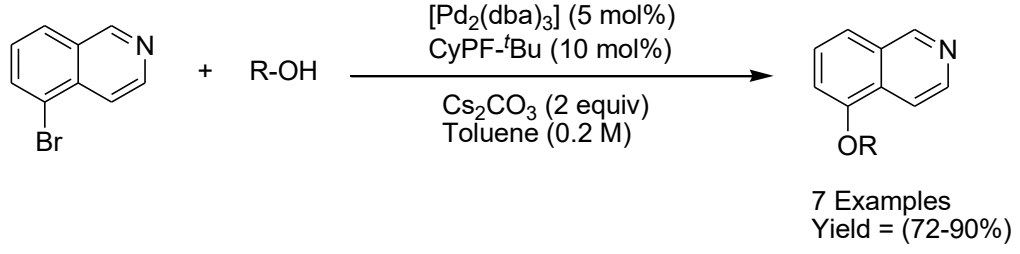
Scheme 14: Iron oxide catalyzed cross-coupling reaction of aryl magnesium halides

Another robust and simple Pd/Josiphos catalyst system was applied[10] for the alkoxylation of hetero-arylhalides with primary, secondary and some tertiary alcohols without any need of excess coupling reagent (Scheme 15). Here, in contrast to electron-deficient aromatic halides, electron-neutral aryl halides reacted with less conversion rate. Tertiary alcohols were also found to couple successfully but sterically bulky alcohols failed to provide significant conversion to their corresponding product.



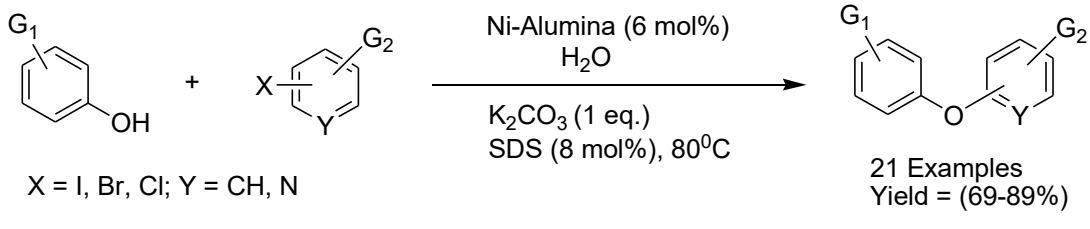
Scheme 15: C-O cross-coupling of aryl halides with alcohols

Commercially available Josiphos ligand was an excellent regioselective ligand which had broad functional-group tolerance making this process a complementary approach to all the existing protocols for C-O bond formation (Scheme 16). This was one of the pioneer examples of intermolecular Pd-catalyzed C-O cross-coupling reaction applicable to primary, secondary and some tertiary alcohols using a comparatively mild base.



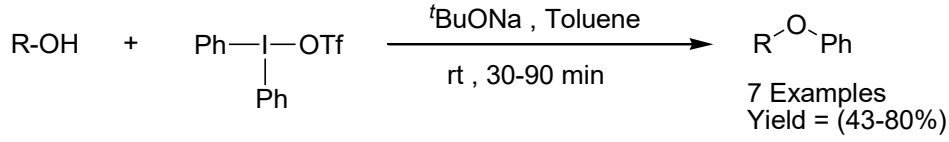
Scheme 16: C-O cross-coupling of 5-bromoquinoline with alcohols

An eco-compatible and ligand-free protocol was developed[11] by Ghatak *et al*. for the synthesis of diaryl ethers using easily accessible alumina-supported nickel nanoparticles as a recyclable heterogeneous catalyst in aqueous medium with sodium dodecyl sulfate (SDS) as surfactant and K_2CO_3 as mild base (Scheme 17). Along with excellent chemoselectivity, various sensitive functional groups like formyl, allyl, alkoxycarbonyl, chloro, bromo, oxo, amine and nitro were successfully tolerated in this method.



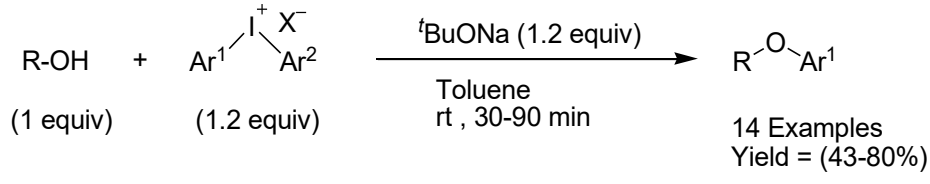
Scheme 17: Synthesis of diaryl ethers in aqueous medium using alumina-supported Ni nanoparticles

The first efficient arylation[12] of aliphatic alcohols using diaryliodonium salts was developed by employing simple and metal-free conditions (Scheme 18 and Scheme 19).



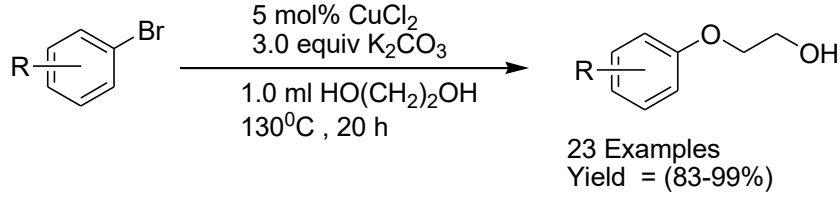
Scheme 18: Phenylation of aliphatic alcohols

Aryl groups with electron-withdrawing groups were transformed in excellent yields for a broad range of alcohols, while phenylation worked best for unactivated primary, secondary, allylic and benzylic alcohols. But *ortho*-substituted and electron-rich diaryliodonium salts gave slow reactions surprisingly. Compared to aromatic nucleophilic substitutions, this current arylation methodology required no excess reagents, high temperature or extended reaction time.



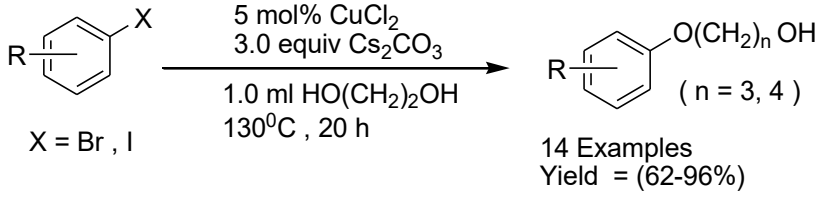
Scheme 19: Arylation of aliphatic alcohols

A highly proficient copper-catalyzed[13] C–O cross-coupling between aliphatic diols and aryl bromides was developed utilizing a more efficient, much cheaper and easily removable copper catalyst (Scheme 20). A wide range of aryl bromides were coupled using 5 mol% $CuCl_2$ with 3 equivalents of K_2CO_3 without any other ligands or solvents to provide the hydroxyl alkyl aryl ethers in high to excellent yields.



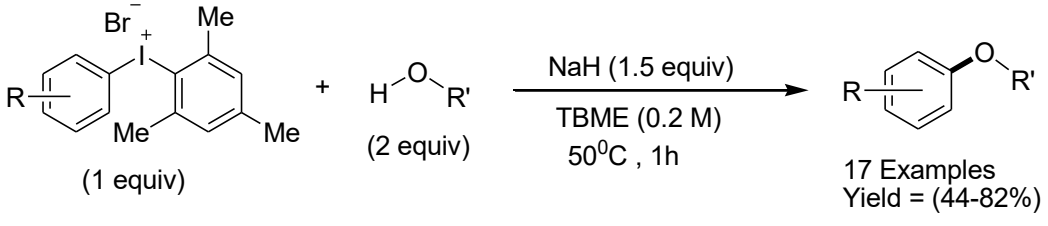
Scheme 20: Copper(II)-catalyzed C–O coupling reaction of arylbromides with ethylene glycol

The current catalytic system featured good tolerance towards a variety of functional groups such as phenolic hydroxyl, trifluoromethyl, aliphatic hydroxyl and even carboxylic acids. Resulting ethers were further converted into their corresponding phenols, giving an alternative pathway to make phenols from aryl bromides (Scheme 21).



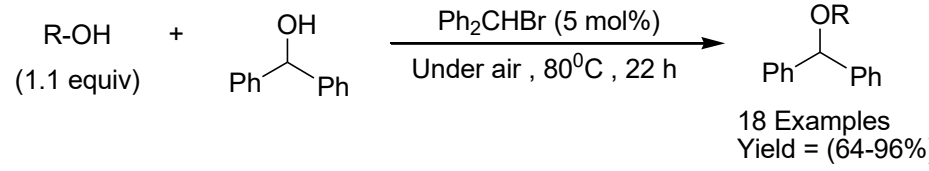
Scheme 21: Copper(II)-catalyzed C–O coupling reactions of aryl bromides with aliphatic diols

A broad range of alkyl-aryl ethers was produced[14] by using readily assembled unsymmetric diaryliodonium salts combining with primary, secondary, tertiary and even allylic, benzylic aliphatic alcohols (Scheme 22). *Ortho*-, *meta*-, and *para*- Substitutions in the aryl groups were tolerated and variety of functionalgroups including halides (excluding iodo), nitrile, nitro, trifluoromethyl, trifluoromethoxy, methyl and methoxy were efficient as substituents on the aromatic ring of the electrophile under the optimised reaction condition. They utilised an inexpensive and recoverable auxiliary in this strategy which was sustainable and environmentally attractive.



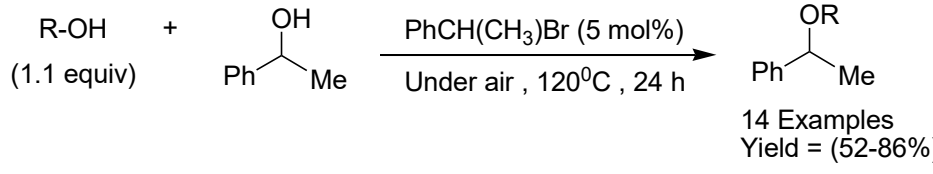
Scheme 22: Synthesis of alkyl-aryl ethers from aliphatic alcohols

Another efficient method provided[15] a green, selective, practical and easily applicable route for preparing useful symmetric and unsymmetric aliphatic ethers from alcohols, generating water as the most innocuous by-product (Schemes 23-26).

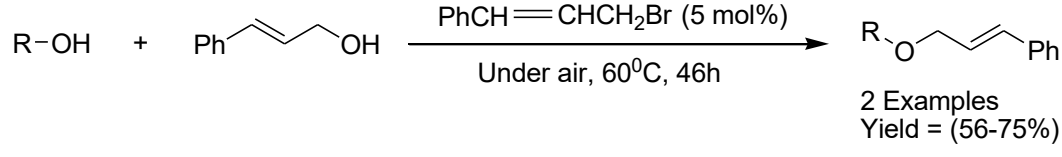


Scheme 23: Ph_2CHBr catalyzed *O*-alkylative cross-etherification (1)

This result showed that addition of organohalides could be an alternative for activating alcohols, which not only led to *O*-selective alkylation but also suggested that alcohols could be activated using halogenation reactions to provide more reactive organo halides and further work as alkylating agents.

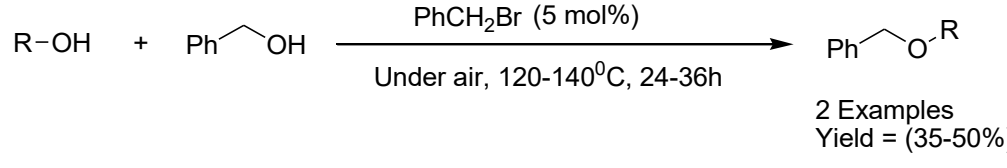


Scheme 24: $PhCH(CH_3)Br$ catalyzed *O*-alkylative cross-etherification



Scheme 25: $PhCH{=}CHCH_2Br$ catalyzed *O*-alkylative cross-etherification

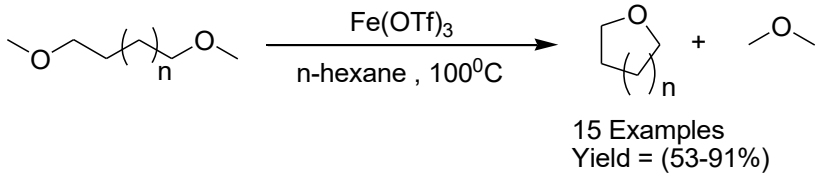
Mechanistic studies suggested that organohalides were reformed as reactive intermediates and reused to further catalyze the reactions.



Scheme 26: Ph_2CHBr catalyzed *O*-alkylative cross-etherification (2)

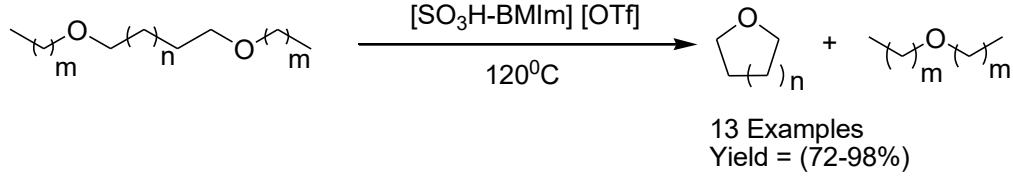
Morandi *et al*. reported[16] an iron-catalyzed C-O bond metathesis reaction for preparing tetrahydrofurans, tetrahydropyrans and morpholines from aliphatic diethers. Five as well as six membered rings could be attained using this reaction by simply varying the chain length

of the aliphatic ethers (Scheme 27). Sterically more challenging substrate with a *gem*-dimethyl group at 3-position was also converted into the corresponding product in good yield. But benzylic and secondary ethers as well as other substrates with amide or alkene groups within them were not transformed in this reaction. Mechanistic studies supported Lewis acid-catalyzed pathway proceeding via a cyclic oxonium intermediate.



Scheme 27: Iron-catalyzed ring-closing metathesis

Liu and his team reported[17] a novel and efficient H-bond catalyzed pathway for synthesizing *O*-heterocycles through ring-closing metathesis of aliphatic ethers using [SO_3H-BMIm][OTf] under metal-free condition (Scheme 28). Mechanistic investigation indicated that both the cation and anion of the ionic liquid could form H-bonds with the substrates catalyzing the reaction to a large extent. Furthermore, the immiscibility of the catalyst and the products made the separation and purification easily attainable. Additionally, kinetic studies demonstrated that the rate of the reaction could be significantly altered by the interface effect.



Scheme 28: IL-catalyzed metathesis of aliphatic ethers to *O*-heterocycles

Thus, an ample record of recent protocols for the formation of C-O bond as well as *O*-heterocycles through ring-closing has been demonstrated with different reagents, catalysts and solvents to validate the consequence, timeliness and essentiality of our investigation described hereafter.

II.3.3. Present investigation:

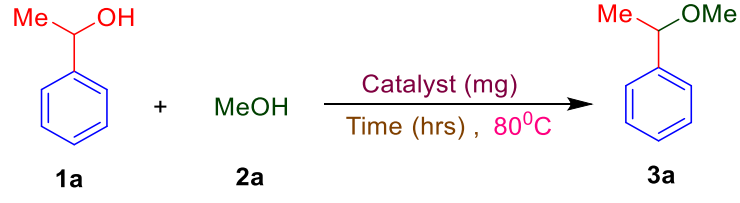
II.3.3.1. Background of the investigation:

Development of an efficient protocol to generate C-O-C bond in aliphatic framework using easily accessible reagents as well as mild and eco-friendly experimental conditions constitutes a demanding challenge towards the synthetic organic chemists. The pioneer reactions in this field often use an organohalide and a deprotonated alcohol (alkoxide) to produce the ether molecule. But most of them are associated with prolonged reaction time,[1, 2, 6, 7, 13, 15] high temperature[1, 6, 13] and different side reactions[4] giving rise to a set of unwanted by-products. Resins bearing acidic sites have the capability to execute subtle catalytic attributes with simple and easy procedure of catalyst separation and recyclability.

We, therefore, demonstrate the catalytic application of Amberlyst®-15(H) in different alcohols used as reaction medium for the formation of C-O-C bond with wide structural variation. With the help of this method both acyclic and cyclic ethers are produced starting from their corresponding secondary alcohols with suitable functional group assistance. This experimental study led to the exploration of a highly utilitarian and eco-compatible method for the synthesis of molecules with important structural motifs.

II.3.3.2. Results and Discussion:

To check the applicability of Amberlyst®-15(H) in this reaction, the reaction was carried out with 1-phenylethanol (**1a**, 1 mmol), MeOH (**2a**, 1 mmol) in presence of various catalysts along with different solvents at 80°C to produce 1-(1-methoxyethyl)benzene (**3a**) (Scheme 29). The results are furnished in Table 1.



Scheme 29: Reaction of 1-phenylethanol (**1a**) using different catalysts and reaction medium

Studying the results as shown in Table 1, we standardized the reaction with 50 mg Amberlyst®-15(H) in methanol solvent at 80°C for 6h affording 86% of the corresponding ether (Entry 8). But the reaction with another well-known resin Dowex-50 gave only 26% of the product in toluene (Entry 1) and no product when DMF was used as solvent (Entry 2).

Table 1: Optimization of the reaction conditions[a] using different catalysts and solvents

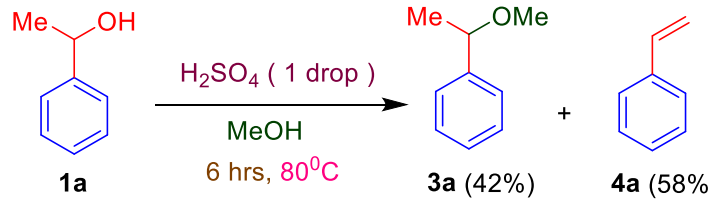
Entry	Catalyst	Amount (mg)	Solvent	Time (h)	Yield of 3a (%)[b]
1	Dowex-50	40	Toluene	6	26
2	Dowex-50	50	DMF	8	- -
3	Amberlite (IR-45)	40	Toluene	6	- -
4	Amberlite (IR-45)	50	DMF	8	- -
5	Amberlyst®-15(H)	50	DMF	8	- -
6	Amberlyst®-15(H)	40	Toluene	6	28
7	Amberlyst®-15(H)	50	Toluene	6	38
8	**Amberlyst®-15(H)**	**50**	**Methanol**	**6**	**86**
9	Urea nitrate	80	Toluene	6	16
10	Urea nitrate	100	Toluene	8	24
11	Alumina (acidic)	70	Methanol	6	--
12	Ni- Alumina	70	Methanol	6	--

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0mmol), catalyst and time (as indicated), solvent (2 ml)

[b]Yield of the isolated product

In the same way Amberlite (IR-45) resin failed to give the product in both of the solvents (Entries 3 and 4). Amberlyst®-15(H) was used in both DMF and toluene, in spite of giving no yield of product in DMF (Entry 5) it gave 28% of the desired product in toluene (Entry 6). The amount of the catalyst was then slightly increased to give the product in better quantity but it only gave 38% of the ether in that case (Entry 7). Then the reaction was done in methanol itself and was found to be quite suitable (Entry 8). Searching for another potential alternative of Amberlyst®-15(H) the reaction was carried out with urea nitrate in a catalytic amount giving the product only in trace amount (Entries 9 and 10).

In this way the essentiality and applicability of the solid acid resin Amberlyst®-15(H) was established for such organic transformation. Even the other acidic supports such as acidic alumina and Ni-alumina also did not respond in this case to provide the desired product (entries 11 and 12). The reaction was then carried out with 1-phenylethanol (**1a**) under optimised reaction condition using 1 drop of conc. H_2SO_4 as the catalyst instead of Amberlyst®-15(H) and a mixture of **3a** and styrene (**4a**) was obtained in 1:1.4 ratio (Scheme 30), but in case of Amberlyst®-15(H) **3a** was obtained exclusively from **1a**.



Scheme 30: Reaction of 1-phenylethanol (**1a**) with 1 drop H_2SO_4 under optimised condition

This reaction bears the merit as an effective method for converting secondary alcohols to their corresponding ethers even at sterically hindered sites with no extra reagent. Amberlyst®-15(H) used in this process was recovered by simple filtration, washed repeatedly with ethyl acetate, dried and further reused successively with marginal loss of its catalytic activity (Figure 1).

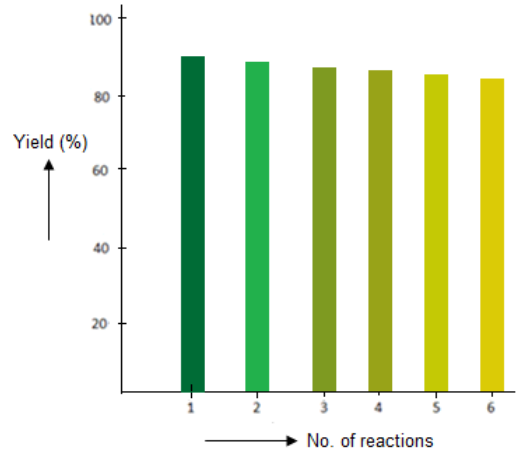
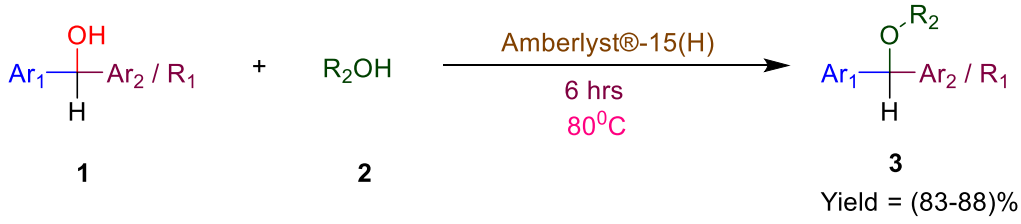


Figure 1: Recycling of Amberlyst®-15(H) using **1a** in methanol at 80°C for 6 hours;

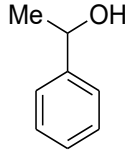
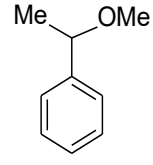
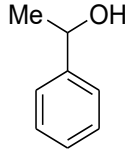
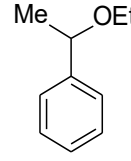
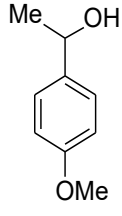
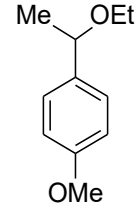
% of yield was the isolated yield of **3a**

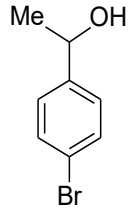
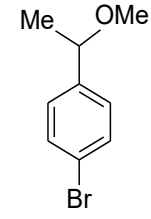
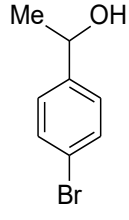
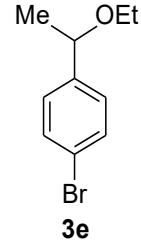
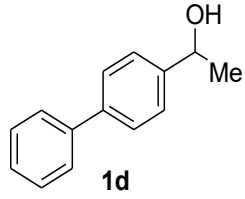
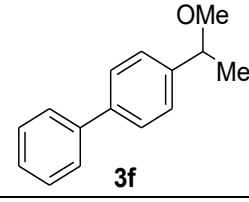
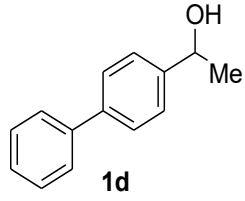
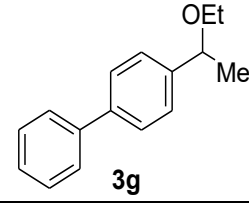
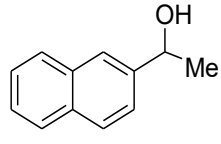
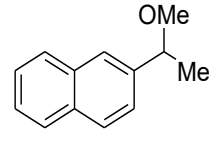
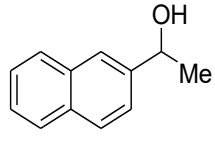
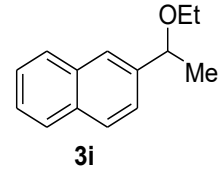
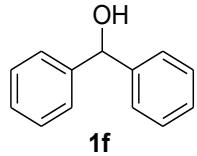
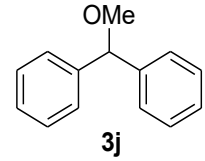
A range of diverse useful aryl-substituted aliphatic ethers were prepared using this method (Scheme 31) where by changing the reacting alcohol, ethers with different alkyl-oxygen units were formed with excellent yield. Results are shown in Table 2.

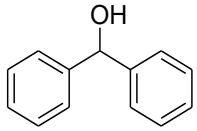
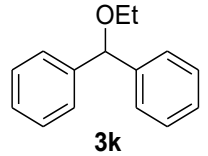
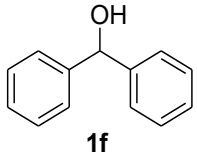
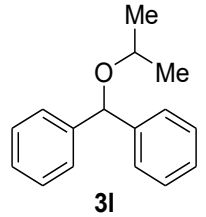
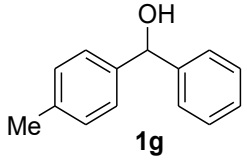
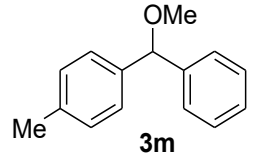
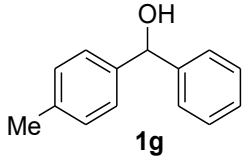
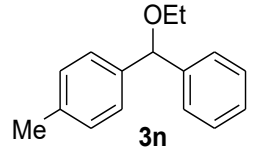
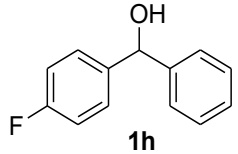
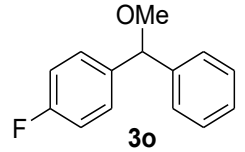
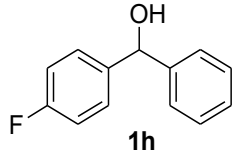
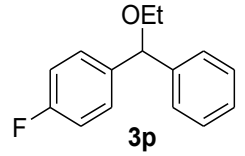
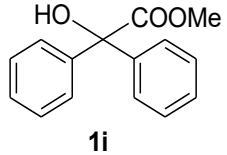
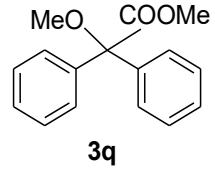
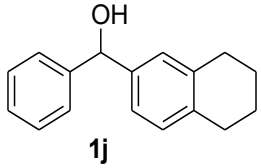
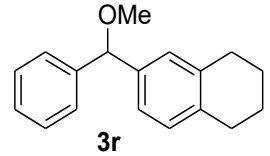


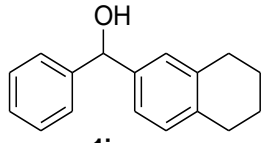
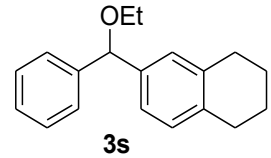
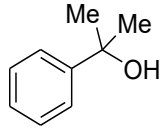
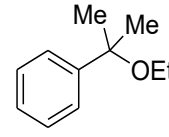
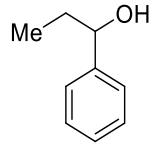
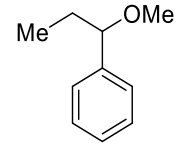
Scheme 31: Synthesis of substituted acyclic ethers (**3**) using Amberlyst®- 15(H) as the catalyst

Table 2: Reaction of different secondary alcohols with different alcohols under optimized reaction conditions using Amberlyst®-15(H) as a catalyst

Entry	Secondary alcohols (1)	Alcohols (2)	Ethers (3)	Time (h)	Yield (%)
1	 **1a**	MeOH **2a**	 **3a**	4.5	86
2	 **1a**	EtOH **2b**	 **3b**	4.5	87
3	 **1b**	EtOH **2b**	 **3c**	4.5	86

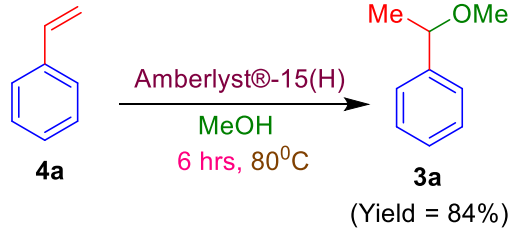
4	 **1c**	MeOH **2a**	 **3d**	5	87
5	 **1c**	EtOH **2b**	 **3e**	5	85
6	 **1d**	MeOH **2a**	 **3f**	5.5	83
7	 **1d**	EtOH **2b**	 **3g**	6	84
8	 **1e**	MeOH **2a**	 **3h**	6	83
9	 **1e**	EtOH **2b**	 **3i**	5	87
10	 **1f**	MeOH **2a**	 **3j**	5	86

11	 **1f**	EtOH **2b**	 **3k**	5	88
12	 **1f**	^{i}PrOH **2c**	 **3l**	5	86
13	 **1g**	MeOH **2a**	 **3m**	4.5	85
14	 **1g**	EtOH **2b**	 **3n**	4.5	86
15	 **1h**	MeOH **2a**	 **3o**	6	83
16	 **1h**	EtOH **2b**	 **3p**	6	83
17	 **1i**	MeOH **2a**	 **3q**	6	84
18	 **1j**	MeOH **2a**	 **3r**	5.5	85

19	 **1j**	EtOH **2b**	 **3s**	5.5	86
20	 **1k**	EtOH **2b**	 **3t**	6	84
21	 **1l**	MeOH **2a**	 **3u**	6	83

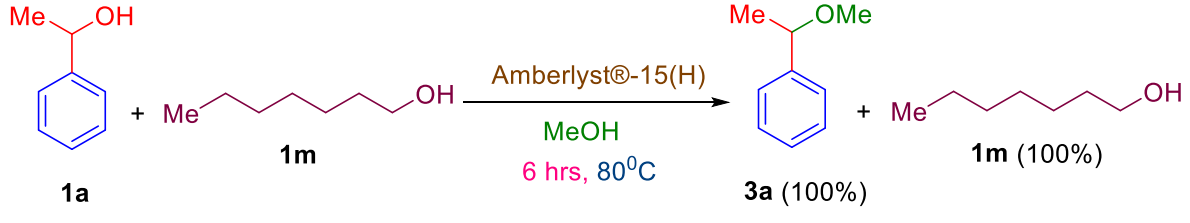
Under the optimised condition unsubstituted 1-phenylethanol (**1a)** gave rise to 1-(1-methoxyethyl)benzene (**3a)** in good yield (Here yield refers to that of the isolated pure product fully characterized spectroscopically). The formation of **3a** was established by appearance of a new singlet peak in ^{1}H NMR at δ 3.24 (at δ 56.4 in ^{13}C NMR) due to the new -OCH_3 group, which was not present in **1a**. When an equimolecular mixture of **1a** and **1f** was reacted under the current protocol both of the products **3a** and **3j** were obtained in 1:1 ratio. This reaction efficiently took place with both ring-unsubstituted and alkyl/aryl-substituted secondary benzylic alcohols to provide **3b**, **3c**, **3f** and **3g** with satisfactory yield. Even the unsubstituted and alkyl-substituted benzhydrols reacted smoothly under this present protocol giving **3j**, **3k, 3l, 3m** and **3n** with high yield. The reaction was successful for halogen substituted (-bromo and -fluoro) benzhydrols to provide **3d**, **3e**, **3o** and **3p** respectively. Especially in **1i**, where the reacting alcohol was sterically congested; it was expected that the reaction might not occur. But here also the reaction went on very effectively giving the product **3q** with 84% yield. Next 1-(naphthalen-2-yl)ethanol (**1e**) was subjected to react with methanol and ethanol in the optimised reaction condition which furnished **3h** and **3i** respectively with 83% and 87% yield. The formation of **3h** was established by two consecutive signals for the methyl groups where one doublet came at δ 1.57 (for –CH***CH$_3$***) and one singlet came at δ 3.31(for –O***CH$_3$***), same conclusion was drawn also from the ^{13}C NMR spectra where the peaks of the methyl groups appeared at δ 23.9 (for –CH***C*H$_3$**) and δ

56.5(for –O**C**$\mathbf{H_3}$) respectively. Even tetrahydro-naphthalene system also responded very well in the present protocol to provide **3r** and **3s** with 85% and 86% yield. To our great surprise 2-phenylpropan-2-ol (**1k**) responded in the reaction scheme without any breakage of the C-C bond to give the product **3t** exclusively with no extra side product coming from very common elimination reaction. The formation of **3t** was clearly noticeable by one triplet at δ 1.24 and one quartet around δ 3.30 in the ^{1}H NMR due to ethyl chain added to the oxygen atom. The substrate **1l** smoothly underwent substitution to give the product **3u** without any elimination. However no such reaction took place with aromatic or aliphatic primary alcohols where the substrates were recovered unaffected. Even with dialkyl secondary alcohol the reaction was unproductive under this protocol. Therefore this protocol is very much selective for only secondary alcohols and only few tertiary alcohols where one aromatic ring must be connected with the carbinol carbon. The theme of the reaction was further extended when styrene (**4a**) was reacted with methanol under the optimized condition and produced 1-(1-methoxyethyl)benzene(**3a**) as the only product (Scheme 32). This crucial observation recommended that this reaction might proceed by forming a carbocationic intermediate.



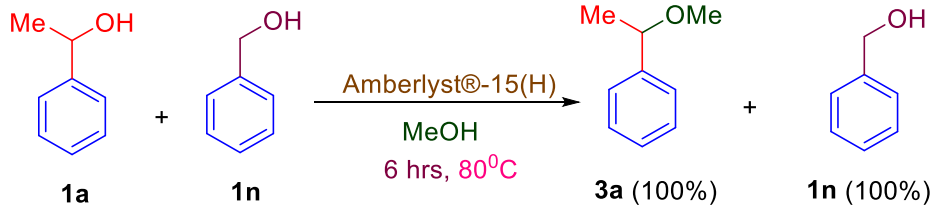
Scheme 32: Reaction of styrene with methanol under optimised condition

The selectivity between aromatic alcohol and aliphatic alcohol was confirmed by the intermolecular competition experiment which was carried out under optimized reaction condition taking equimolar proportions of 1-phenylethanol (**1a**) and heptanol (**1m**) where the product **3a** was obtained successfully by converting **1a**; leaving **1m** unaltered (Scheme 33).



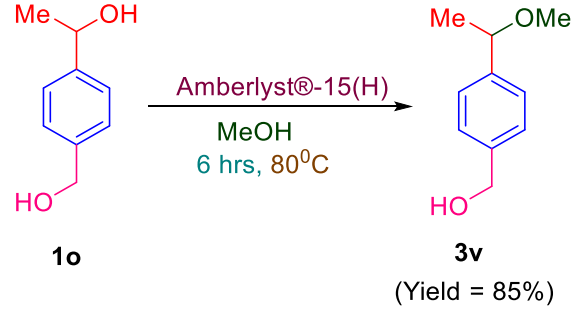
Scheme 33: Intermolecular competition experiment (1)

Similarly, another type of intermolecular selectivity study was performed to further substantiate the efficacy of the current protocol. When 1-phenylethanol (**1a**) was subjected to the optimized reaction condition along with equimolecular quantity of benzyl alcohol (**1n**), the product1-(1-methoxyethyl)benzene (**3a**) was obtained completely starting from 1-phenylethanol (**1a**) and left behind benzyl alcohol (**1n**) as it is (Scheme 34). These studies established that the protocol is inefficient for both aliphatic and aromatic primary alcohols and highly selective for secondary aromatic alcohols only.



Scheme 34: Intermolecular competition experiment (2)

When the substrate **1o** comprising of both aromatic primary and secondary alcohol moieties in a single molecule was treated in the present protocol, the product **3v** was formed exclusively (Scheme 35) with 85% yield, where only the aromatic secondary carbinol moiety was chemoselectively transformed to the corresponding ether functionality and the aromatic primary carbinol moiety was not affected. This study convincingly proved excellent chemoselectivity of the aforesaid protocol as its most significant feature.

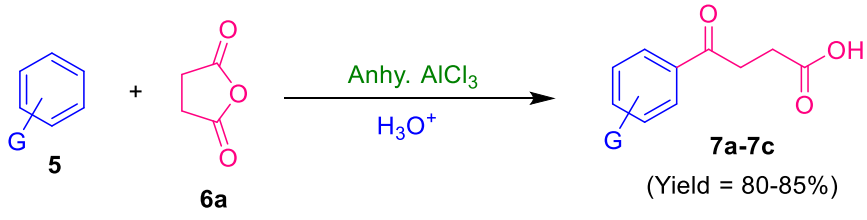


Scheme 35: Intramolecular competition experiment

The formation of **3v** as the sole product was established by both ^{1}H and ^{13}C NMR spectroscopic studies. A doublet at δ 1.41 in ^{1}H NMR (δ 23.8 in ^{13}C NMR) and a singlet at δ 3.20 in ^{1}H NMR (δ 56.4 in ^{13}C NMR) substantiated the presence of one alkyl methyl and one methoxy moieties in the structure. A singlet at δ 4.66 in ^{1}H NMR (δ 64.9 in ^{13}C NMR) further elaborated the presence of the benzylic hydrogens due to undisturbed benzylic primary

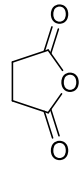
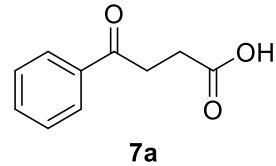
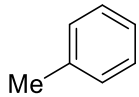
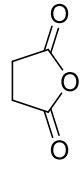
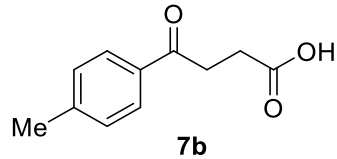
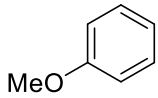
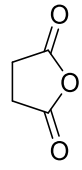
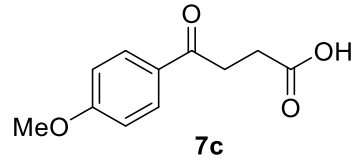
carbinol functionality. This study firmly established the merit of this protocol for chemoselective transformation of the aromatic secondary alcohol group to the corresponding ether keeping the aromatic primary alcohol group intact.

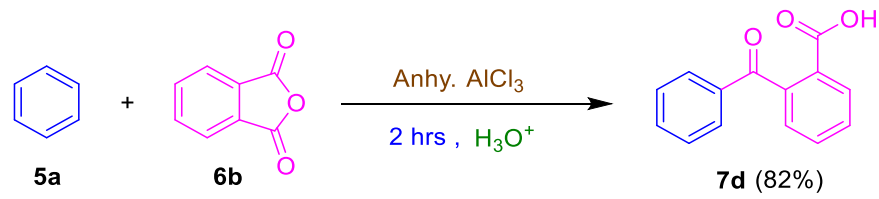
At this point, the observations triggered the preparation of a new set of starting materials which led to some extremely beneficial utilization of the protocol. In this connection, differently substituted benzenes (**5**) were reacted (Schemes 36-38) with various anhydrides (**6**) via Friedel-Craft acylation to provide the corresponding γ-keto acids (**7**).



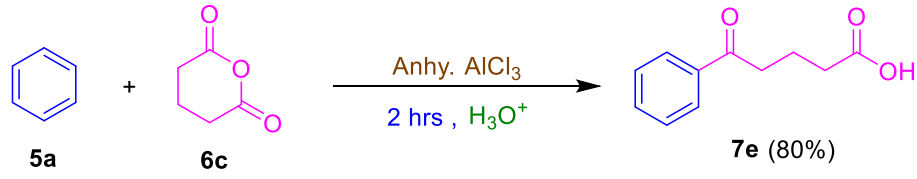
Scheme 36: Friedel craft acylation using succinic anhydride

Table 3: Reaction of different substrates (**5**) with succinic anhydride (**6a**) to give the products (**7**) (as Scheme 36)

Entry	Substrates (5)	Reagent (6a)	Products (7)	Time (h)	Yield (%)
1	 5a	 6a	 7a	1.5	80
2	 5b	 6a	 7b	1	85
3	 5c	 6a	 7c	1	83

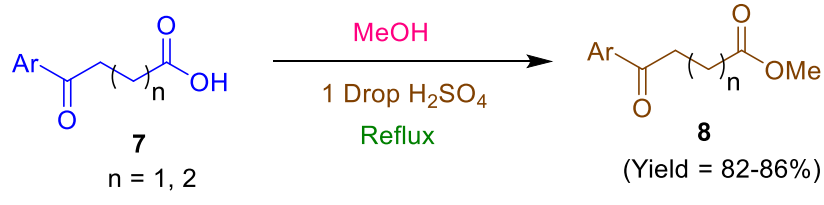


Scheme 37: Friedel craft acylation using phthalic anhydride (**6b**)



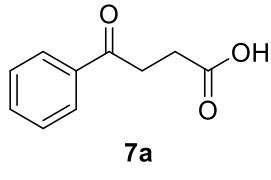
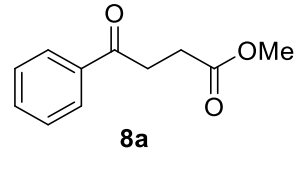
Scheme 38: Friedel craft acylation using glutaric anhydride (**6c**)

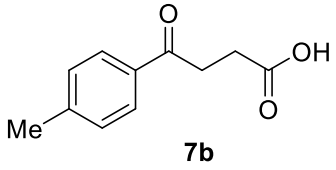
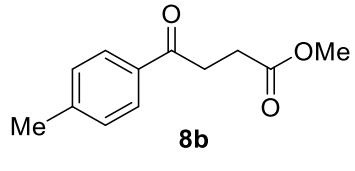
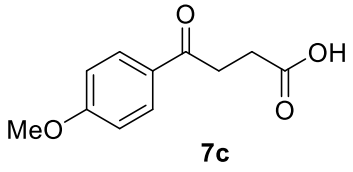
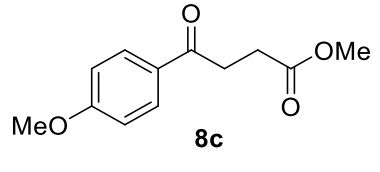
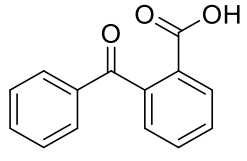
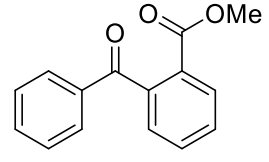
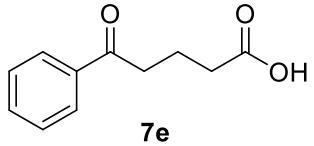
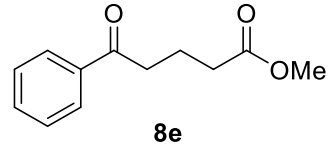
The Friedel-Craft acylation was conducted by reacting benzene (**5a**) with succinic (**6a**), phthalic (**6b**) and glutaric (**6c**) anhydrides giving rise to the corresponding γ-keto acids **7a** and **7d** along with δ-keto acid **7e** respectively. Similarly, when toluene (**5b**) and anisole (**5c**) reacted with succinic anhydride (**6a**), γ-keto acids **7b** and **7c** were obtained as the products as shown in Table 3. These γ-keto acids (**7**) were then esterified with methanol to obtain the corresponding methyl esters (**8a-8e**), as shown in Table 4.



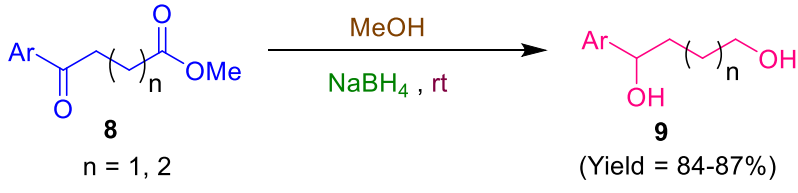
Scheme 39: Preparation of methyl esters from carboxylic acids

Table 4: Reaction of carboxylic acids (**7**) with methanol to give corresponding methyl esters (**8**) (as Scheme 39)

Entry	Carboxylic acids (7)	Products (8)	Time (h)	Yield (%)
1	 7a	 8a	5.5	85

2	 **7b**	 **8b**	5	83
3	 **7c**	 **8c**	5	84
4	 **7d**	 **8d**	6	82
5	 **7e**	 **8e**	5.5	84

The prepared 4-aryl-4-oxoesters (**8a**-**8e**) were then reduced[18] with methanolic sodium borohydride to the diols (**9a**-**9e**), where both of the carbonyl and the ester carbonyl groups were reduced to the secondary and primary alcohol moieties respectively in the same backbone (Scheme 40). The products are listed in Table 5.

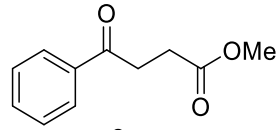
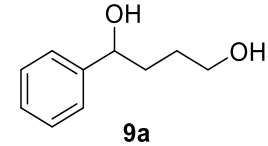
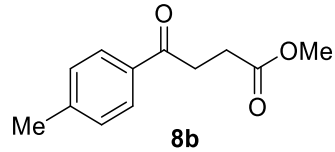
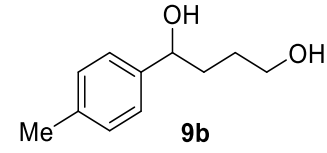
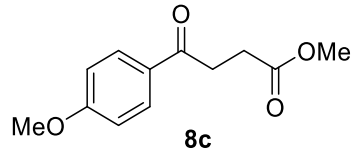
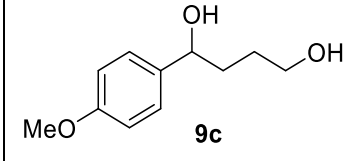
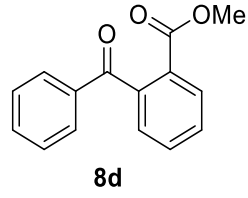
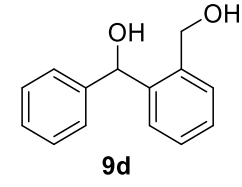
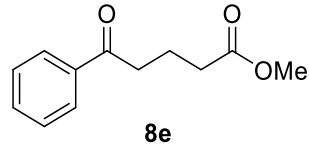
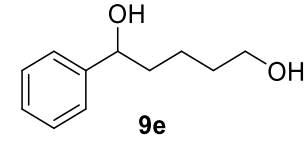


8
n = 1, 2

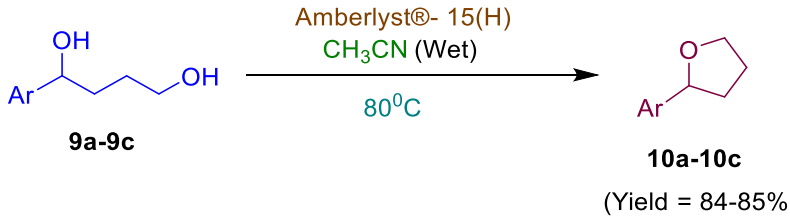
9
(Yield = 84-87%)

Scheme 40: Preparation of alcohols from methyl esters

Table 5: Reduction of methyl esters (**8**) to give corresponding alcohols (**9**) (as Scheme 40)

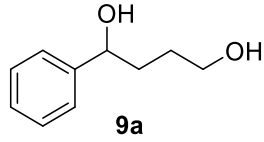
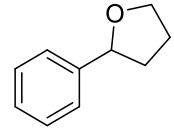
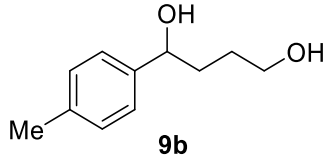
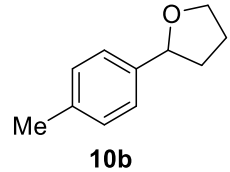
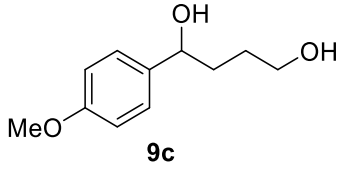
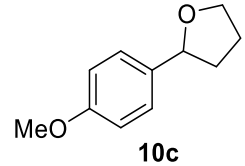
Entry	Methyl esters (8)	Alcohols (9)	Time (h)	Yield (%)
1	 **8a**	 **9a**	5	84
2	 **8b**	 **9b**	4.5	85
3	 **8c**	 **9c**	5	87
4	 **8d**	 **9d**	5.5	84
5	 **8e**	 **9e**	5	86

The primacy of this reaction was recognized by taking the 1-aryl-1, 4-butanediols (**9a-9c**) as the starting material. It was found that when a secondary alcohol was in a suitable position to be assisted by a distant primary alcohol group, an intramoleculer cyclisation reaction took place and we got the corresponding cyclic ethers (**10a-10c**) as the exclusive product (Scheme 41). The products are listed in Table 6.



Scheme 41: Synthesis of substituted cyclic ethers (**10**) using Amberlyst®- 15(H) as the catalyst

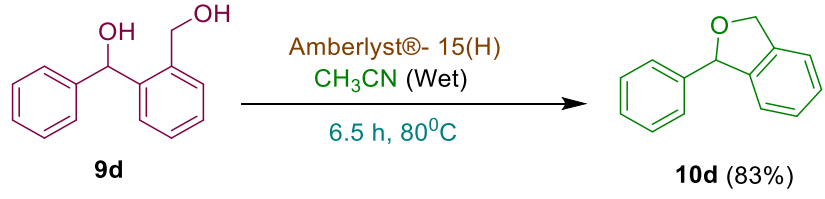
Table 6: Reaction of different secondary alcohols (**9**) under optimized reaction conditions using Amberlyst®-15(H) as a catalyst (as scheme 41)

Entry	Alcohols (9)	Cyclic ethers (10)	Time (h)	Yield (%)
1	 **9a**	 **10a**	6	85
2	 **9b**	 **10b**	6	85
3	 **9c**	 **10c**	6.5	84

The reaction was first tried under methanol solvent system, but we found a mixture of inseparable products which contained some of the eliminated alkene with the desired ether molecule. Then the solvent was switched to acetonitrile and in this case, the cyclised products (**10**) were obtained exclusively. Using the optimized reaction condition **9a, 9b** and **9c** were successfully converted to their corresponding cyclic product **10a, 10b** and **10c** with around 85% yield. Widely used industrial process to form tetrahydrofuran (THF) skeleton generally involves the acid-catalyzed dehydration of 1, 4-butanediol, which is derived by the condensation of acetylene with formaldehyde followed by hydrogenation. But here the

substituted THF skeleton was prepared by taking properly oriented aromatic secondary alcohols where entropically favoured cyclization is promoted with a distant aliphatic primary alcohol unit. Formation of 2-aryltetrahydrofuran was established by spectroscopic analysis. As a representative example, for **10b**, a triplet at δ 4.85 with J = 6.8 Hz in ^{1}H NMR (at δ 80.6 in ^{13}C NMR) corresponded to the aryl-bearing carbon α to oxygen of the tetrahydrofuran ring along with a multiplet at δ 3.91-4.09 in ^{1}H NMR (at δ 68.6 in ^{13}C NMR) corroborated with the –OCH_2– of the tetrahydrofuran ring.

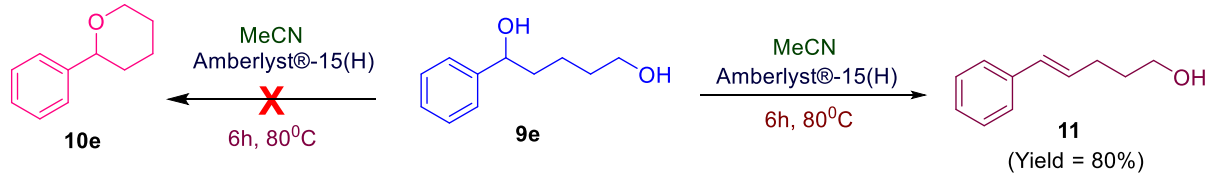
Extending the scope of the reaction, previously prepared **9d** was employed in the reaction condition, and as expected we found the highly beneficial substituted coumaran naming 2, 3-dihydro-2-phenylbenzofuran **(10d)** as the product with 83% yield (Scheme 42).



Scheme 42: Synthesis of cyclic ether (**10d**) using Amberlyst®- 15(H) as the catalyst

The formation of **10d** was confirmed by both ^{1}H and ^{13}C NMR spectroscopic studies. A multiplet at δ 5.24-5.42 in ^{1}H NMR (δ 73.3 in ^{13}C NMR) and a singlet at δ 6.22 in ^{1}H NMR (δ 86.3 in ^{13}C NMR) substantiated the presence of –CH_2- and –CH units respectively.

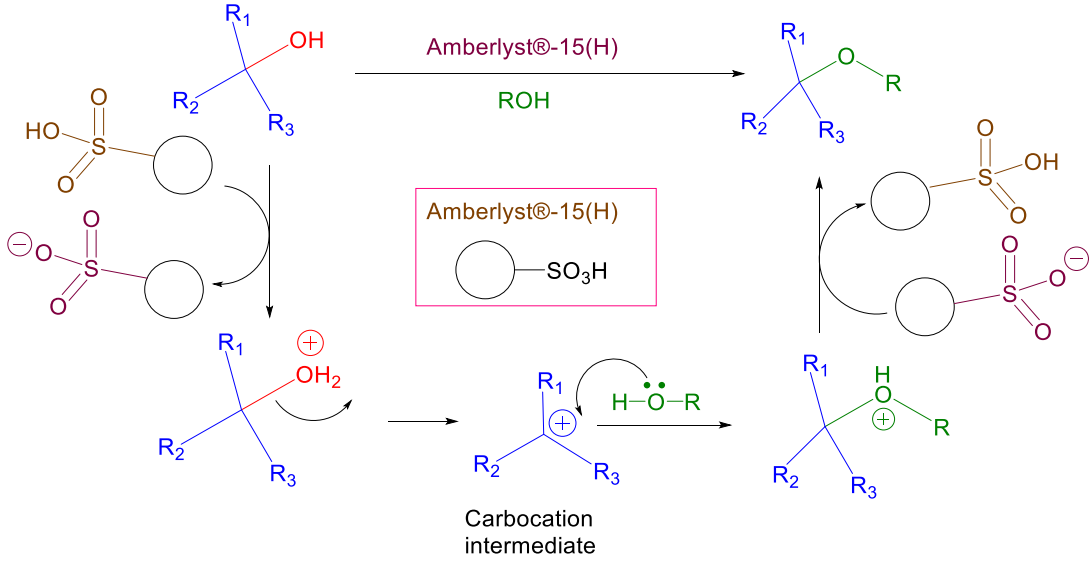
Surprisingly, when **9e** was reacted with MeCN under the optimized condition, 2-phenyltetrahydro-2H-pyran (**10e**) was expected as the final product, but it was not obtained. Rather, 5-phenylpent-4-en-1-ol (**11**) was obtained as the product with 80% yield (Scheme 43). An elimination reaction seemed to be dominated over the cyclization reaction supposed to be less preferred entropically (6-membered *versus* 5-membered ring formation).



Scheme 43: Unexpected result with **9e** using Amberlyst®- 15(H) as the catalyst

These observations along with the chemoselectivity associated with these reactions recommended that the effects might be initiated due to privileged formation of the comparatively more stable carbocationic intermediate. The results obtained in the studies described in Schemes 32-35 also indicated the contribution of carbocationic intermediates. Moreover, when the reaction was carried out with enantiopure *R*-1 phenylethanol under the optimized condition, the product **3a** was formed as a racemic mixture. This particular observation also supported the development of planar carbocation during the reaction which was further racemized to finally give the optically inactive product **3a** starting from an optically pure substrate.

On the basis of these outcomes, a probable mechanistic scheme is put forward (Scheme 43) involving the formation of carbocation by solid acid-catalyzed dehydration of alcohol followed by nucleophilic attack by alcohol and subsequent deprotonation with the conjugate base of the solid acid to afford the product ether. This mechanism also supported the catalytic role of Amberlyst®-15(H) to account for its Bronsted acidity and recyclability.



Scheme 43: Proposed mechanism for the reaction

II.3.3.3. Conclusion:

In this report, readily available, inexpensive and air stable Amberlyst®-15(H) was successfully utilized as a reusable and recyclable heterogeneous solid acid catalyst for the formation of C-O bond through the formation of widely O-substituted ethers through a chemoselective pathway. The aforesaid method utilized both substituted and unsubstituted benzylic secondary alcohols as well as benzylic tertiary alcohols under environmentally favourable conditions without any necessity of inert and anhydrous condition. Use of mild reagents, easily available solvents, catalyst of minimum toxicity, straightforward reaction conditions, procedural simplicity, exceptional chemoselectivity, large substrate scope, enriched atom economy, generation of the most harmless by-product (water), high yields, reusability and recyclability of the catalyst are the salient features of this protocol with wider applicability compared to other existing methods.

II.3.3.4. Experimental

General:

All organic solvents used for the reaction were purchased from Merck and SRL, and were distilled before use. Melting points were recorded in open capillary on electrical bath which are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker–300 (300 MHz) and Bruker–400 (400 MHz) spectrometer in $CDCl_3$ solvent with TMS as internal reference. Mass spectrums were measured on HRMS (Qtof micro YA263). Column chromatography were performed on silica gel (60–120 mesh) supplied by SRL, India. Thin layer chromatographic separations were performed on pre-coated glass plates using silica gel G for TLC (E. Merck).

(i) <u>Representative procedure for the reaction</u>:

A. To a mixture of 1-phenylethanol (**1a**, 122 mg, 1.0 mmol) and MeOH (**2a**, 2 ml) the catalyst Amberlyst®-15(H) (50 mg) was added. The reaction mixture was stirred for the required period of time at 80°C till the reaction was completed (monitored with TLC). Then the reaction mixture was cooled to room temperature, excess MeOH was removed under reduced pressure, keeping a cotton plug on a funnel the catalyst were filtered out and washed repeatedly by ethyl acetate (4×5 ml) to dissolve and collect the product in the mother liquor. The organic extract was thoroughly washed with water (3×10 ml) to remove remaining MeOH and dried over anhydrous Na_2SO_4. The crude product was obtained by removal of the solvent under reduced pressure and purified by column chromatography on a short column of silica gel using 1-4% ethyl acetate-hexane as eluent to afford **3a** (117 mg, Yield 86%).

B. To a mixture of 1-phenylbutane-1, 4-diol (**9a**, 166 mg, 1.0 mmol), and MeCN (2ml), the catalyst Amberlyst®-15(H) (50 mg) was added. The reaction mixture was stirred for the required period of time at 80°C till the reaction was complete (monitored with TLC). Then the reaction mixture was cooled to room temperature, excess MeCN was removed under reduced pressure, keeping a cotton plug on a funnel the catalyst were filtered out and washed repeatedly by ethyl acetate (4×5 ml) to dissolve and collect the product in the mother liquor.

The organic extract was thoroughly washed with water (3×10 ml) to remove remaining MeCN and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure furnished the product **10a** (126 mg, Yield 85%) without any further purification.

(ii) <u>Spectral and analytical data of the compounds</u>:

1. **1-(1-methoxyethyl)benzene (3a)**[19] Colourless liquid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.45 (3H, d, *J* = 6.4 Hz), 3.24 (3H, s), 4.28-4.34 (1H, m), 7.26-7.36 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.9, 56.4, 79.7, 126.2, 127.5, 128.4, 143.5

2. **1-(1-ethoxyethyl)benzene (3b)**[20] Colourless liquid (Yield 87%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.20 (3H, t, *J* = 6.9 Hz), 1.46 (3H, d, *J* = 6.5 Hz), 3.34-3.41 (2H, q), 4.39-4.51 (1H, q), 7.28-7.35 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.4, 24.3, 63.9, 77.8, 126.1, 127.4, 128.4, 144.3

3. **1-(1-ethoxyethyl)-4-methoxybenzene (3c)**[21] Yellowish liquid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.19 (3H, t, *J* = 6.9 Hz), 1.45 (3H, d, *J* = 6.4 Hz), 3.31-3.39 (2H, q), 3.81 (3H, s), 4.37-4.41 (1H, q), 6.88-6.91 (2H, m), 7.13-7.32 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.7, 21.1, 56.2, 64.9, 79.3, 115.2, 128.6, 129.2, 160.1

4. **1-bromo-4-(1-methoxyethyl)benzene (3d)**[20] Yellow liquid (Yield 87%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.39 (3H, d, *J* = 6.4 Hz), 3.21 (3H, s), 4.23-4.28 (1H, q), 7.25 (2H, d, *J* = 7.9 Hz), 7.46 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.8, 56.5, 79.0, 121.2, 128.0, 131.4, 142.6

5. **1-bromo-4-(1-ethoxyethyl)benzene (3e)**[22] Yellow liquid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.18 (3H, t, *J* = 7.2 Hz), 1.40 (3H, d, *J* = 6.4 Hz), 3.32-3.34 (2H, q), 4.32-4.39 (1H, q), 7.19 (2H, d, *J* = 8 Hz), 7.45 (2H, d, *J* = 8 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.4, 24.1, 64.0, 76.6, 121.0, 127.8, 131.5, 143.3

6. **4-(1-methoxy-ethyl)-biphenyl (3f)**[20] Yellow liquid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.48 (3H, d, *J* = 6.4 Hz), 3.27 (3H, s), 4.34-4.36 (1H, q), 7.34-7.59 (9H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.8, 56.5, 79.4, 126.6, 127.0, 127.1, 127.3, 128.8, 140.1, 140.4, 140.9, 142.6

7. **4-(1-ethoxy-ethyl)-biphenyl (3g)**[23] Colorless liquid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.23 (3H, t, *J* = 6.6 Hz), 1.48 (3H, s), 3.37-3.43 (2H, q), 4.45-4.47 (1H, q), 7.34-7.61 (9H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 16.1, 21.3, 64.8, 79.2, 127.8, 128.2, 135.2, 136.6

8. **2-(1-methoxyethyl)naphthalene (3h)**[19] Colorless liquid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.57 (3H, d, *J* = 6.4 Hz), 3.31 (3H, s), 4.49-4.51 (1H, q), 7.51-7.53 (3H, m), 7.78 (1H, s), 7.87-7.90 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.9, 56.5, 79.8, 124.1, 125.2, 125.8, 126.1, 127.7, 127.8, 128.4, 133.1, 133.3, 140.9

9. **2-(1-ethoxyethyl)naphthalene (3i)**[24] Yellowish liquid (Yield 87%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.26 (3H, t, *J* = 6.9 Hz), 1.57 (3H, d, *J* = 6.4 Hz), 3.40-3.47 (2H, q), 4.57-4.64 (1H, q), 7.49-7.54 (3H, m), 7.78 (1H, s), 7.86-7.88 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.5, 24.3, 64.0, 77.9, 124.2, 125.7, 126.1, 126.3, 127.8, 128.2, 133.0, 133.4, 137.0, 141.7

10. **methoxydiphenylmethane (3j)**[25] Colourless liquid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.45 (3H, s), 5.31 (1H, s), 7.30-7.41 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 57.0, 85.5, 127.0, 127.6, 128.5, 142.2

11. **ethoxydiphenylmethane (3k)**[26] Colourless liquid (Yield 88%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.36 (3H, t, *J* = 6.9 Hz), 3.58-3.65 (2H, q), 5.45 (1H, s), 7.31-7.44 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.5, 64.6, 83.6, 127.1, 127.5, 128.2, 128.5, 142.8

12. **isopropoxydiphenylmethane (3l)**[26] Colourless liquid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.21 (6H, d, *J* = 6.9 Hz), 3.61-3.69 (1H, m), 5.48 (1H, s), 7.26-7.36 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.4, 71.6, 81.4, 126.4, 128.4, 129.5, 140.5

13. **1-(methoxy(p-tolyl)methyl)benzene (3m)**[27] Yellowish liquid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.39 (3H, s), 3.45 (3H, s), 5.30 (1H, s), 7.20-7.58 (9H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.1, 56.9, 85.3, 126.4, 126.8, 127.4, 128.4, 129.1, 130.0, 130.3, 132.2, 137.1, 137.9, 139.2, 142.4

14. **1-(ethoxy(p-tolyl)methyl)benzene (3n)**[25] Yellowish liquid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.37 (3H, t, *J* = 6.9 Hz), 2.41 (3H, s), 3.58-3.65 (2H, q), 5.43 (1H, s), 7.22-7.48 (9H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.4, 21.2, 64.5, 83.4, 126.9, 127.0, 127.3, 128.4, 129.1, 137.0, 139.6, 142.9

15. **1-((4-fluorophenyl)(methoxy)methyl)benzene (3o)**[28] Yellow liquid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.41 (3H, s), 5.26 (1H, s), 7.04 (2H, t, *J* = 8.6 Hz), 7.29-7.53 (7H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 56.7, 86.3, 116.6, 126.2, 128.4, 129.5, 129.9, 136.1, 140.5, 160.6

16. **1-(ethoxy(4-fluorophenyl)methyl)benzene (3p)** Yellow liquid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.29 (3H, t, *J* = 6.9 Hz), 3.51-3.57 (2H, q), 5.37 (1H, s), 6.96-7.05 (2H, t, *J* = 8.6 Hz), 7.29-7.37 (7H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.5, 64.4, 82.7, 116.2, 126.4, 128.4, 129.6, 129.9, 135.7, 141.2, 160.5

17. **methoxydiphenylmethyl acetate (3q)**[29] Colourless semisolid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.18 (3H, s), 3.77 (3H, s), 7.25-7.45 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 52.8, 53.4, 96.2, 126.4, 128.4, 129.4, 144.8, 174.2

18. **1, 2, 3, 4-tetrahydro-6-(methoxy(phenyl)methyl)naphthalene (3r)** Yellowish semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.78 (4H, s), 2.74 (4H, s), 3.38 (3H, s), 5.18 (1H, s), 7.03-7.06 (2H, m), 7.24-7.36 (6H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 22.8, 31.6, 56.4, 86.4, 125.4, 126.4, 128.3, 129.3, 133.1, 136.1, 137.4, 140.2

19. **6-(ethoxy(phenyl)methyl)-1, 2, 3, 4-tetrahydronaphthalene (3s)** Yellow semisolid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.26 (3H, t, J = 6.9 Hz), 1.77 (4H, s), 2.73 (4H, s), 3.48-3.56 (2H, q), 5.29 (1H, s), 6.98-7.05 (2H, m), 7.23-7.38 (6H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.4, 22.9, 31.6, 64.5, 83.5, 125.4, 126.4, 128.4, 129.8, 133.2, 136.1, 137.4, 140.3

20. **1-(2-ethoxypropan-2-yl)benzene (3t)**[30] Colourless semisolid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.24 (3H, t, J = 6.9 Hz), 1.62 (6H, s), 3.26-3.33 (2H, q), 7.31-7.56 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 16.2, 30.2, 62.4, 80.2, 126.2, 128.5, 150.2

21. **(1-methoxypropyl)benzene (3u)**[19] Yellowish semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.84-0.93 (3H, m), 1.62-1.82 (2H, m), 3.20 (3H, s), 4.57-4.60 (1H, m), 7.24-7.36 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.2, 31.9, 56.6, 85.6, 125.8, 126.8, 128.5, 129.3, 144.7

22. **(4-(1-methoxyethyl)phenyl)methanol (3v)** Yellowish semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.41 (3H, d, J = 6.6 Hz), 2.1 (1H, bs), 3.2 (3H, s), 4.26-4.32 (1H, q), 4.66 (2H, s), 7.26-7.35 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.7, 56.3, 64.7, 79.5, 126.3, 127.2, 140.4, 142.6. HRMS (ESI-TOF): m/z calculated for $C_{10}H_{14}O_2$ [M]: 166.22146; found: 166.0966.

23. **tetrahydro-2-phenylfuran (10a)**[26] Yellow semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.78-2.36 (4H, m), 3.93-4.12 (2H, m), 4.89 (1H, t, J = 9 Hz), 7.27-7.35 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.5, 35.5, 70.8, 90.6, 126.5, 128.6, 129.6, 140.2

24. **tetrahydro-2-p-tolylfuran (10b)**[26] Yellow semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.78-1.82 (2H, m), 1.95-2.02 (2H, m), 2.34 (3H, s), 3.91-4.09 (2H, m), 4.85 (1H, t, J = 6.8 Hz), 7.13-7.24 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.1, 26.1, 34.6, 68.6, 80.6, 125.4, 128.2, 136.7, 140.4

25. **tetrahydro-2-(4-methoxyphenyl)furan (10c)**[26] Yellowish semisolid (Yield 84%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.75-2.30 (4H, m), 3.79 (3H, s), 3.86-4.11(2H, m), 4.82

(1H, t, *J* = 6.9 Hz), 6.87 (2H, d, *J* = 7.8 Hz), 7.26 (2H, d, *J* = 7.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.5, 35.5, 56.1, 70.8, 90.7, 114.2, 129.3, 131.6, 158.2

26. **2, 3-dihydro-2-phenylbenzofuran (10d)**[31] Yellowish semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.24-5.42 (2H, m), 6.22 (1H, s), 7.07-7.70 (9H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 73.3, 86.3, 120.9, 122.4, 127.0, 127.6, 127.7, 128.1, 128.6, 139.2, 142.1, 142.3

27. **5-phenylpent-4-en-1-ol (11)**[32] Colourless semisolid (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.50-1.90 (2H, m), 2.01-2.21 (2H, m), 3.58-3.69 (2H, m), 6.20-6.26 (1H, m), 6.39-6.43 (1H, m), 7.17-7.36 (5H, m)

^{1}H, ^{13}C, DEPT and HRMS spectra of some representative compounds:

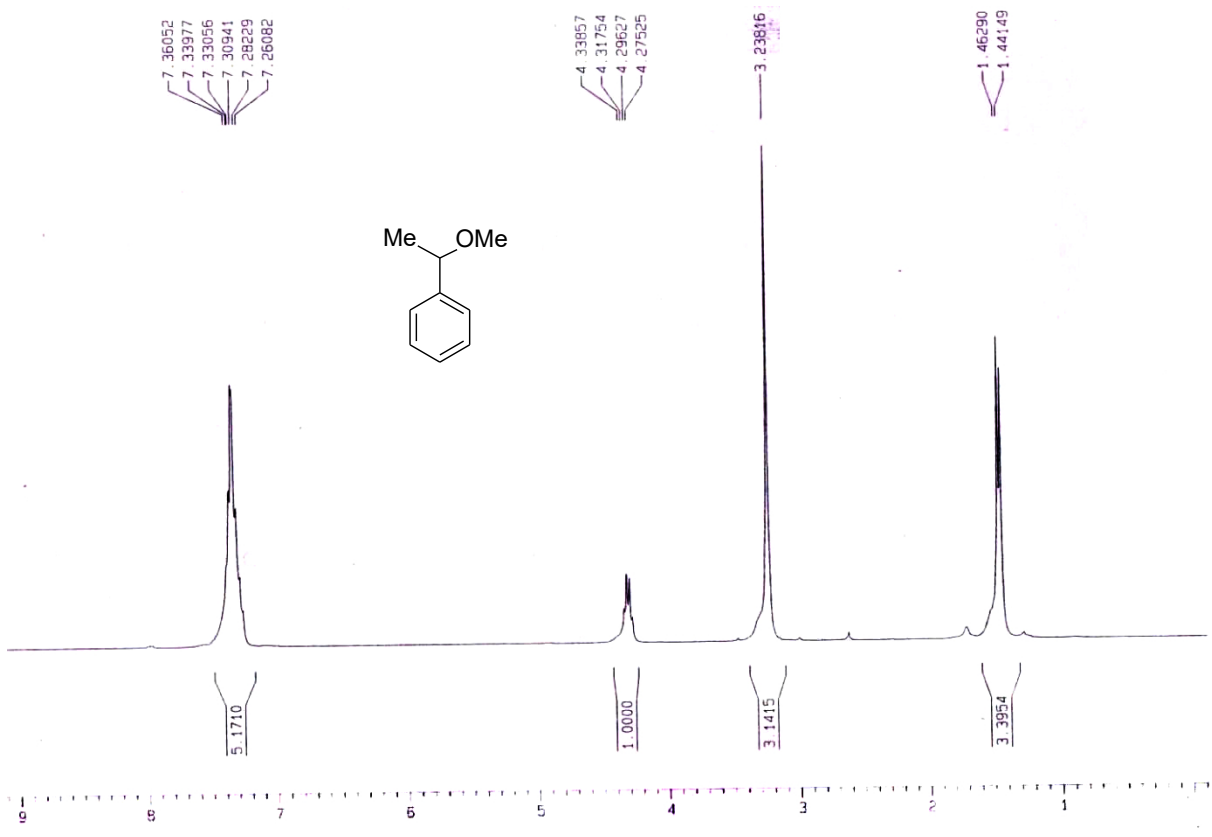


Figure 1: ^{1}H NMR of 1-(1-methoxyethyl)benzene (**3a**)

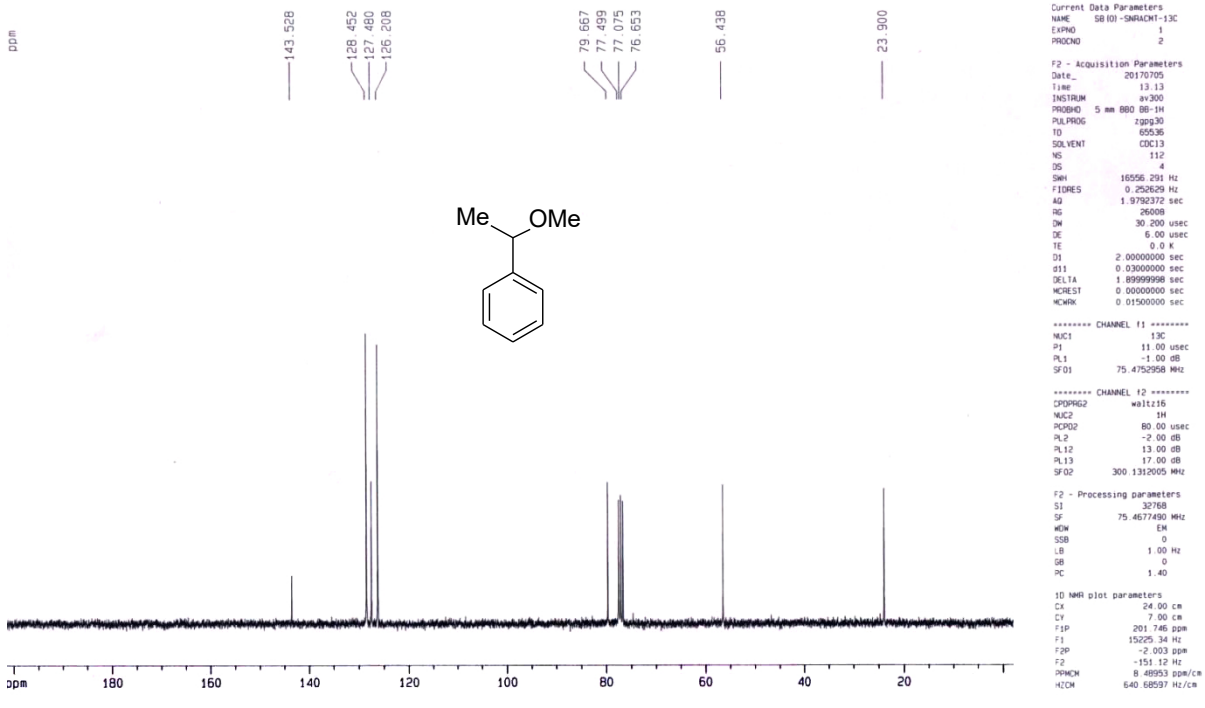


Figure 2: ^{13}C NMR of 1-(1-methoxyethyl)benzene (**3a**)

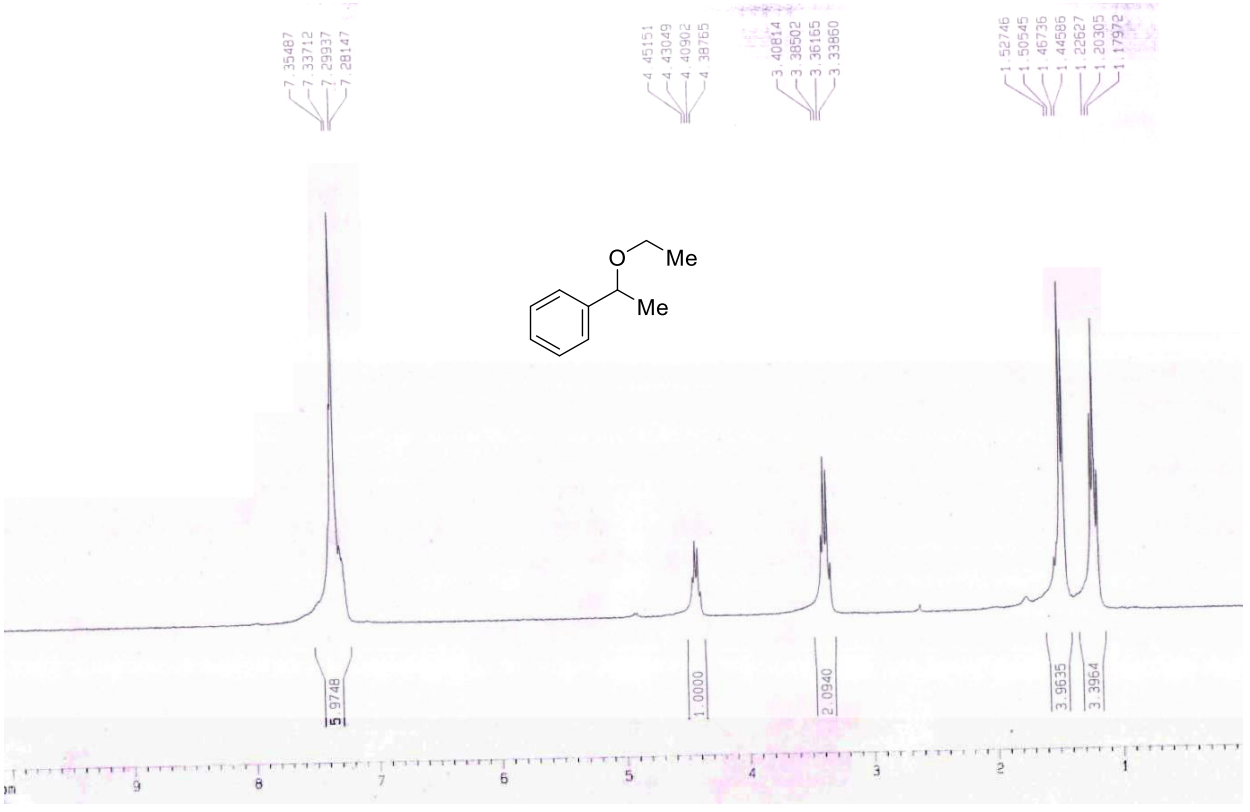


Figure 3: ^{1}H NMR of 1-(1-ethoxyethyl)benzene (**3b**)

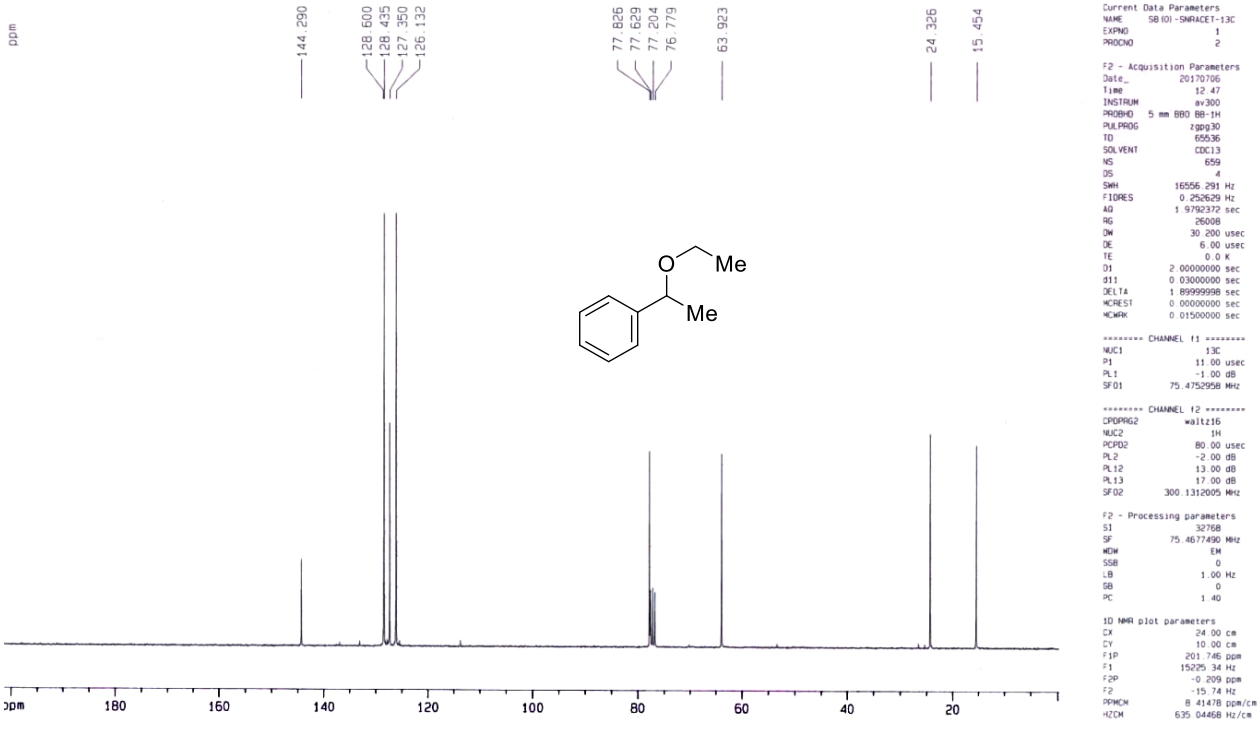


Figure 4: ^{13}C NMR of 1-(1-ethoxyethyl)benzene (**3b**)

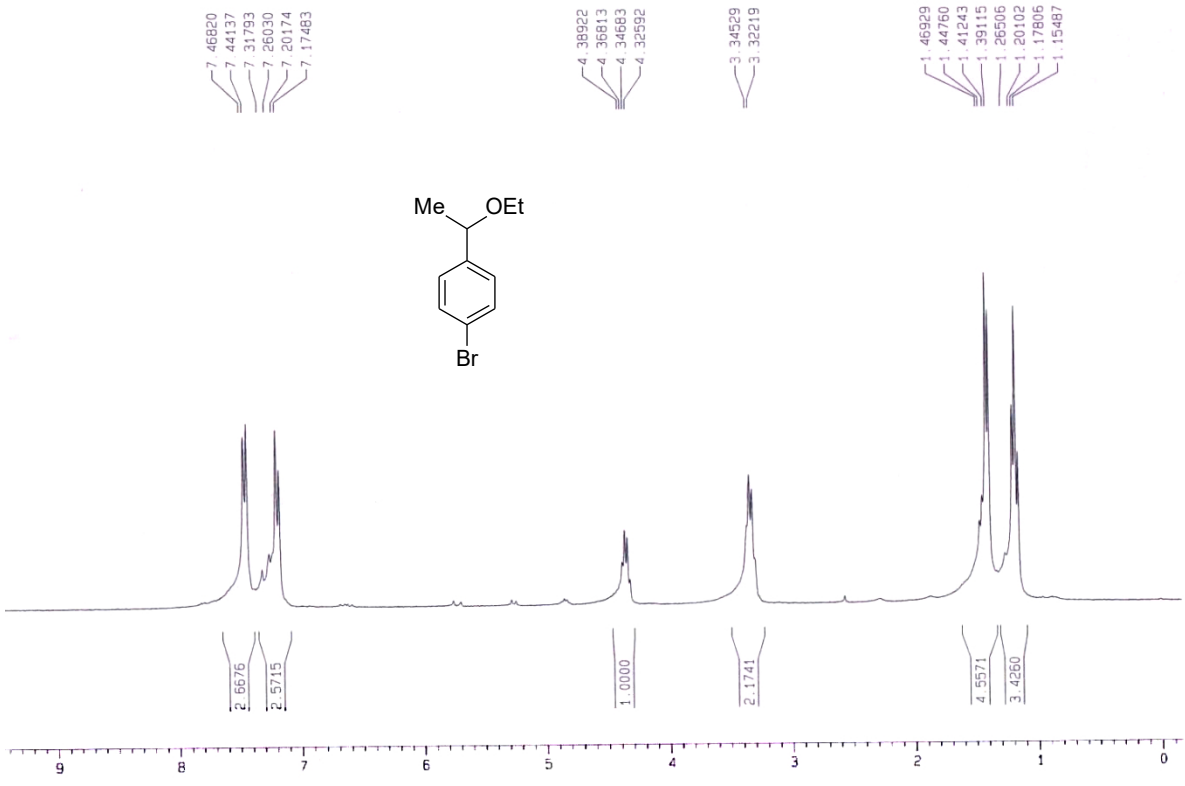


Figure 5: ^{1}H NMR of 1-bromo-4-(1-ethoxyethyl)benzene (**3e**)

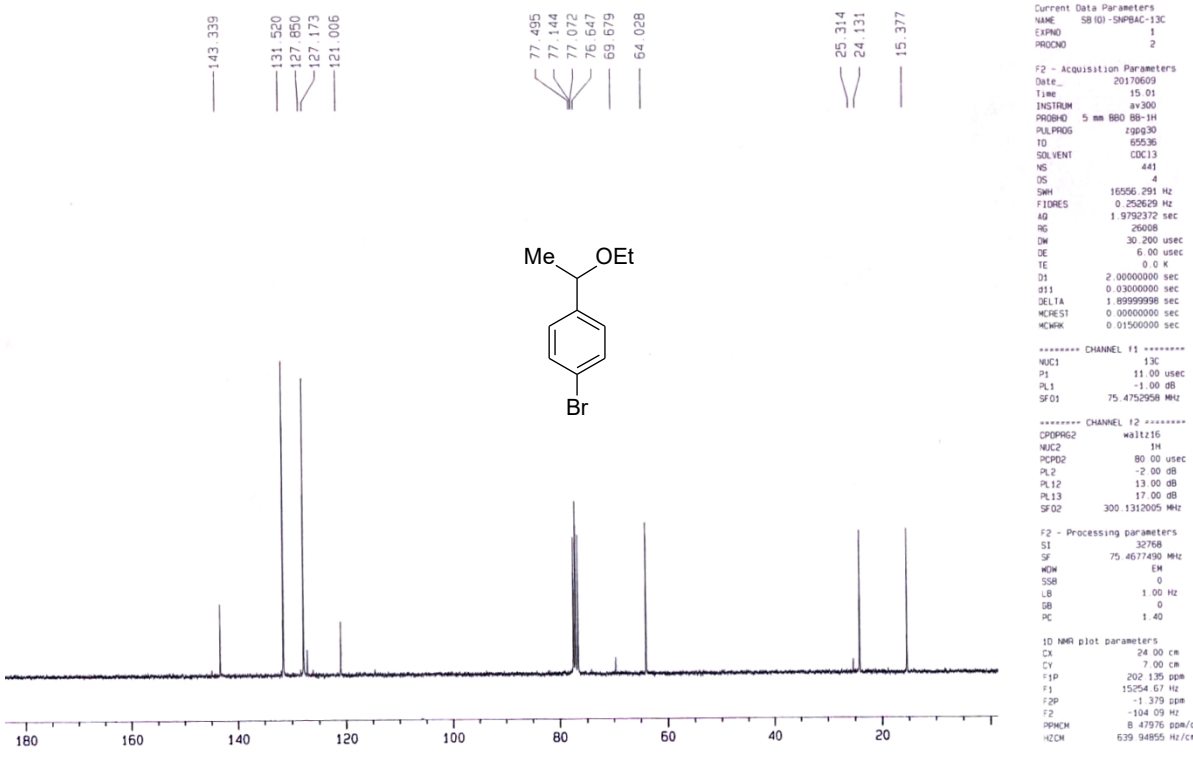


Figure 6: ^{13}C NMR of 1-bromo-4-(1-ethoxyethyl)benzene (**3e**)

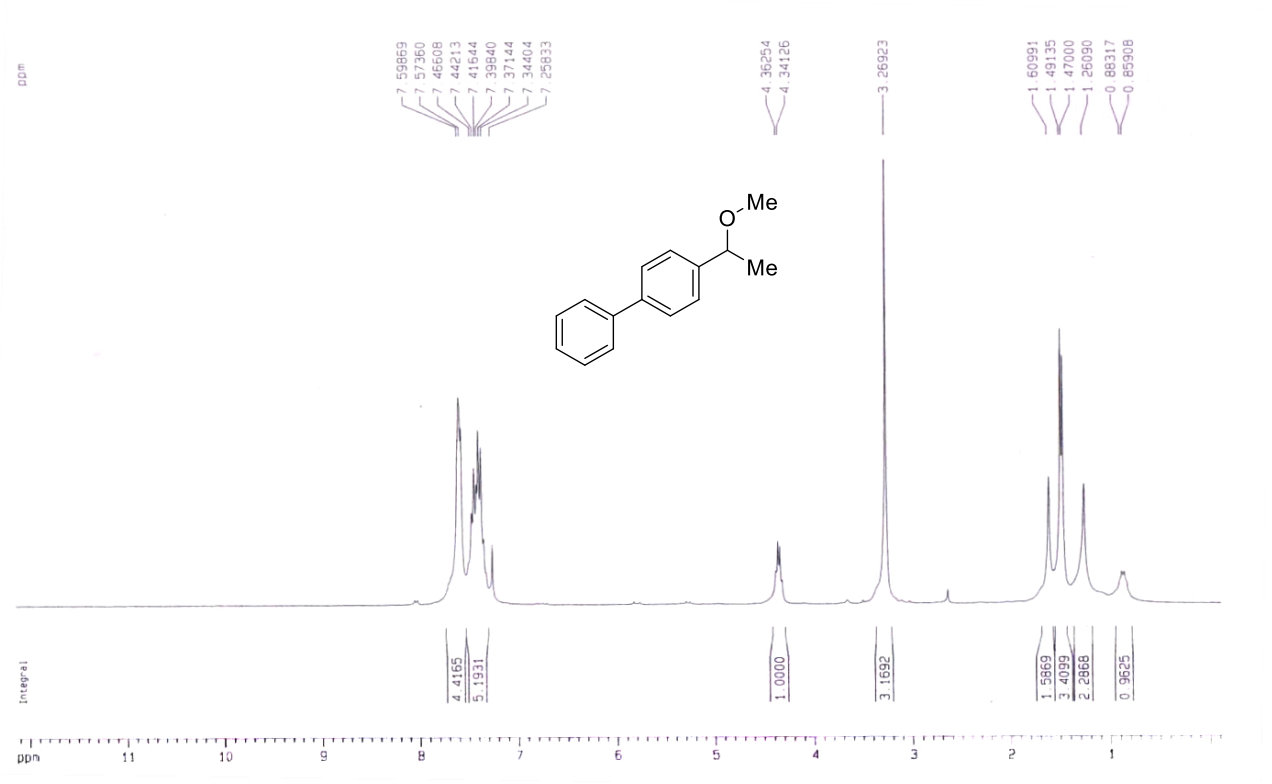


Figure 7: ^{1}H NMR of 4-(1-methoxy-ethyl)-biphenyl (**3f**)

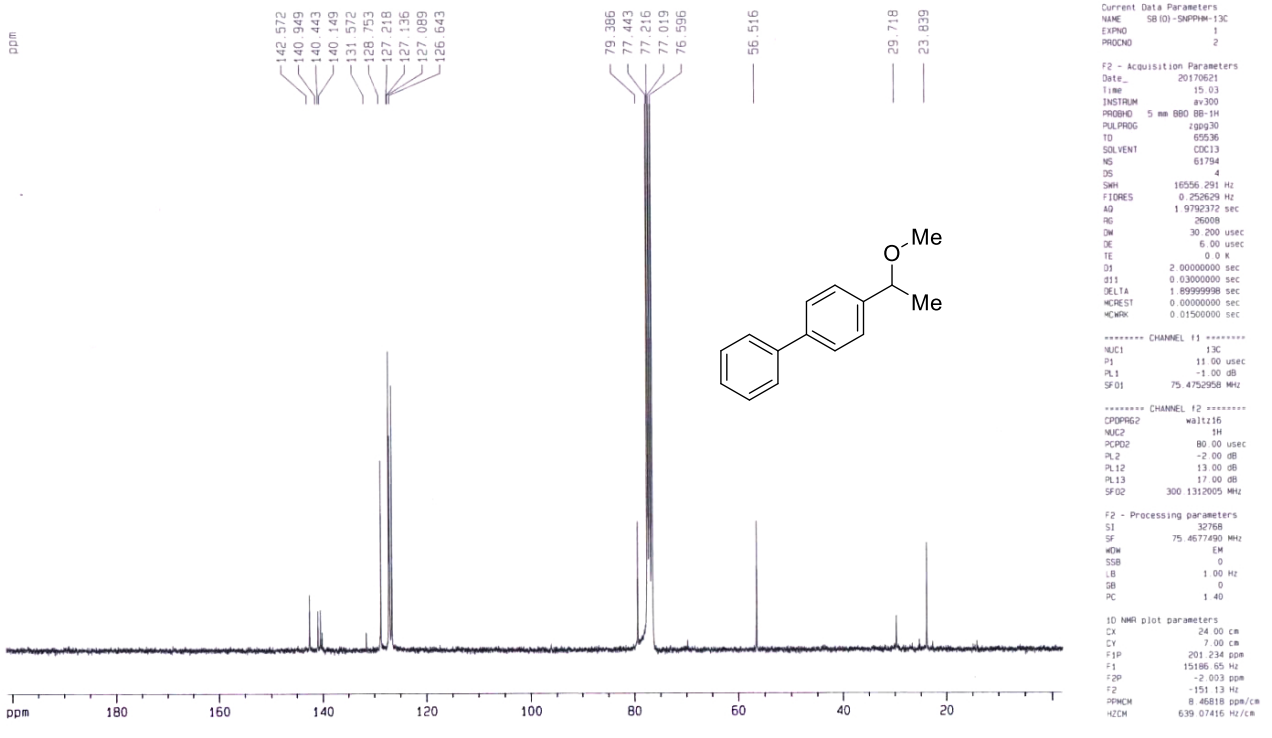


Figure 8: ^{1}H NMR of 4-(1-methoxy-ethyl)-biphenyl (**3f**)

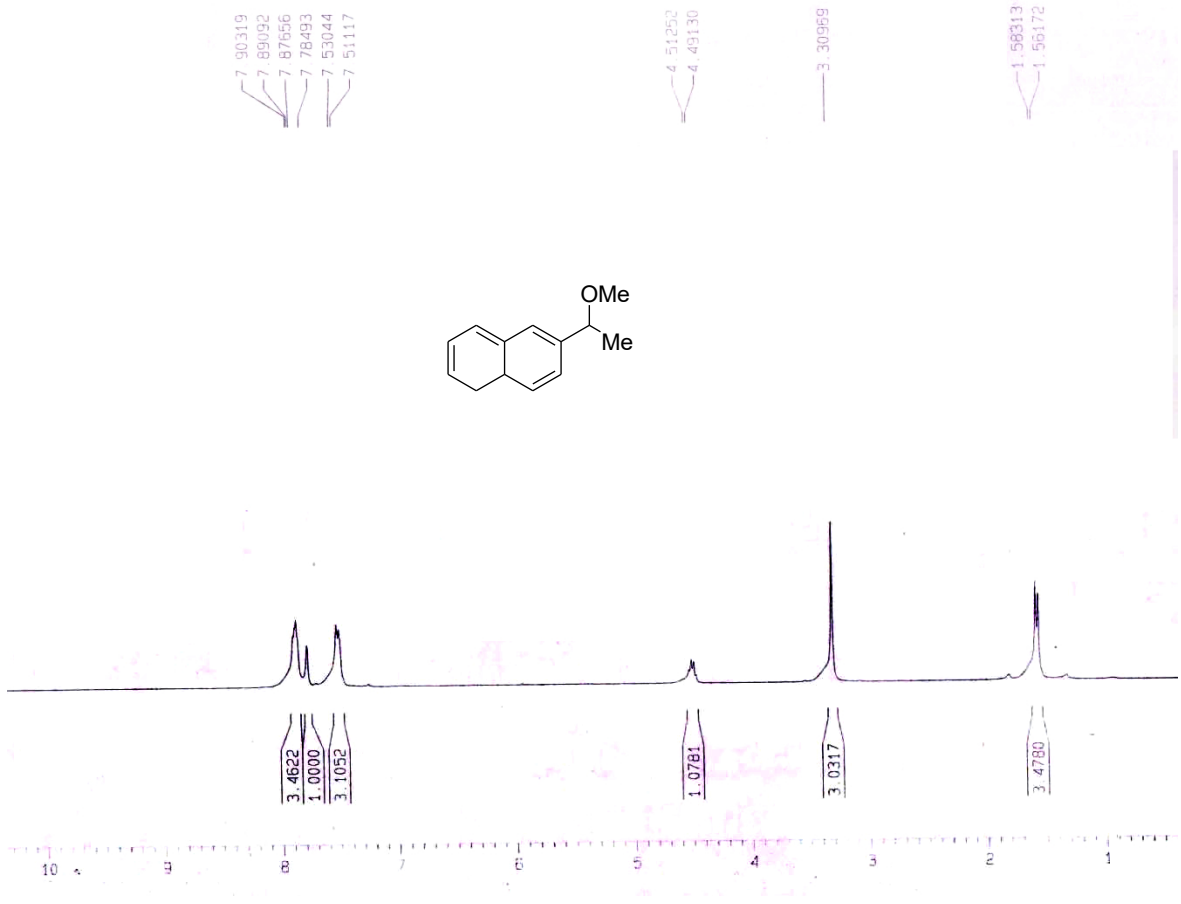


Figure 9: ^{1}H NMR of 2-(1-methoxyethyl)naphthalene (**3h**)

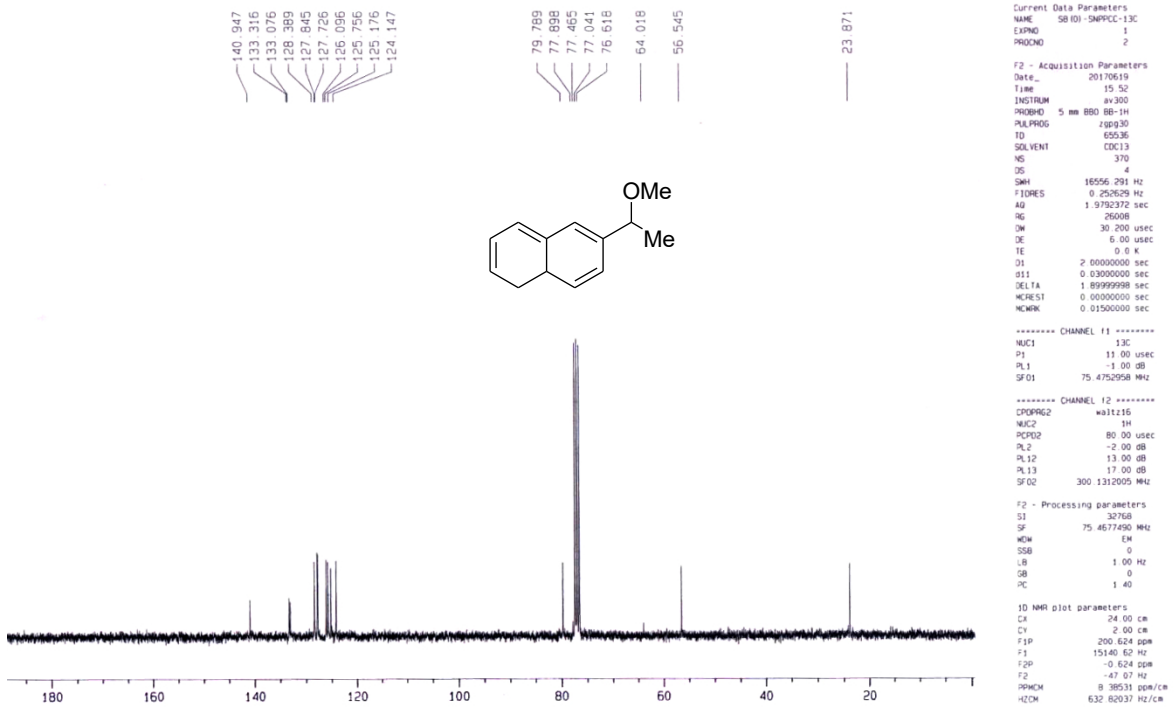


Figure 10: ^{13}C NMR of 2-(1-methoxyethyl)naphthalene (**3h**)

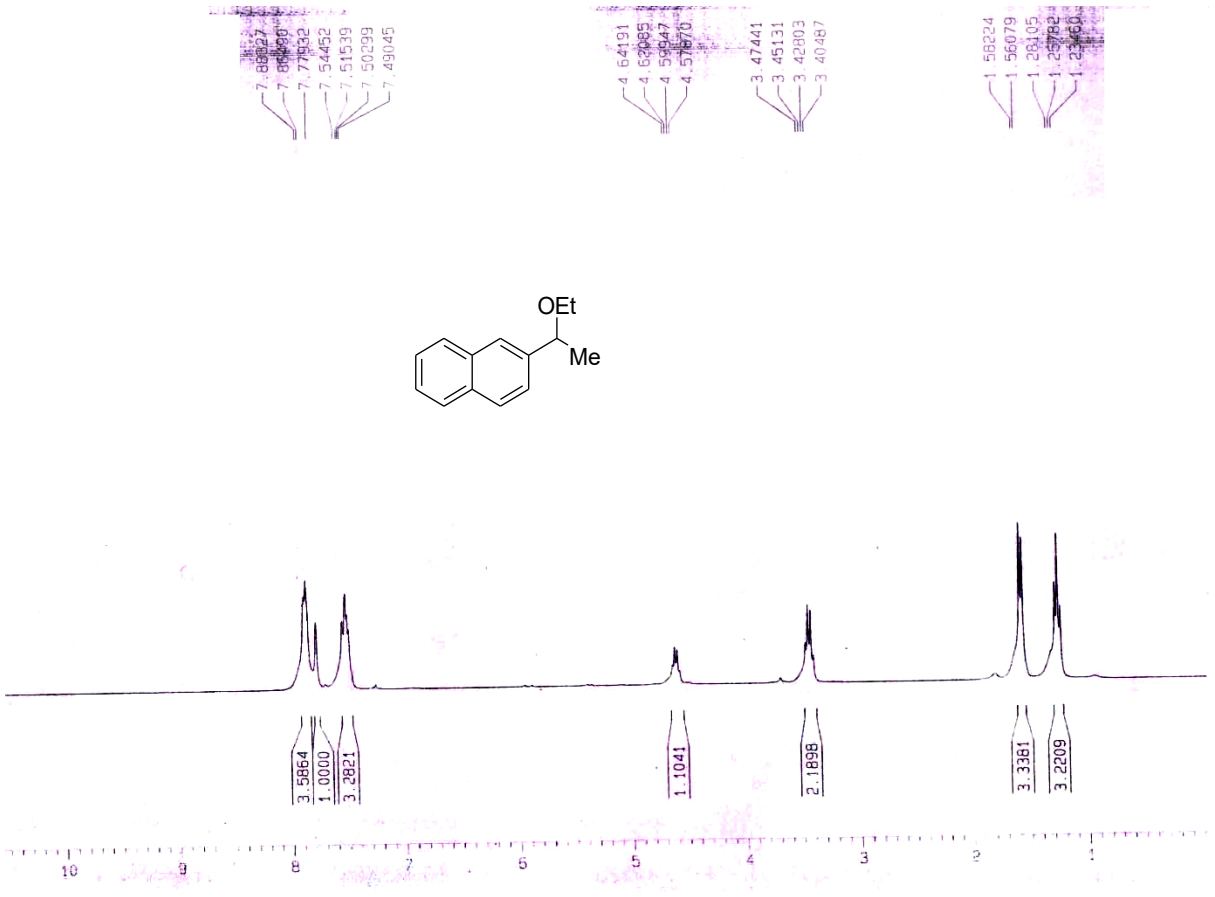


Figure 11: ^{1}H NMR of 2-(1-ethoxyethyl)naphthalene (**3i**)

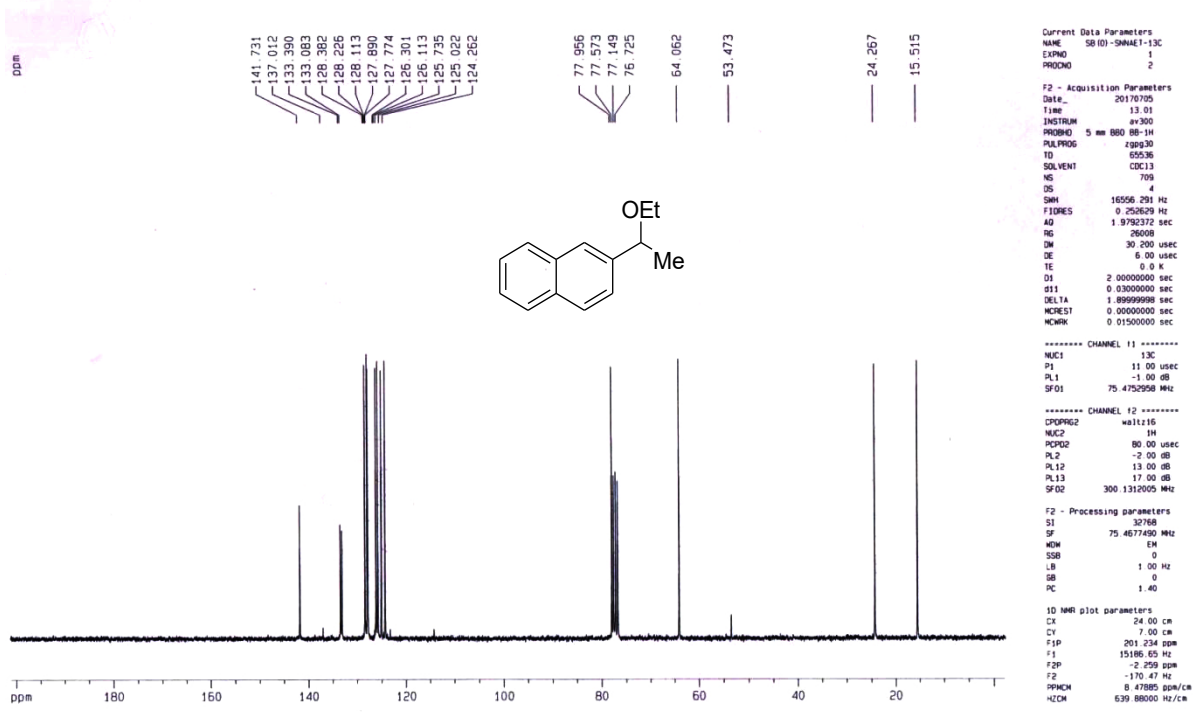


Figure 12: ^{13}C NMR of 2-(1-ethoxyethyl)naphthalene (**3i**)

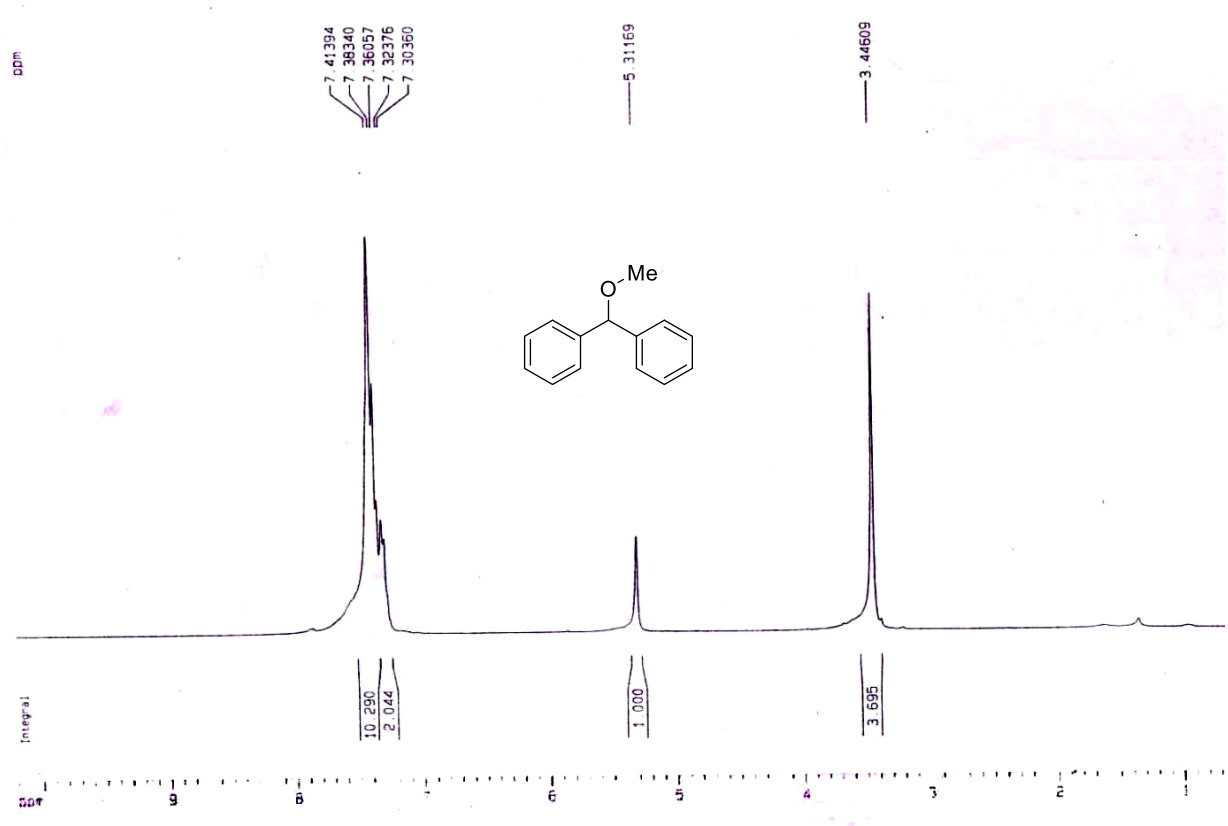


Figure 13: ^{1}H NMR of methoxydiphenylmethane (**3j**)

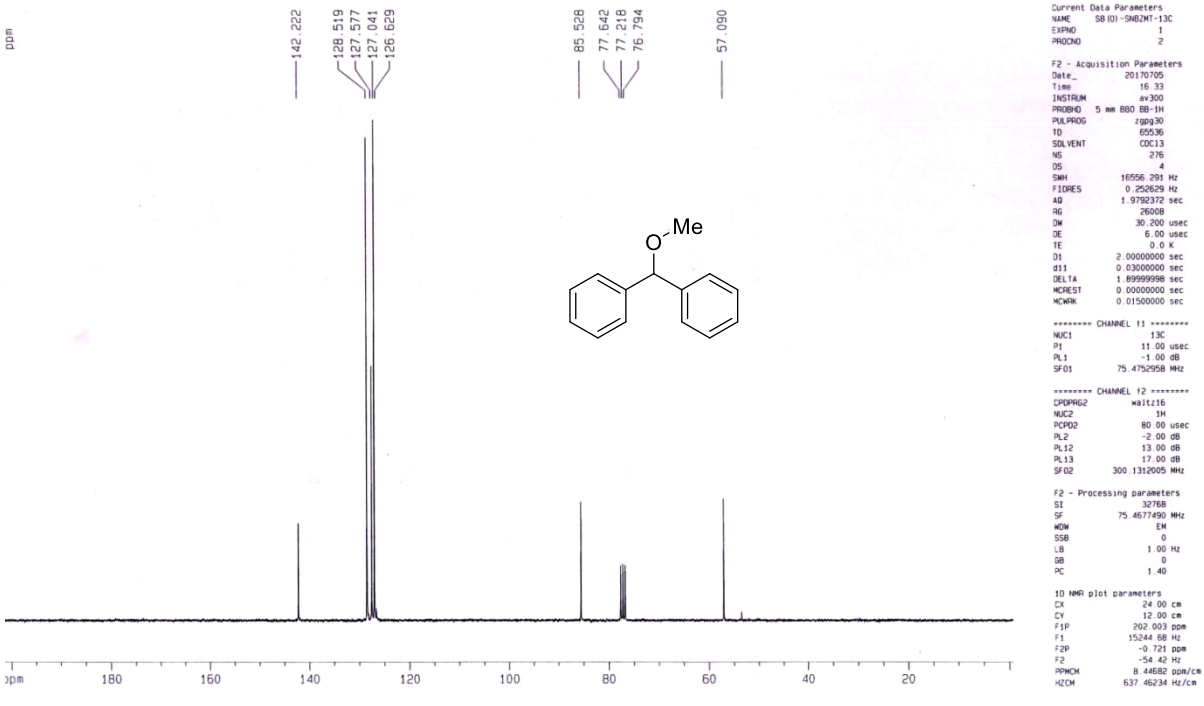


Figure 14: ^{13}C NMR of methoxydiphenylmethane (**3j**)

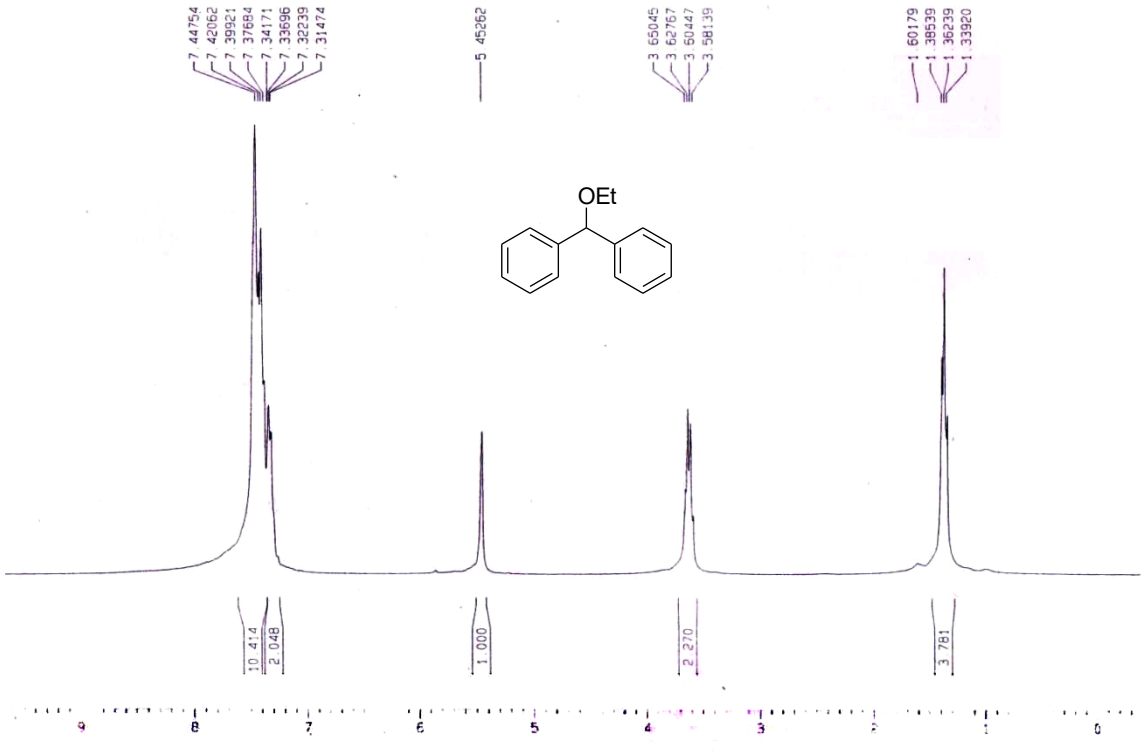


Figure 15: ^{1}H NMR of ethoxydiphenylmethane (**3k**)

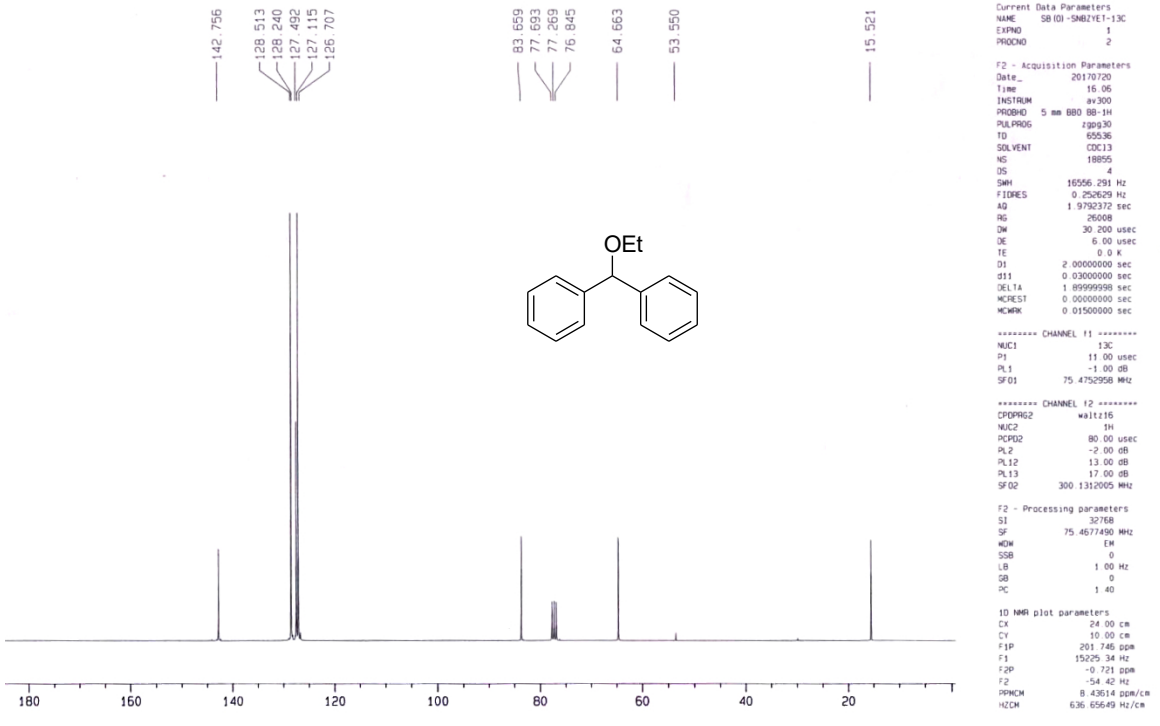


Figure 16: ^{13}C NMR of ethoxydiphenylmethane (**3k**)

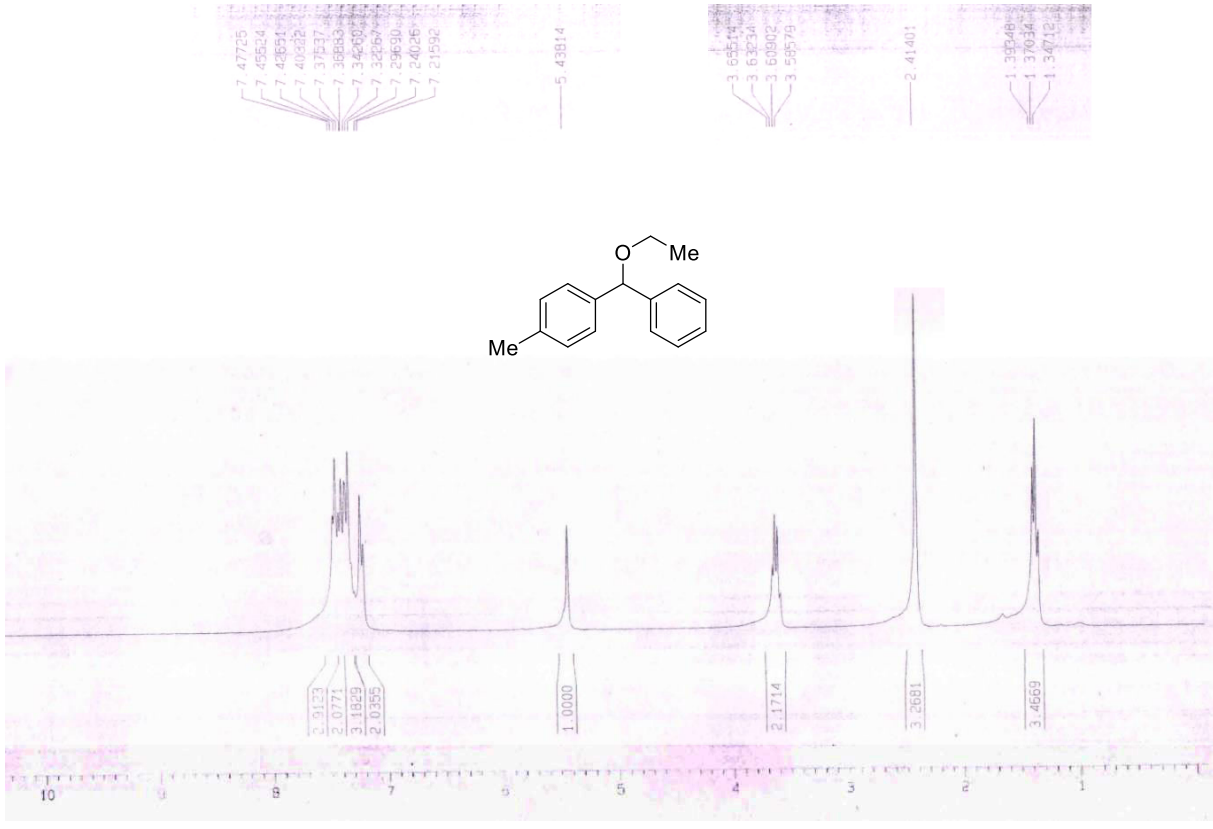


Figure 17: ^{1}H NMR of 1-(ethoxy(p-tolyl)methyl)benzene (**3n**)

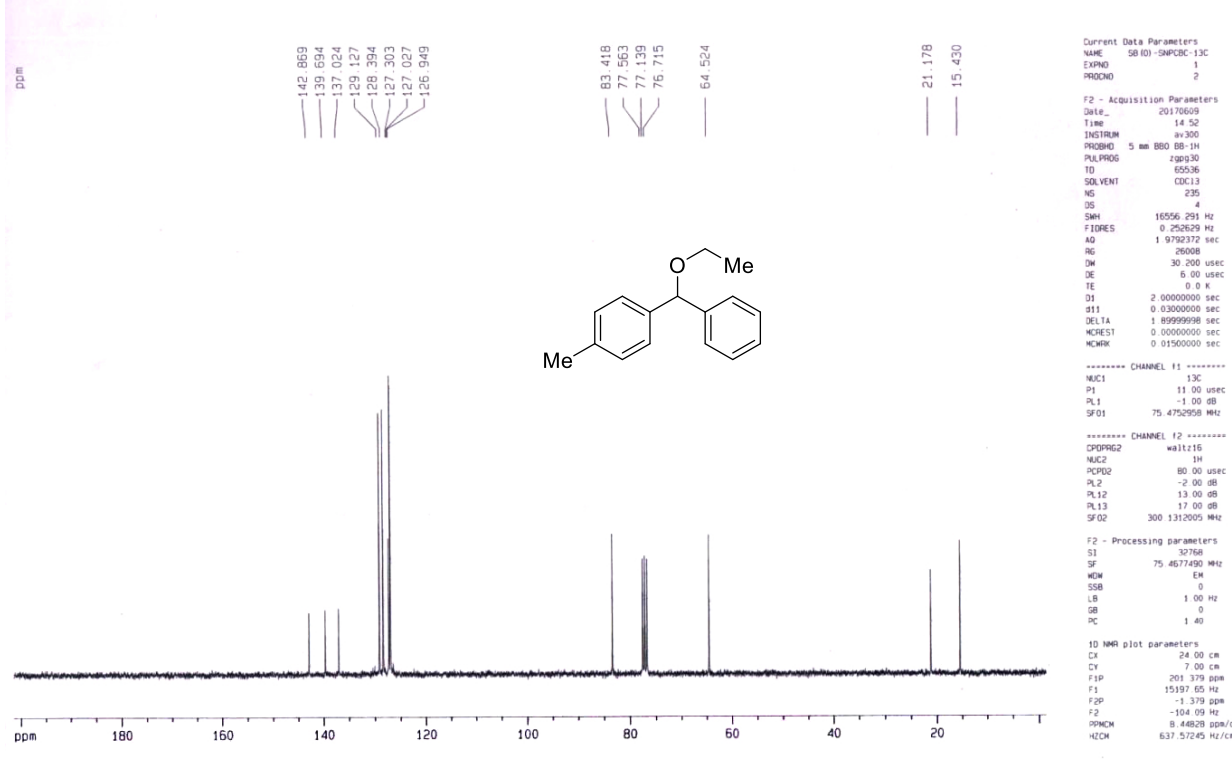


Figure 18: ^{13}C NMR of 1-(ethoxy(p-tolyl)methyl)benzene (**3n**)

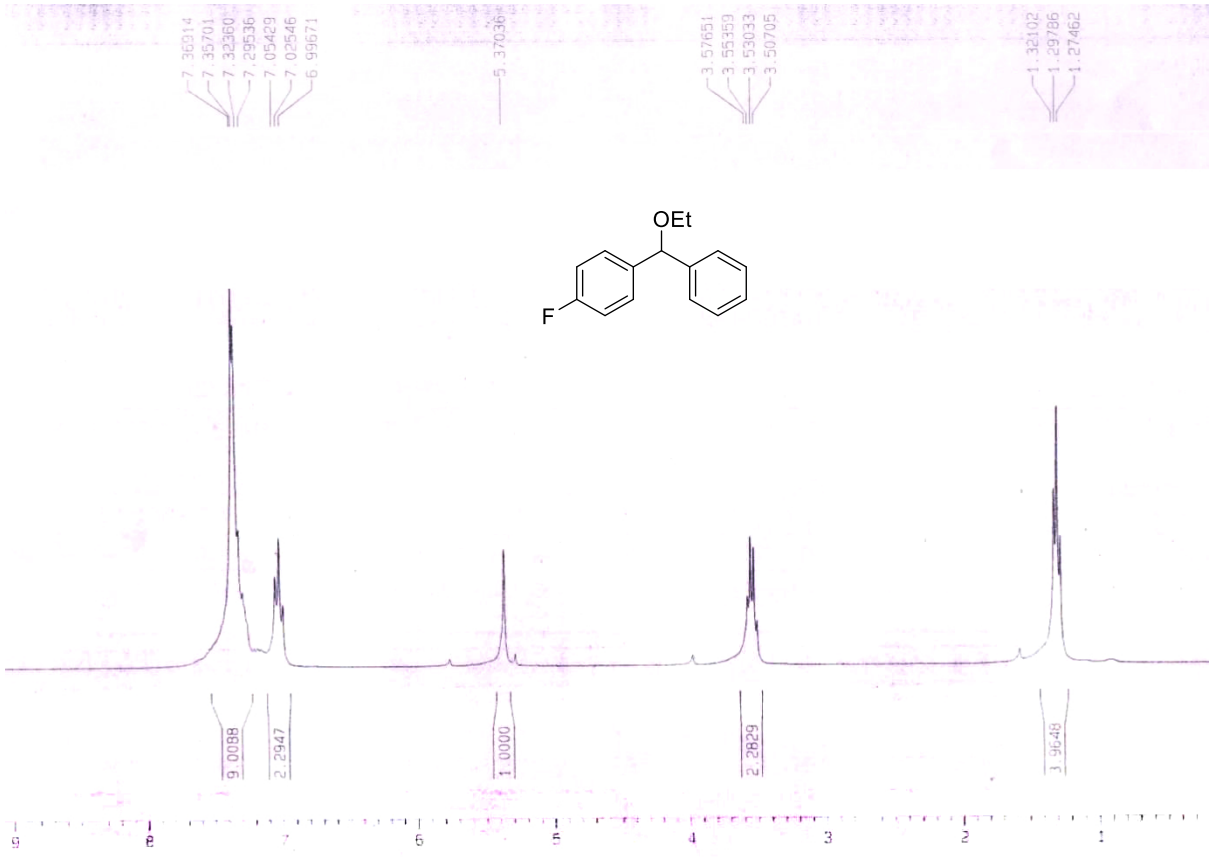


Figure 19: ^{1}H NMR of 1-(ethoxy(4-fluorophenyl)methyl)benzene (**3p**)

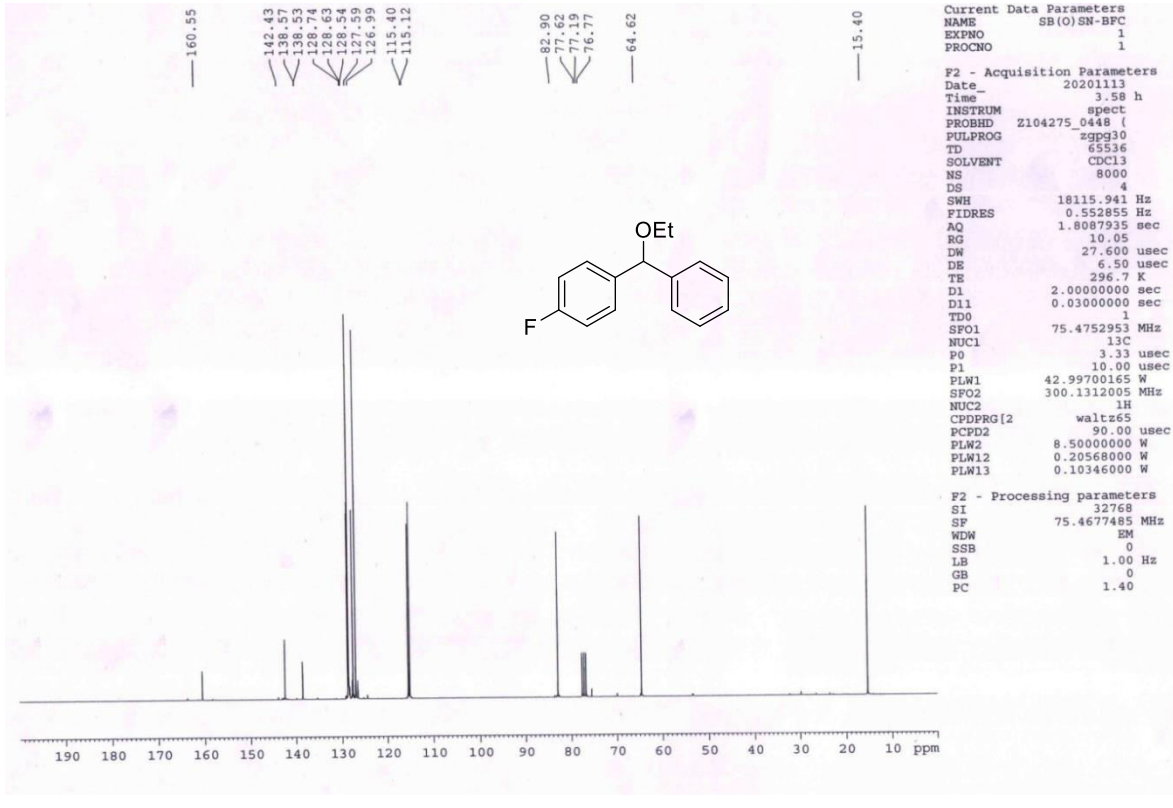


Figure 20: ^{13}C NMR of 1-(ethoxy(4-fluorophenyl)methyl)benzene (**3p**)

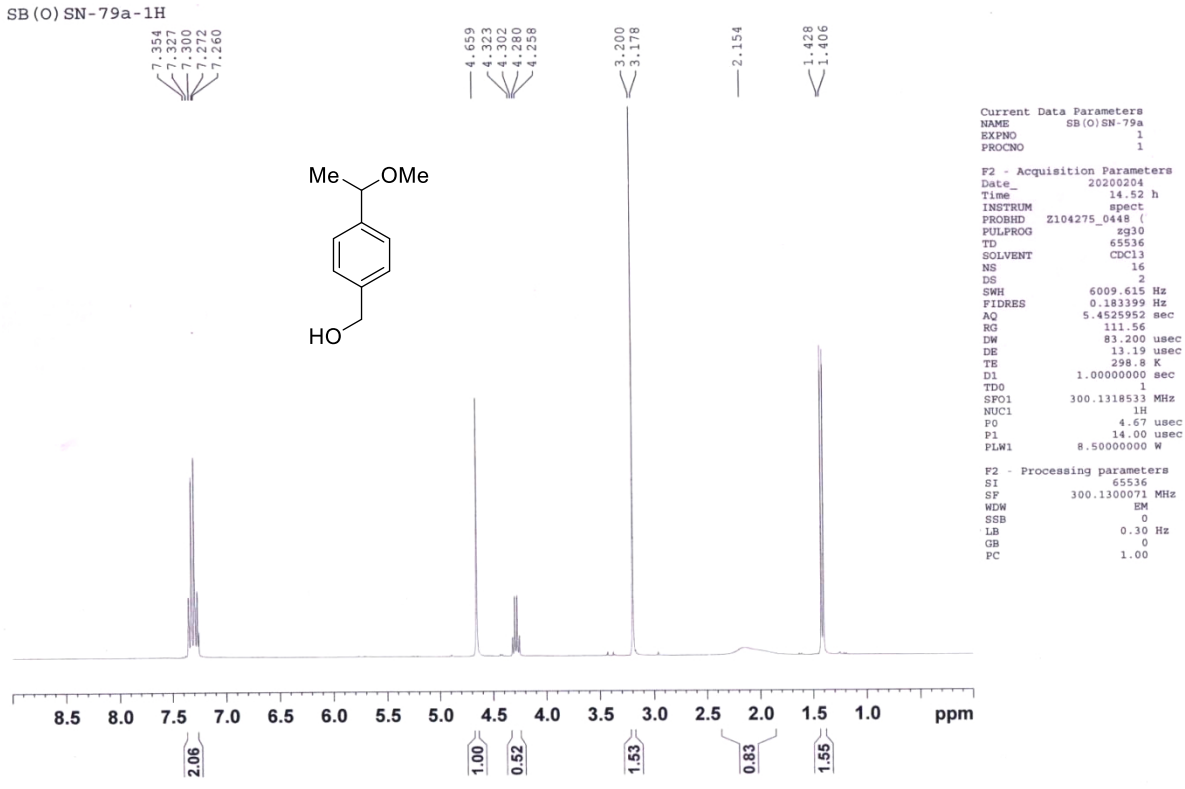


Figure 21: ^{1}H NMR of (4-(1-methoxyethyl)phenyl)methanol (**3v**)

Figure 22: ^{13}C NMR of (4-(1-methoxyethyl)phenyl)methanol (**3v**)

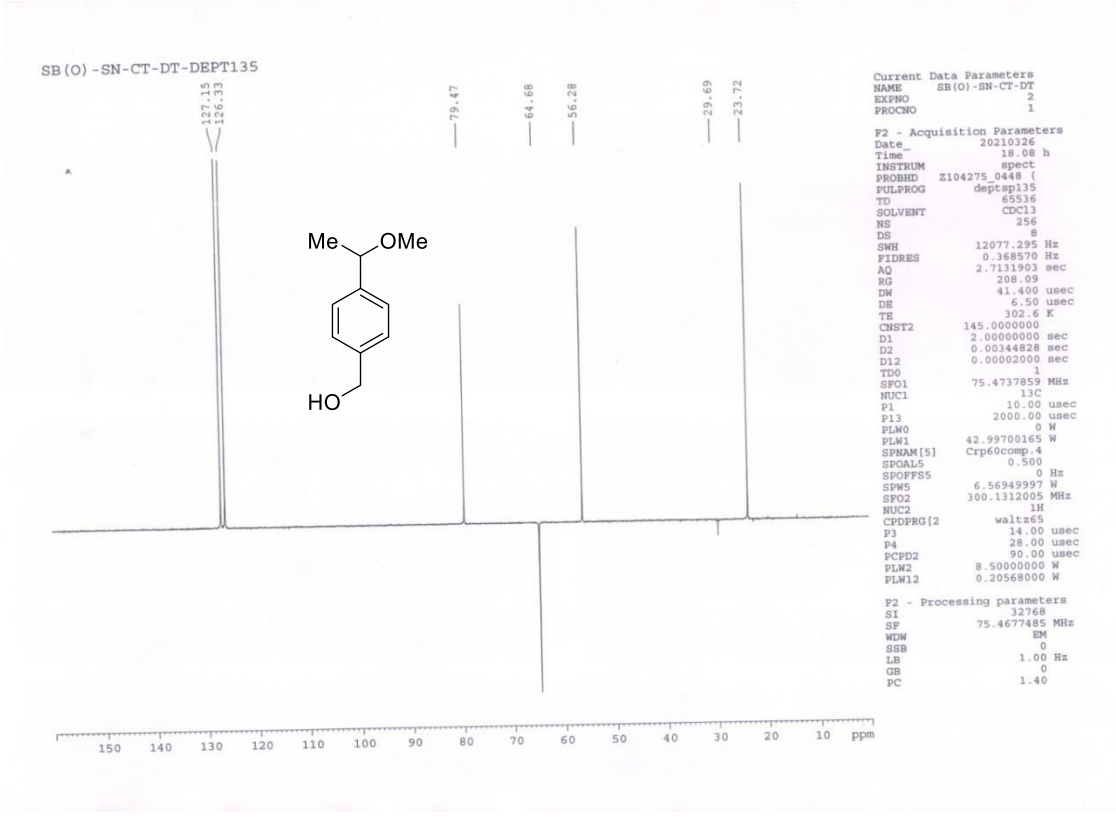


Figure 23: DEPT-135 NMR of (4-(1-methoxyethyl)phenyl)methanol (**3v**)

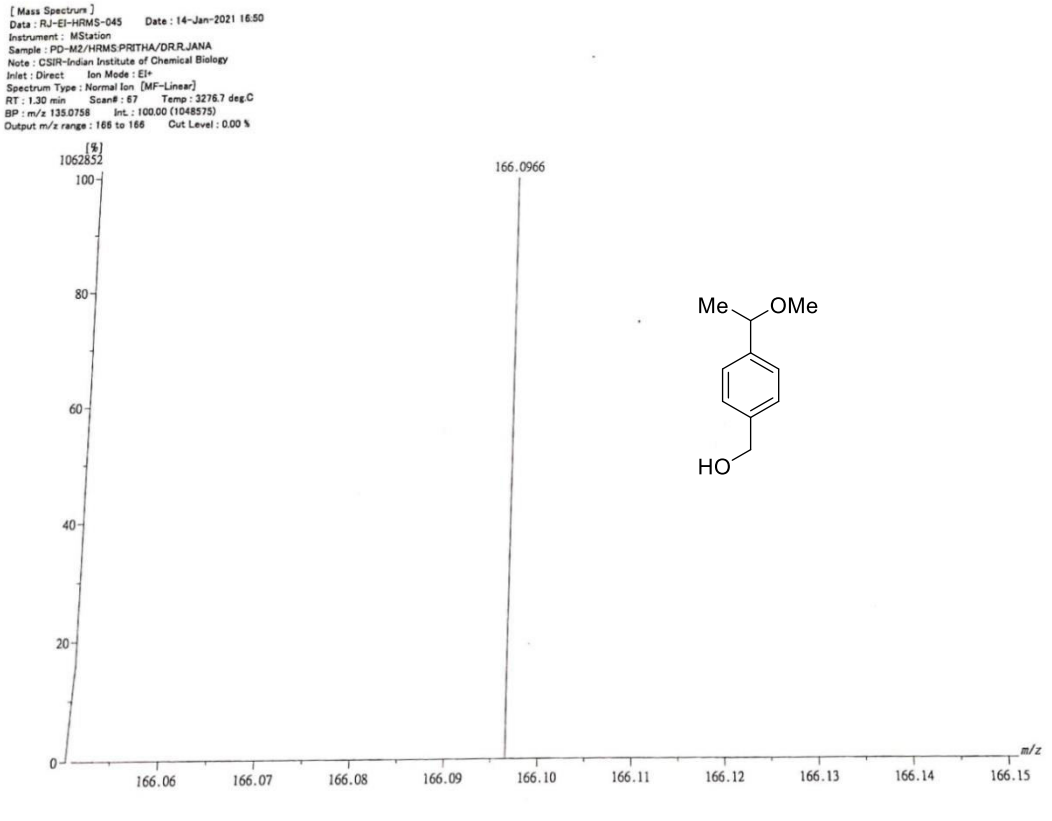


Figure 24: HRMS of (4-(1-methoxyethyl)phenyl)methanol (**3v**)

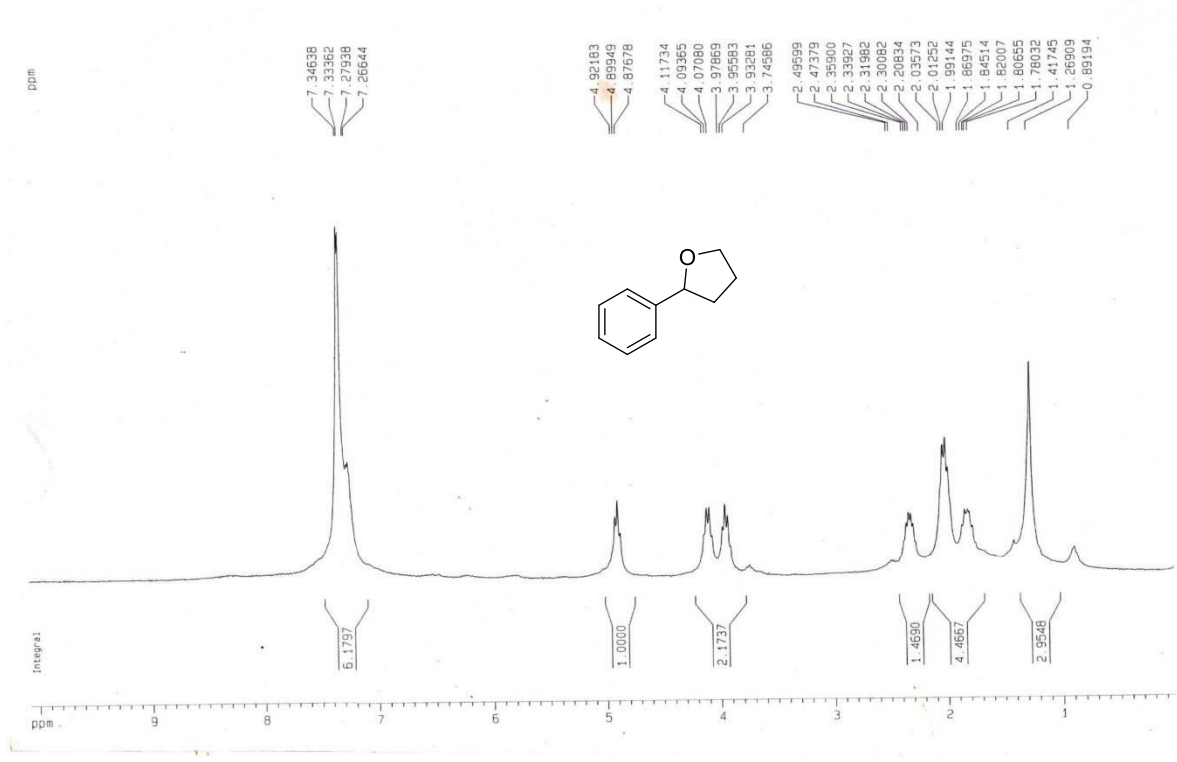


Figure 25: ^{1}H NMR of tetrahydro-2-phenylfuran (**10a**)

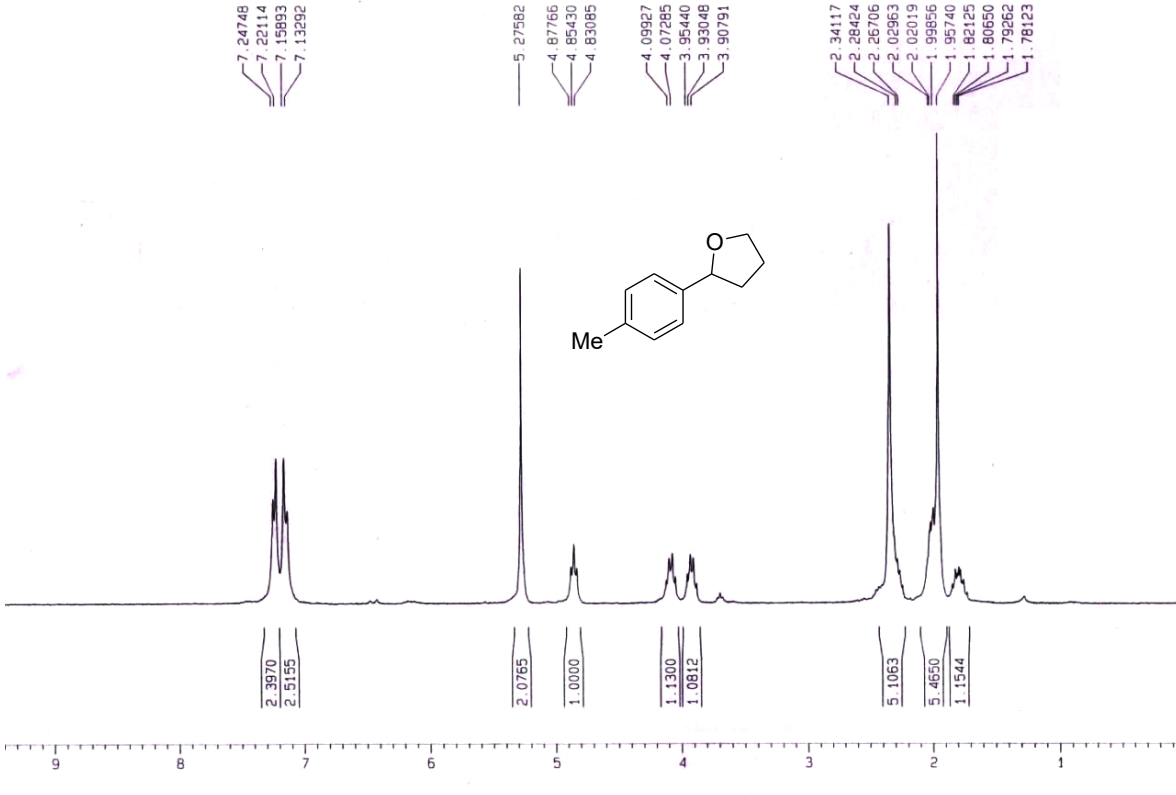


Figure 26: ^{1}H NMR of tetrahydro-2-*p*-tolylfuran (**10b**)

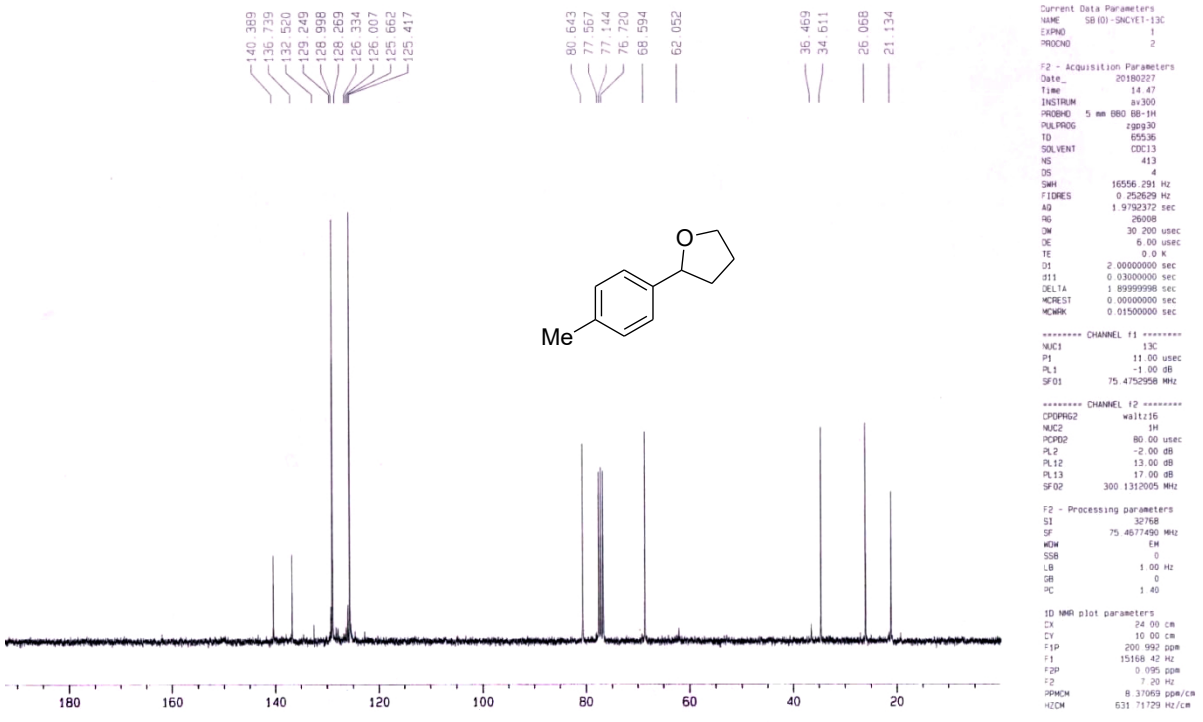


Figure 27: ^{13}C NMR of tetrahydro-2-*p*-tolylfuran (**10b**)

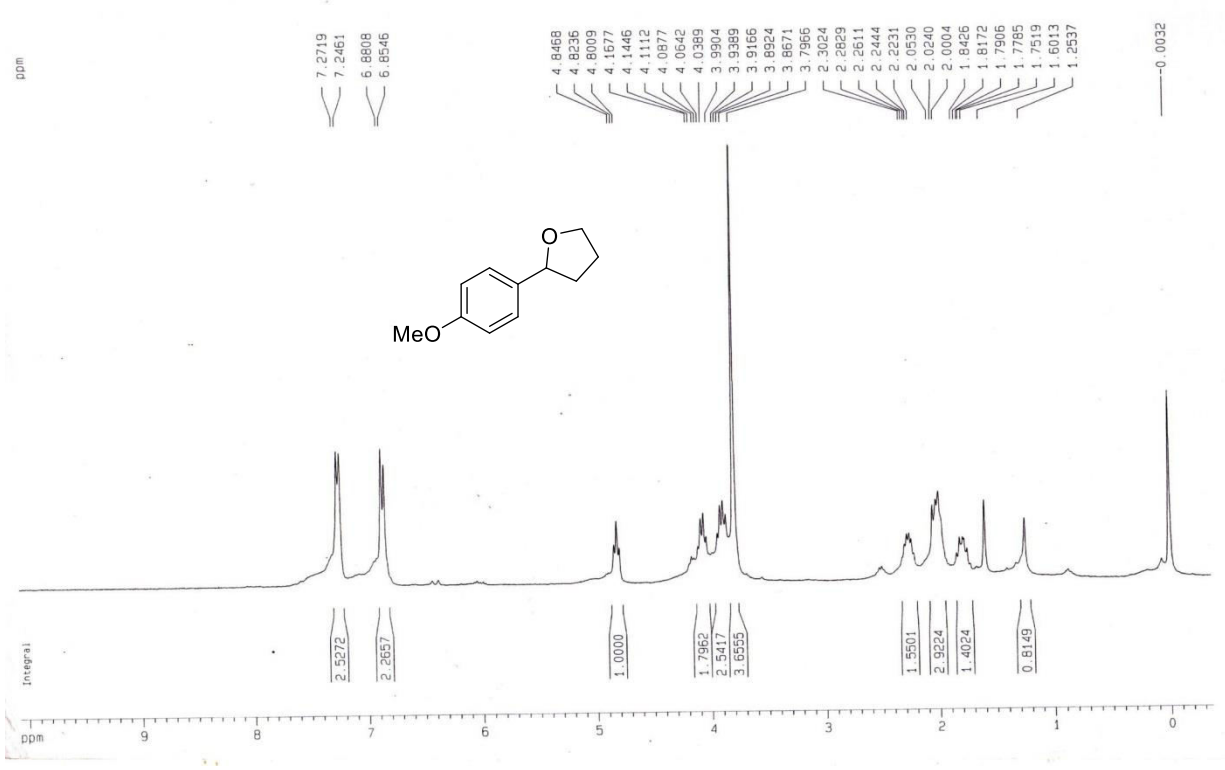


Figure 28: ^{1}H NMR of tetrahydro-2-(4-methoxyphenyl)furan (**10c**)

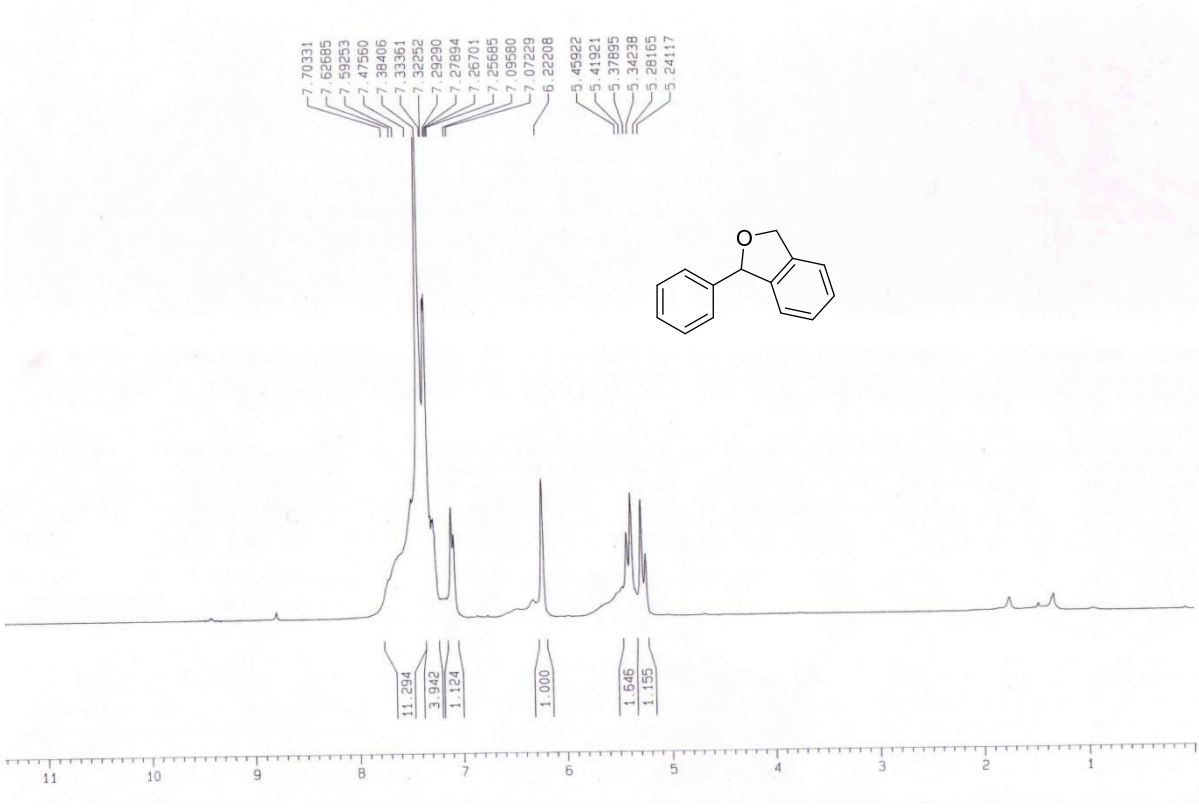


Figure 29: ^{1}H NMR of 2, 3-dihydro-2-phenylbenzofuran (**10d**)

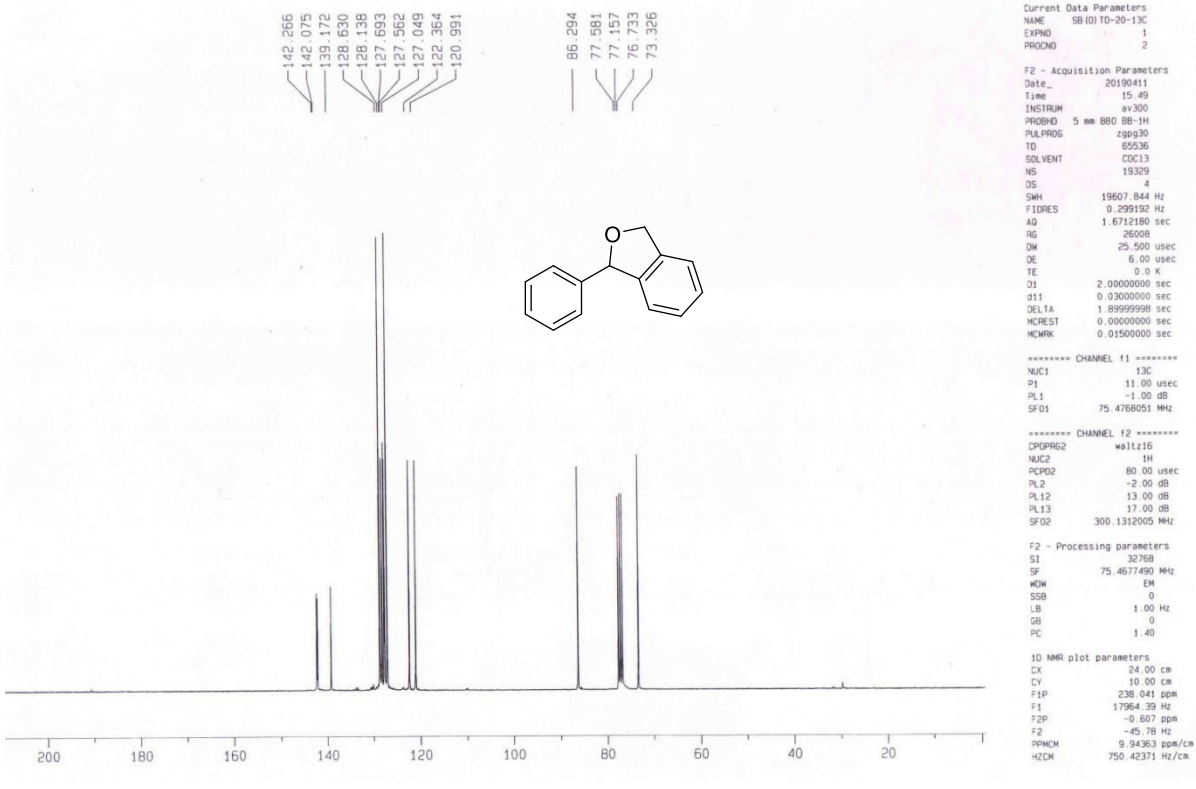


Figure 30: ^{13}C NMR of 2, 3-dihydro-2-phenylbenzofuran (**10d**)

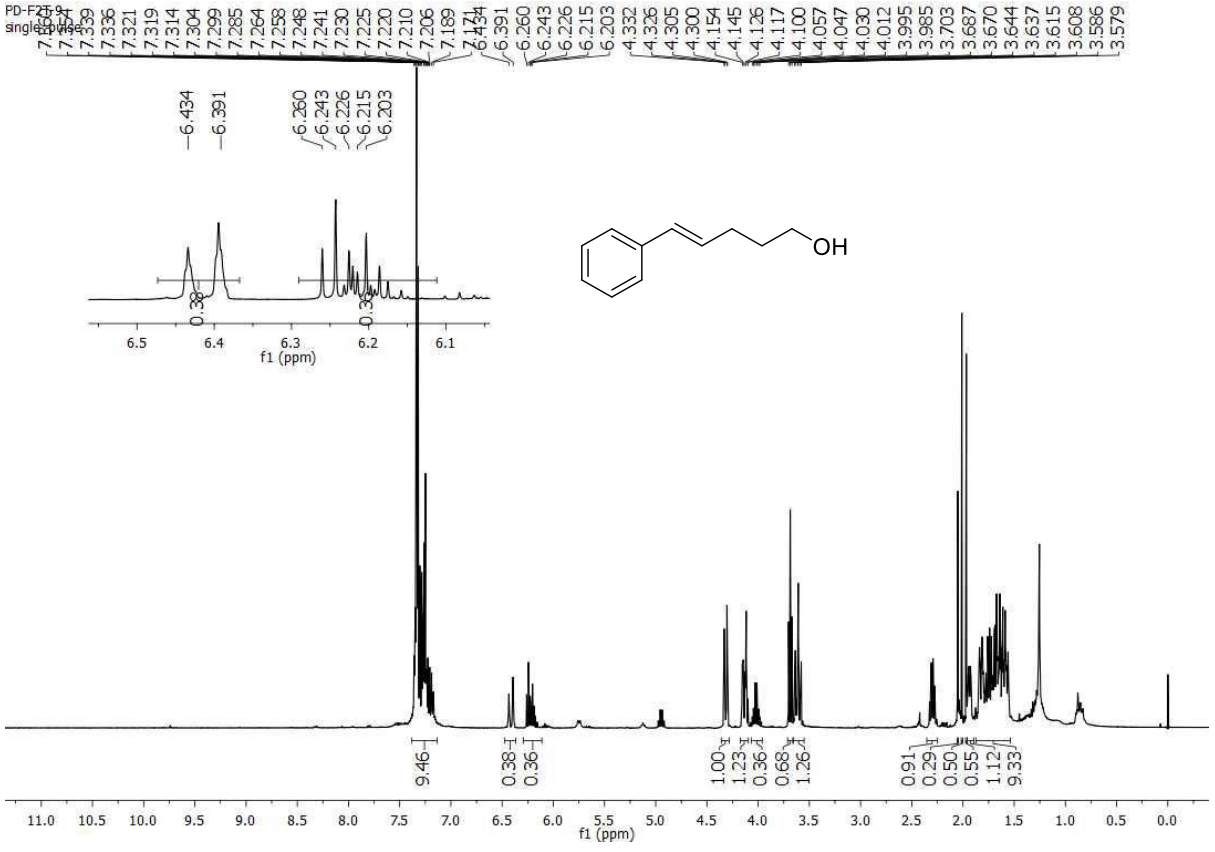


Figure 31: ^{1}H NMR of 5-phenylpent-4-en-1-ol (**11**)

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CHAPTER-II; SECTION-4

C-C bond cleavage in cyclopropane ring system using Amberlyst®-15(H) as a recyclable catalyst

CHAPTER-II; SECTION-4

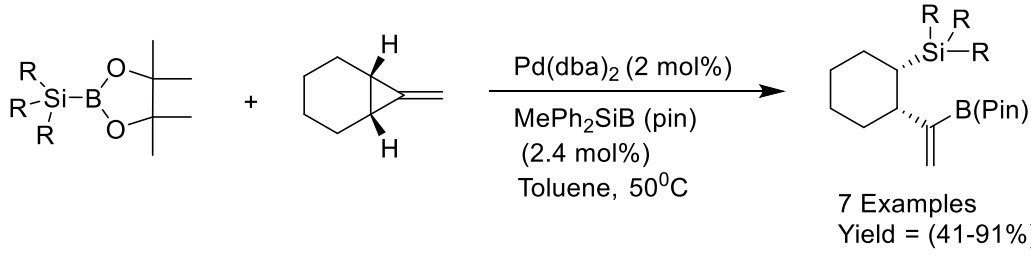
II.4. C-C bond cleavage in cyclopropane ring system using Amberlyst®-15(H) as a recyclable catalyst

II.4.1. Introduction:

Cyclopropanes are the smallest carbocycles, having large amount of ring strain and this strain can be utilized to reveal unusual reactivity providing access to chemical methodologies that are usually difficult to attain using conventional strategy. This unique property also made this molecule appropriate for synthetic organic chemists to study several ring-opening and functional group transformation reactions through decades.

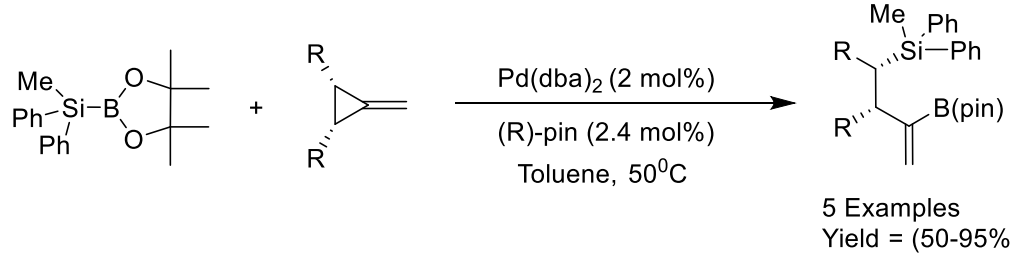
II.4.2. C-C bond cleavage of cyclopropane ring: A Review

In the realm of cyclopropyl ring cleavage reactions Suginome and his team contributed a lot in this field by developing[1] a transitionmetal-catalyzed silaborative C-C bond cleavage of methylene cyclopropanes (MCPs) (Scheme 1), which further showed distinctive reaction pathways depending critically on the catalyst and the structure of MCPs.



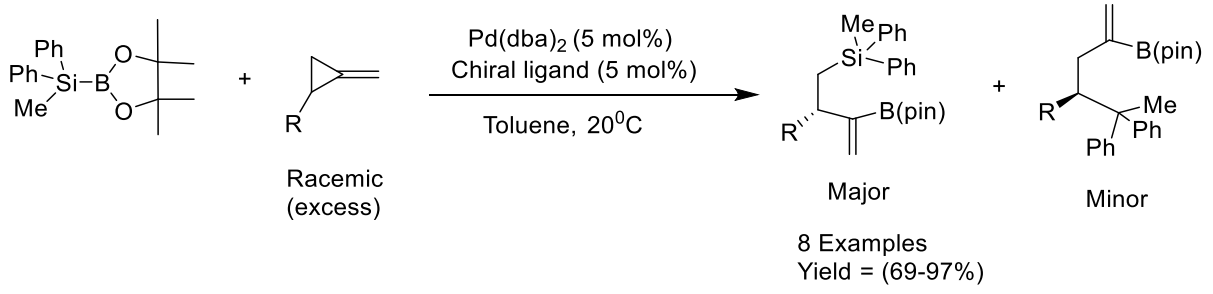
Scheme 1: Pd-catalyzed asymmetric silaborative C-C bond cleavage

In this method, symmetric desymmetrization was also explained utilizing silaborative C-C cleavage of *meso*-MCPs, which were prepared from *cis*-alkenes, using palladium catalyst having optically active monodentate phosphorus ligand (Scheme 2).



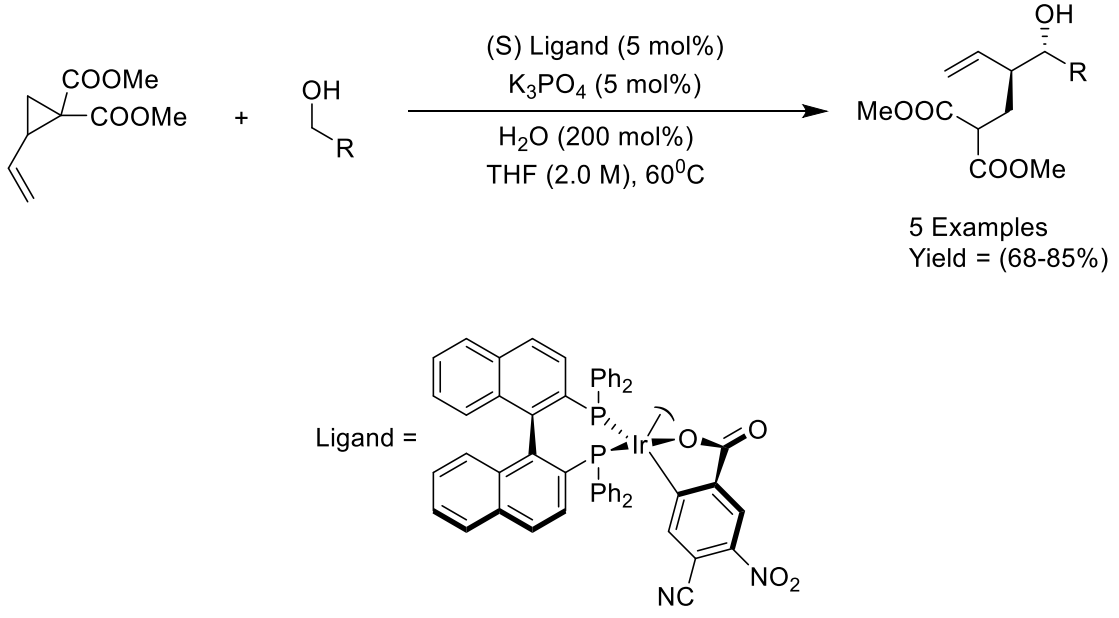
Scheme 2: Asymmetric silaborative C-C bond cleavage of MCPs

The team also reported[2] a unique kinetic resolution system using palladium-catalyzed silaborative C-C bond cleavage of 1-alkyl-2-methylene cyclopropanes, which resulted in highly enantio-enriched alkenyl boronic acid derivatives (Scheme 3).

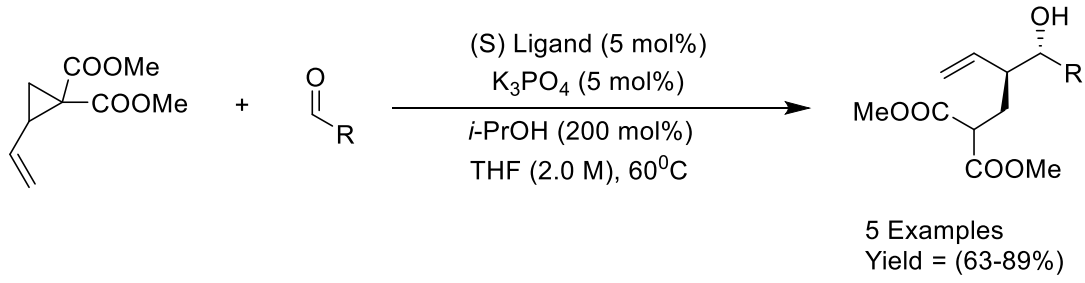


Scheme 3: Silaborative C-C bond Cleavage in the presence of Pd catalyst

Another novel report in this area emphasized[3] on the reactions of donor-acceptor cyclopropanes, with the help of diastereo- and enantioselective iridium-catalyzed cyclopropane mediated carbonyl allylations, using alcohol (Scheme 4) or aldehyde (Scheme 5). This study also explored new routes to generate optically enhanced *cis*-4, 5-disubstituted δ-lactones. The identification of the interactional and structural features of the system including polarity inversion provided an outline for designing other C-C coupling processes.

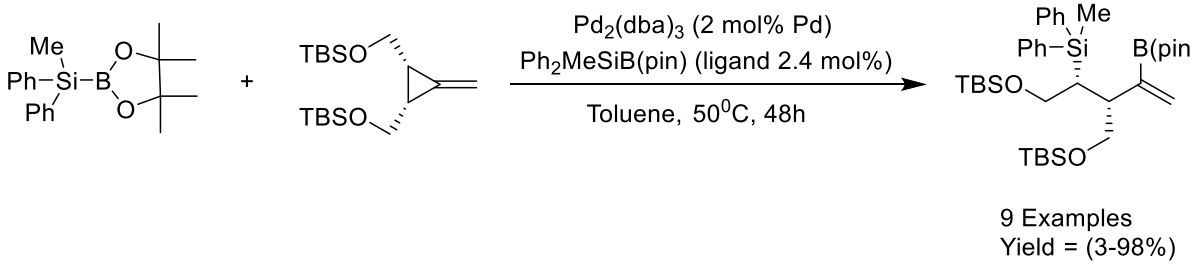


Scheme 4: D-A cyclopropane-mediated carbonyl allylation from the alcohol oxidation level



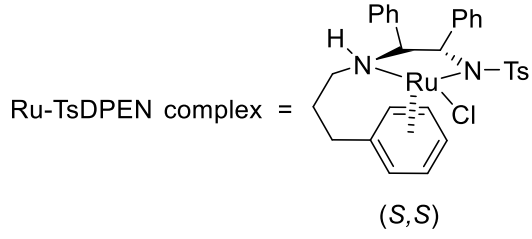
Scheme 5: D-A cyclopropane-mediated carbonyl allylation from the aldehyde oxidation level

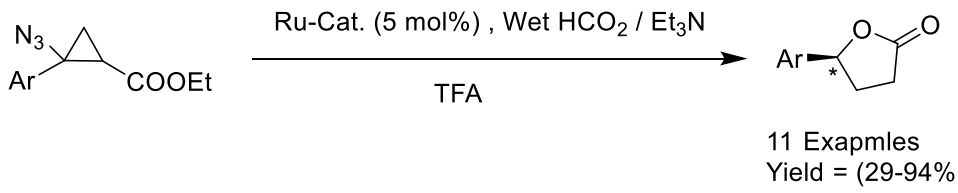
Akai *et al*.explored[4] the properties of poly(quinoxaline-2,3-diyl)-based chiral phosphine ligands (PQX-phos) for excellent enantioselectivities (up to 97% ee) in palladium-catalyzed desymmetrization of *meso*-1, 2-dialkylsubstituted-3-methylene cyclopropanes through silaborative cleavage of the C−C bond (Scheme 6). They also observed remarkable rate enhancement with a series of PQX-phos when compared to the corresponding lower molecular weight ligands.



Scheme 6: Asymmetric silaborative C−C Cleavage using PQX-phos as chiral ligands

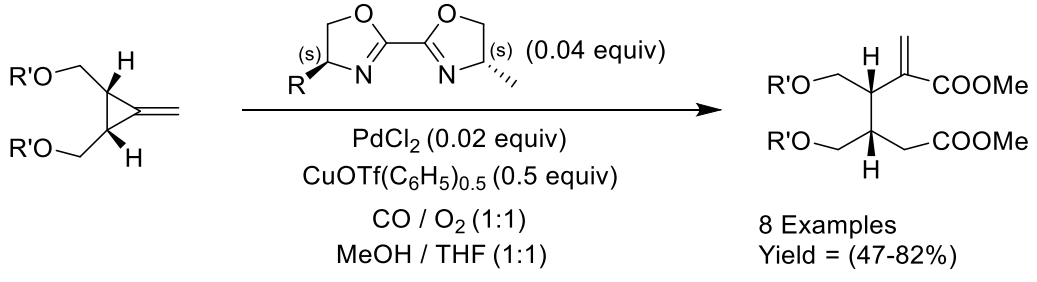
Su *et al*. demonstrated[5] very interesting properties of Ru-TsDPEN complex by using it as a catalyst for the asymmetric H-transfer from racemic β-azidocyclopropane carboxylate to enantioenhanced γ-lactones (Scheme 7). A sequence of cyclopropane ring rearrangement or asymmetric transfer hydrogenation of γ-oxo ester produced several γ-lactones in good to excellent enantioselectivity.





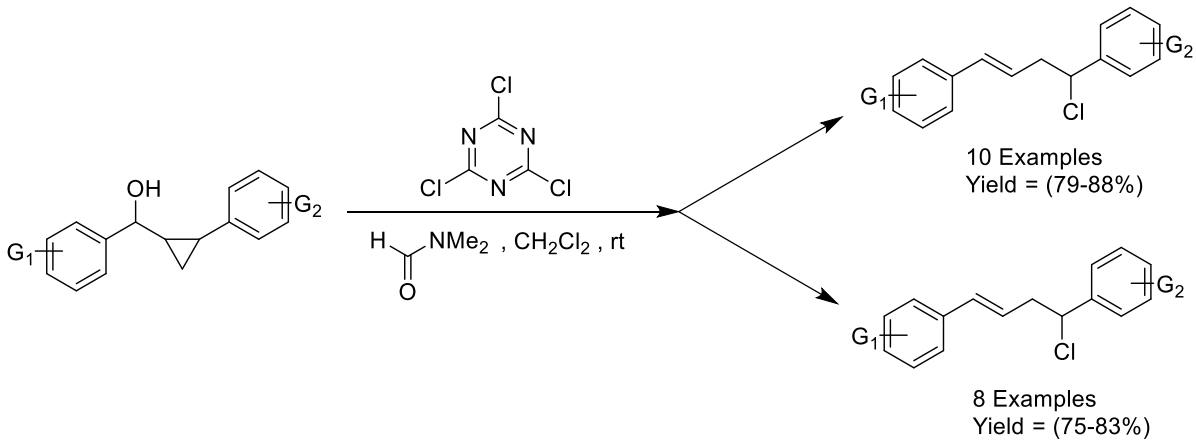
Scheme 7: Asymmetric hydrogenation of ethyl β-azidocyclopropane carboxylate

The desymmetrization of *meso*-methylene cyclopropanes using a palladium-catalyzed asymmetric ring-opening (bis-alkoxycarbonylation) reaction was reported[6] to afford optically active α-methylene glutarates with almost 60% ee (Scheme 8). This asymmetric carbonylation method gave an excellent conceptto synthesize optically active oxygen-functionalized substrates.



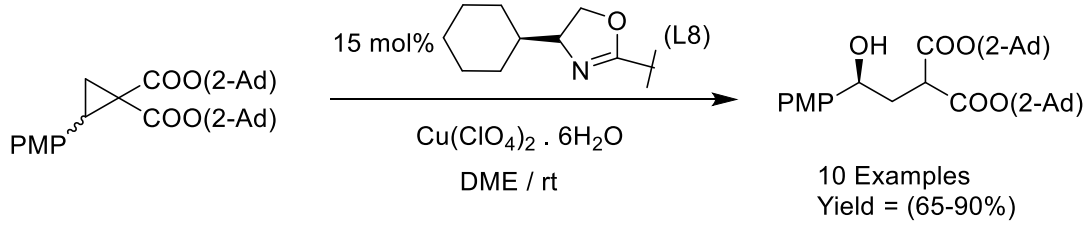
Scheme 8: Palladium-catalyzed asymmetric ring-opening bis(alkoxycarbonylation) reaction

Khan *et al*. established[7] a suitable protocol where differently substituted cyclopropylcarbinols went through ring cleavage with easily available cyanuricchloride (TCT)–N, N-dimethyl formamide adducts to provide homoallylic chlorides or the corresponding dienes depending on the nature and position of the substituents (Scheme 9). As a continuation of the investigations, further elucidation of the synthetic protocol was performed by reacting symmetrical bis-cyclopropylcarbinols with substituted aryl moietieswith TCT–DMF complex. Here only one of the cyclopropane rings was selectively cleaved while the other one remained intact giving a novel structural backbone with vinylcyclopropane unit. Also the products were either homoallylic chlorides or dienes based on the nature of the substituents. The mechanistic explanation of this observation provided a utilitarian concept to construct vinylcyclopropanes having homoallylic chloride and diene moieties.



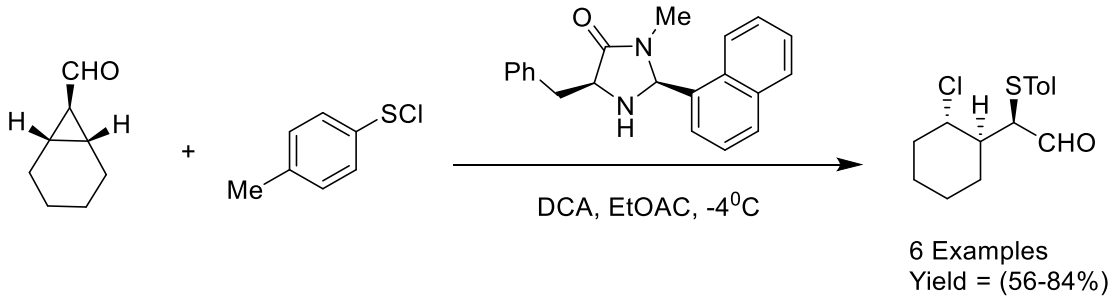
Scheme 9: Cyanuric chloride - N, N-dimethyl formamide mediated cleavage of cyclopropylcarbinols

Kang *et al*. developed[8] a novel strategy using hydrated copper both as a Lewis acid and a source of nucleophile in H_2O mediated cyclopropanering opening reaction in a nucleophilic enantioselective pathway.The reaction was successful over a wide range ofsubstrates, leading to mainly ring-opening products in high yields under mild conditions (Scheme 10). This method further provided a new approach to obtain substituted γ-hydroxybutyric acid (GBH) derivatives directly from activated cyclopropanes.



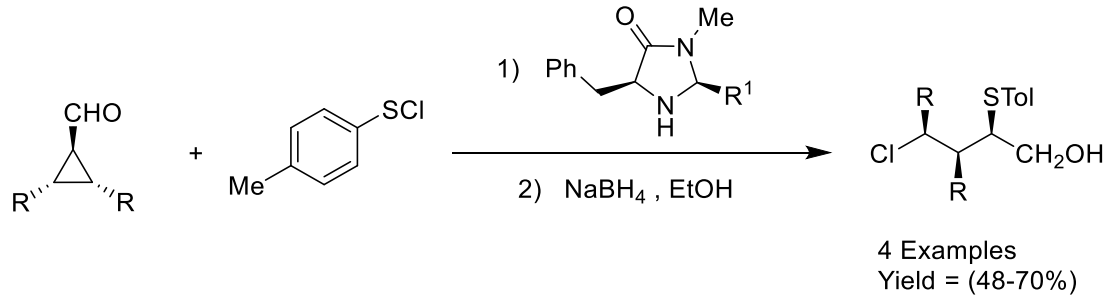
Scheme 10: Asymmetric H_2O-nucleophilic ring opening of D–A cyclopropanes

1, 3-chlorochalcogenation of cyclopropyl-carbaldehydes was introduced[9] by using highly polarized sulfenyl and selenyl chlorides, where the success was found in the application of iminium-enamine catalysis for aldehyde-substituted cyclopropanes, making the way for further ring-opening 1, 3-bisfunctionalization with a nucleophilic and an electrophilic substituent. When achiral *meso*-cyclopropylcarbaldehyde and *p*-tolylsulfenyl chloride were used as substrates for the optimization, the reaction provided the desired product without any enantioinduction (Scheme 11).



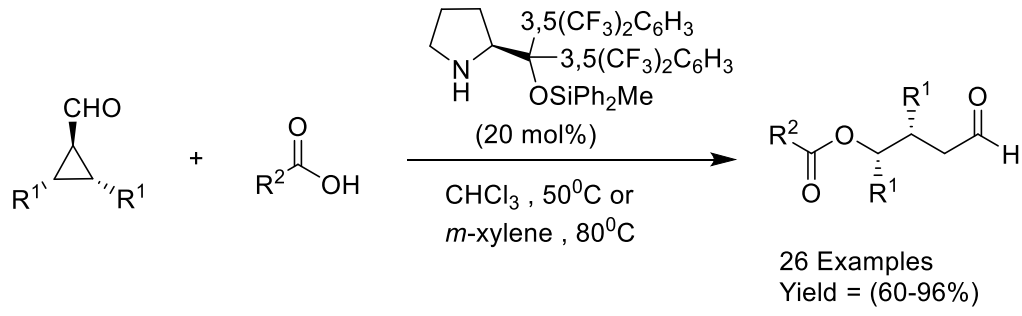
Scheme 11: Reaction with *meso*-cyclopropylcarbaldehyde and *p*-tolylsulfenyl chloride

After evaluating the reaction with respect to *meso*-cyclopropylcarbaldehyde, the scope was varied with the cyclopropylcarbaldehyde to determine the limitations of the strategy. Replacing the cyclohexyl ring with two ethyl moieties resulted in prolonged reaction time, because of the loss of ring strain and greater steric hindrance (Scheme 12).



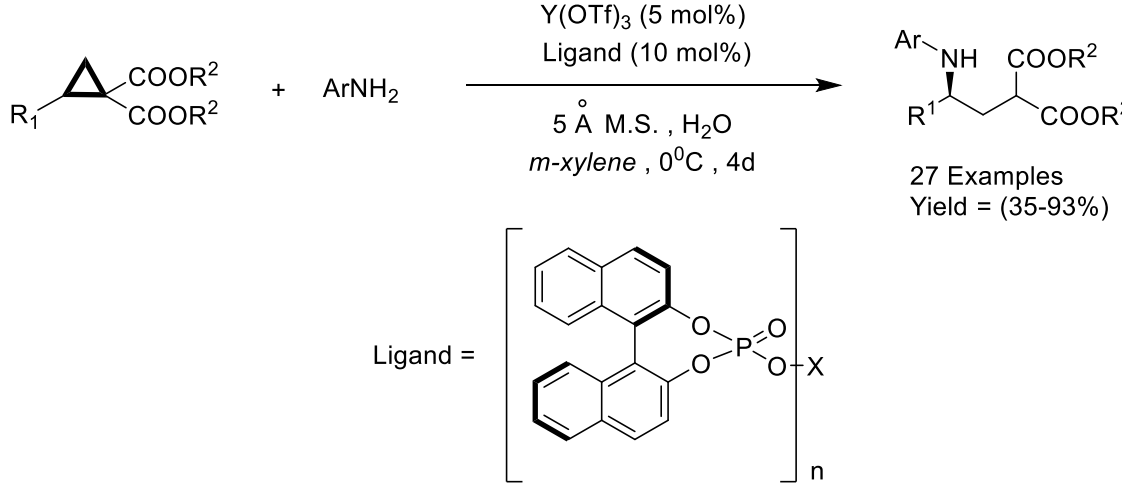
Scheme 12: Reaction with bulky cyclopropylcarbaldehyde and *p*-tolylsulfenyl chloride

Even carboxylic acids were used[10] as proficient pro-nucleophilesfor promoting the ring-opening of formyl cyclopropanes under the presence of chiral catalyst (Scheme 13). The reaction came up with excellent yields and also imposed stereoselectivities after the ring-opening procedure. This versatile reaction methodology was successful with wide range of substrates with the provision of using α and β amino acids as pro-nucleophiles, which widened the possibility of applying the protocol to the bioconjugation of peptide-type molecules. Mechanistic studies indicated that the reaction went through an SN^2 type pathway where catalyst was involved in the stereo-differentiation of the chemically equivalent carbon atoms present in the meso-cyclopropane.



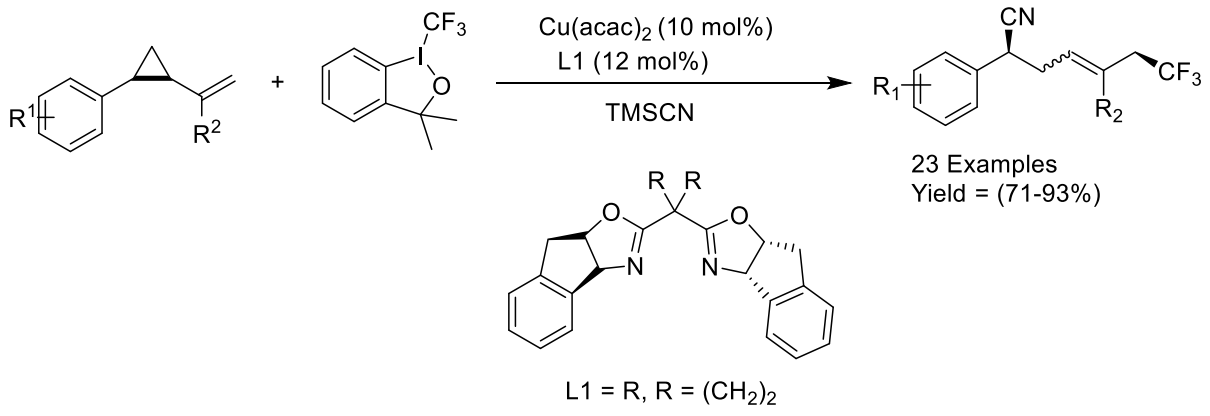
Scheme 13: Enantioselective ring-opening of formylcyclopropanes

Another efficient enantioselective ring-opening reaction using donor-acceptor cyclopropanes with primary arylamines was successfully developed[11] by Luo *et al*. through a chiral Lewis acid catalyst (Scheme 14). This bimetallic catalyst performed bifunctional catalysis, which enabled the reaction to occur with much ease. It also showed that the enantioselectivity of the bimetallic catalyst was related to the size of corresponding metal ions. Further stereochemical experiments suggested that the asymmetric ring-opening reaction could be described as a SN^2 type of ring-opening process confirming the occurrence of ligand exchange or transmetallation in the formation of bimetallic complex.



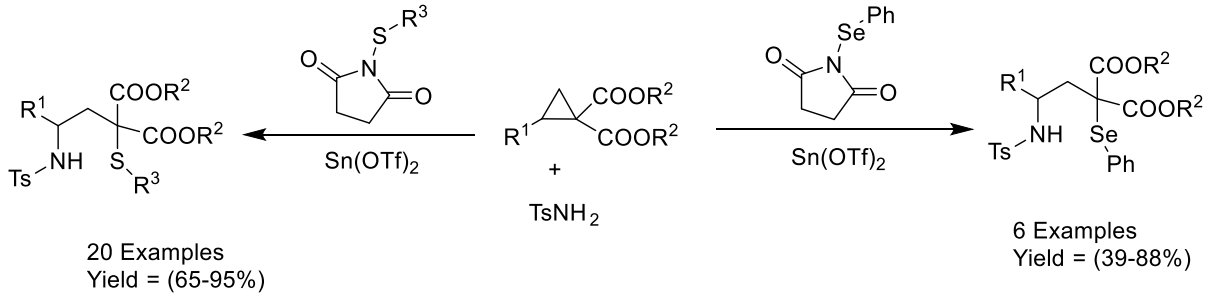
Scheme 14: Asymmetric ring-opening of Donor−Acceptor cyclopropanes with primary arylamines

Wang and his team reported[12] a Cu-catalyzed enantioselective 1, 5-cyano trifluoromethylation with Togni's reagent as the source of trifluoromethyl moiety (Scheme 15). Their method demonstrated high enantioselectivity and wide substrate scope under mild conditions. The novel radical relay strategy offered a new solution for remote enantioselective functionalization of alkenes and further showed the way for facile synthesis of chiral CF_3-containing alkenyl organonitriles.



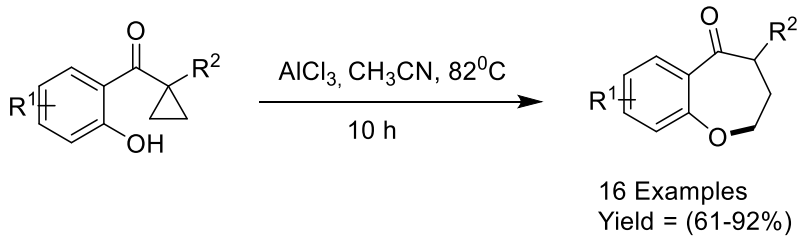
Scheme 15: Enantioselective Cu-catalyzed 1, 5-cyanotrifluoromethylation of vinylcyclopropanes

A new type of 1, 3-aminothiolationand 1, 3-aminoselenation protocol was introduced[13] by ring-opening of Donor-Acceptor cyclopropanes (Scheme 16). The catalyst was chosen as the Lewis acid in this three-component approach with tosyl amides used as nucleophiles. In this process cyclopropanes were utilised as a masked zwitter-ion and chalcogenosuccinimides were used as electrophilic components. The transformation was compatible with various donors including electron-rich and electron-deficient aryl moieties.



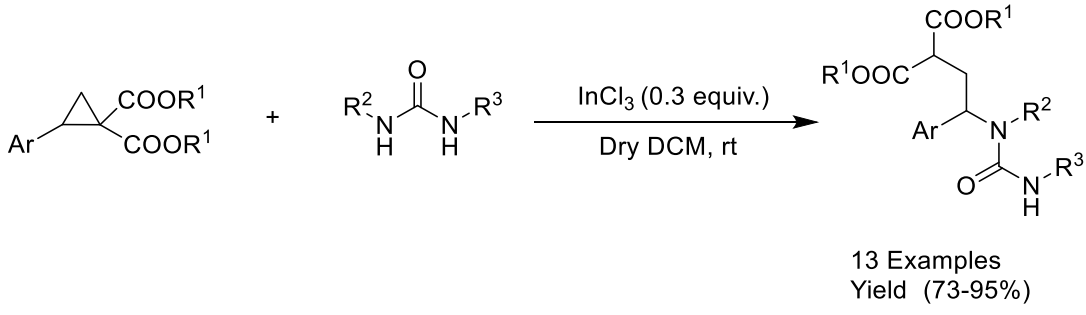
Scheme 16: Ring-opening 1, 3-aminochalcogenation of donor-acceptor cyclopropanes

Cao *et al*. reported[14] an efficient and facile method for the synthesis ofsubstituted 4-benzoyl-3, 4-dihydrobenzo[*b*]oxepin-5(2H)-one derivatives from cyclopropanes (Scheme 17), which involved an intramolecular ring-opening cyclization procedure. This protocol was associated with mild reaction conditions, high atom economy, increased yields and broader synthetic utility of the final product.



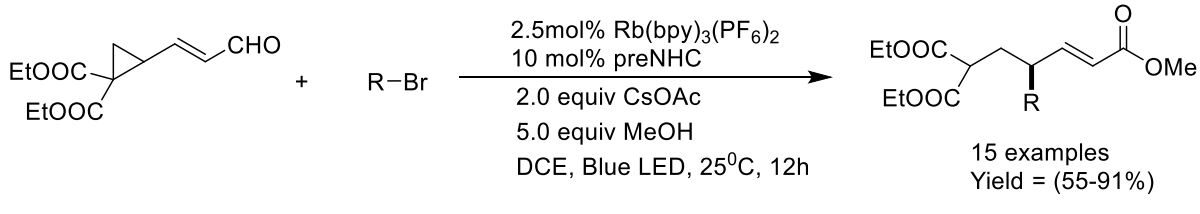
Scheme 17: Intramolecular ring-opening cyclization of specific cyclopropanes

Another methodology[15] made the use of readily available Donor-Acceptor Cyclopropanes (DACs) towards the synthesis of highly functionalized tetrahydropyrimidinones (Scheme 18). The proposed stepwise one-pot methodology worked really well for synthesizing both symmetrical and unsymmetrical urea containing tetrahydro-pyrimidinones. Though electron rich DACs and (di)alkyloxyurea were used as useful substrates in this transformation, electron deficient DACs with dialkylurea showed decreased results.



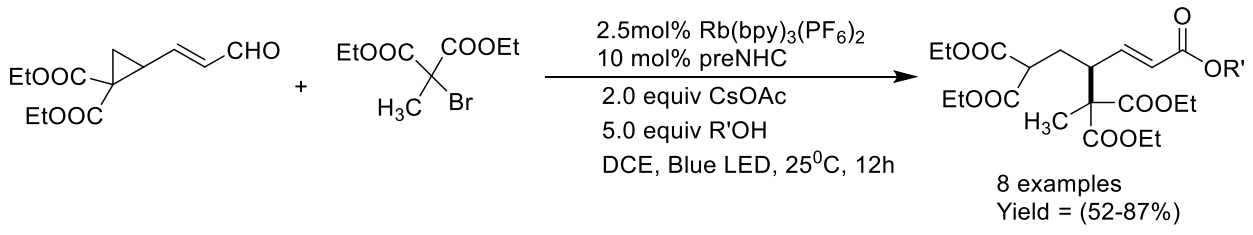
Scheme 18: Reaction of Donor - Acceptor Cyclopropane (DAC) with substituted ureas

Ye and his team established[16] a radical mediated photo N-heterocyclic carrbene (NHC) co-catalyzed ring-opening of C−C bond in cyclopropane-enal system following γ-alkylation with a halogenated compounds (Scheme 19). This reaction had the advantage of exclusive γ-regioselectivity, acceptance of different functional groups and comparatively mild reaction conditions.



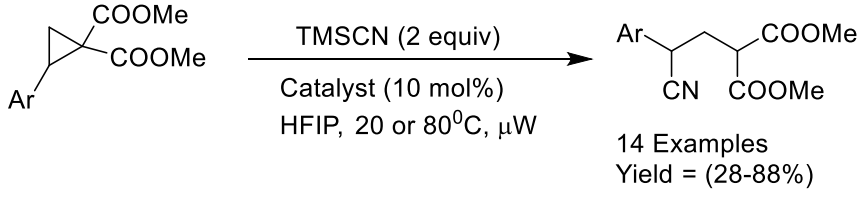
Scheme 19: γ-alkylation of cyclopropaneenals with alkyl electrophiles

It was noted that primary alcohols with both electron-donating and electron-withdrawing groups attached with them worked well for the reaction, furnishing the corresponding desired products with moderate to excellent yields (Scheme 20).



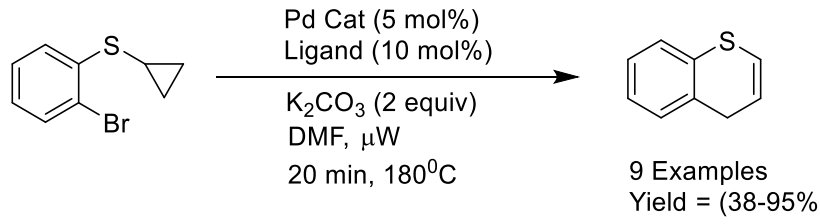
Scheme 20: γ-alkylation of cyclopropane-enals with nucleophiles

A novel technique for the ring opening of Donor-Acceptor (DA) cyclopropanes with trimethylsilyl cyanide was proposed[17] providing direct access to the synthetically important γ-cyanoesters (Scheme 21), which act as important building blocks towards wide range of bioactive skeletons. On the other hand reaction of DA cyclopropanes with sodium cyanide under thermal condition produced 2-arylsuccinonitriles in dipolar solvents. Even when DA cyclopropanes were reacted with trimethylsilyl-isocyanate and *N*-silylated secondary amines under proper reaction condition γ-aminobutyric acid derivatives were prepared via ring opening process.



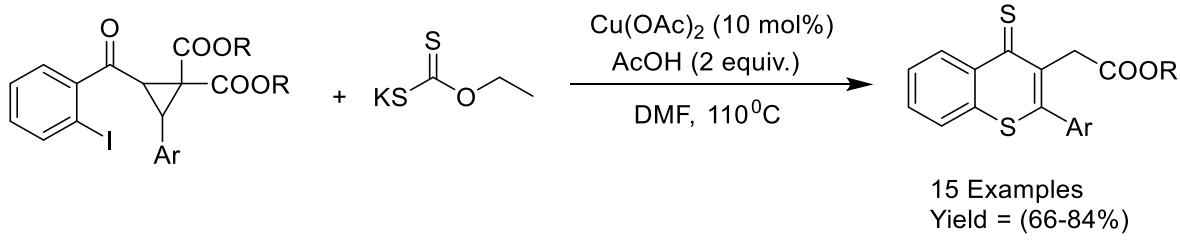
Scheme 21: Ring opening of Donor-Acceptor Cyclopropanes with cyanide

Ponra *et al*. reported[18] new Pd-catalyzed ring-opening of cyclopropane-substituted thioethers involving intramolecular trapping of intermediately formed arylpalladium species to provide thiochromene derivatives (Scheme 22). This method was a modification to other methods where cyclopropylamines underwent ring-opening reaction using bulkier electron-donating phosphines as ligand and explored an unmatched access to thiochromenes.



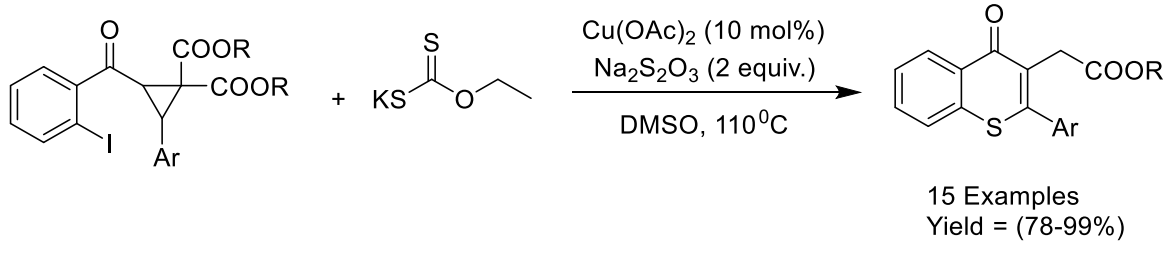
Scheme 22: Palladium catalyzed ring-opening of cyclopropanes

Sundaravelu *et al*. revealed[19] an efficient Cu-catalyzed domino approach for the preparation of 3-alkyl-carbonated thioflavothiones using intramolecular ring opening reaction of easily accessible halosubstituted D-A cyclopropanes with xanthates (Schemes 23 and 24). This was one of the pioneering examples that utilized intramolecular D-A cyclopropane ring opening with xanthate, leading to oxidation and generated molecular I_2.



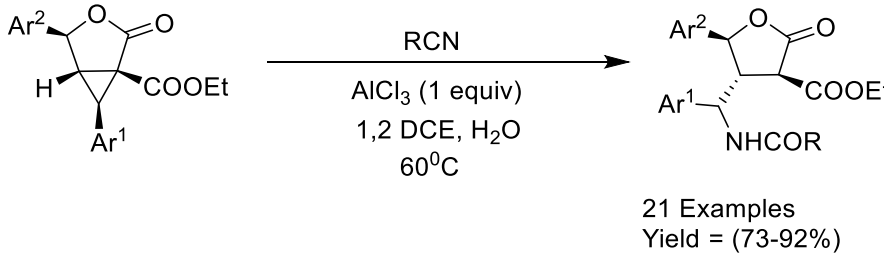
Scheme 23: Synthesis of 3-alkyl-substituted thioflavothiones (I)

Moreover, the methodology was extended towards the domino synthesis of 3-alkyl-carbonated thioflavones in a chemoselective fashion. In the course of reaction it was found that the substituents at the *ortho* and *meta* positions of phenyl ring introduced axial chirality to the molecules. The charge-transfer complex formed by the reaction of in-situ-generated iodine and DMSO was expected to catalyze the conversion of thioketones to ketones.



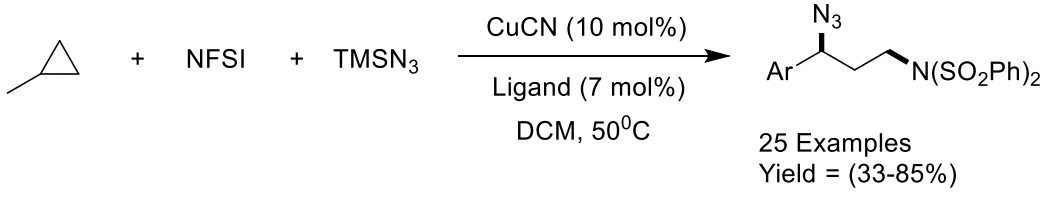
Scheme 24: Synthesis of 3-alkyl-substituted thioflavones (II)

An efficient methodology for aluminium (III) chloride catalysed diastereoselective synthesis of 3, 4, 5-trisubstituted γ-butyrolactones was developed[20] using fused D-A cyclopropanes and aliphatic nitriles (Scheme 25). When D-A cyclopropanes with aryl ring substituted with electron donating, and electron withdrawing substituents were reacted with acetonitrile, the respective trisubstituted γ-butyrolactones were obtained in satisfactory yields. This operationally simple reaction was thought to proceed through a nucleophilc addition of H_2O to the nitrilium ion intermediate and furnish the products in moderate to high yields.



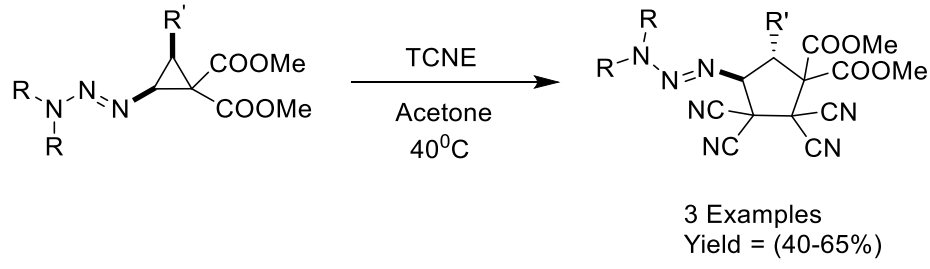
Scheme 25: $AlCl_3$-promoted Ritter type ring opening reaction

Wang *et al*. reported[21] an interesting and effective Cu-catalyzed 1, 3-aminoazidation of arylcyclopropanes using N-fluorobenzenesulfonimide (NFSI) and trimethylsilylazide ($TMSN_3$) for preparing several 1, 3-diamines from readily available starting materials under mild reaction conditions (Scheme 26). Arylcyclopropanes having either electron-donating or electron-withdrawing groups at the *para*-position of the benzene ring reacted smoothly to give the corresponding 1, 3-aminoazidation products in high yields. Even a gram-scale synthesis provided the product in around 80% yield. This transformation represented the example of 1, 3-diamination of cyclopropanes through introducing two different nitrogen sources simultaneously providing a new direction of ring-opening 1, 3-bisfunctionalization of cyclopropanes.



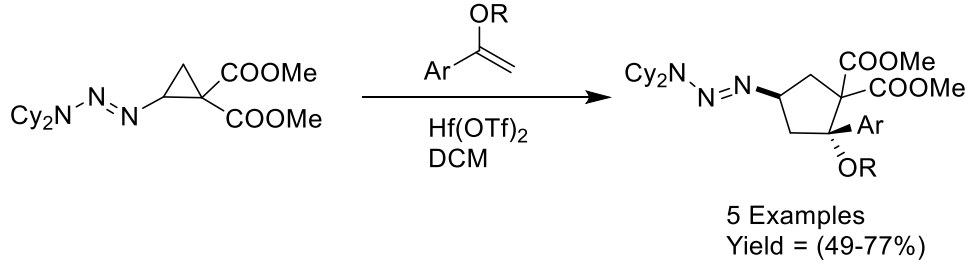
Scheme 26: Cu-catalyzed 1, 3-aminoazidation of arylcyclopropanes

The reaction of dialkyltriazene group substituted D−A cyclopropanes and dimethyl diazomalonate was reported[22] with simple Rh-catalyst (Schemes 27 and 28). In this case, the triazene group was found to promote extremely strong activation to the cyclopropane ring, making the reaction catalyst-free with methanol and tetracyanoethylene (TCNE).



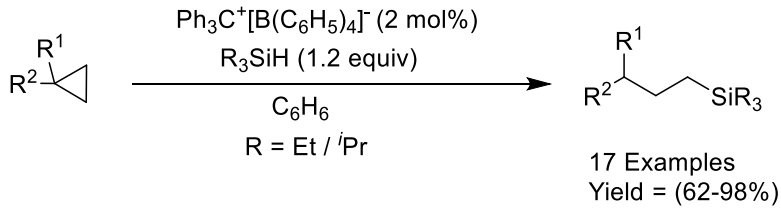
Scheme 27: Ring-opening of triazene-activated Donor−Acceptor Cyclopropanes

The efficacy of triazenylcyclopropanes was further explored by their compatibility to work with Lewis acid in the cycloaddition with silyl-enol ethers to generate functionalized cyclopentanes. Mechanistic investigations revealed that the bond between triazene and diester was broken first, depicting that itwas a better donor than arene or the cyclopropyl group and then methanol addition occurred involving the ester group.



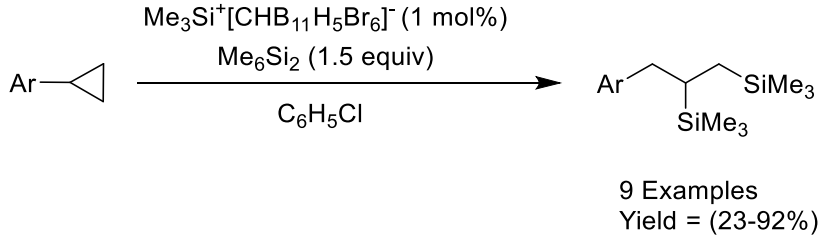
Scheme 28: Stereoselective ring-opening of triazene-activated Donor−Acceptor Cyclopropanes

Oestreich and his team demonstrated[23] a transition-metal-free alternative for C−C bond activation with the help of silylium ions promoted ring opening of unactivated cyclopropanes using hydrosilanes as hydride source (Scheme 29-30). This work demonstrated the ability of silylium ions to isomerize cyclopropyl to corresponding allyl groups, and give the silylium-ion-mediated disilylation with hexamethyl-disilane.



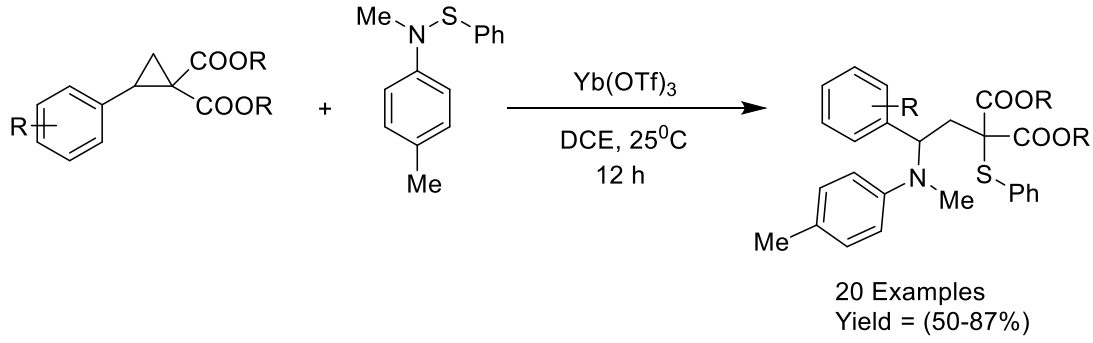
Scheme 29: Silylium-ion-promoted ring-opening hydrosilylation (I)

The process of hydrosilylation occurred with self-regeneration of the silylium ion, when the hydrosilane was not present in the reaction medium, isomerization of the cyclopropyl to an allyl group occurred with the in situ-formaton of α-olefins. These olefins underwent reaction with hexamethyl-disilane to provide the 1, 2-bis-silylated alkane directly.



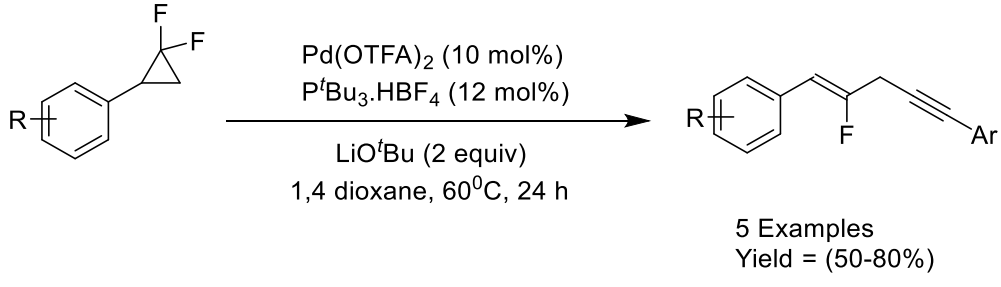
Scheme 30: Silylium-ion-promoted ring-opening hydrosilylation (II)

A unique $Yb(OTf)_3$ catalysed ring opening 1, 3-aminothiolation of D−A cyclopropanes was described[24] with excellent regioselectivity using sulfonamides guiding the synthesis of γ-aminated α-thiolated malonic diesters in high yields (Scheme 31). They first examined the scope of different D−A cyclopropanes in this reaction scheme where a series of D−A cyclopropanes with electron-donating, neutral, and electron-withdrawing substituents at the *para* position on the benzene ring underwent insertion reaction to give the corresponding 1, 3-bifunctionalized derivatives in high yields. But S-alkyl sulfonamides were unable to provide the desired product under the optimized conditions. Selective product formation, mild reaction conditions and wide functional group compatibility with broader substrate scope were some of the noteworthy features of this protocol. The reaction was again monitored using enantiopure D−A cyclopropane which further indicated that the ring opening was stereospecific and went through a SN^2 type pathway.



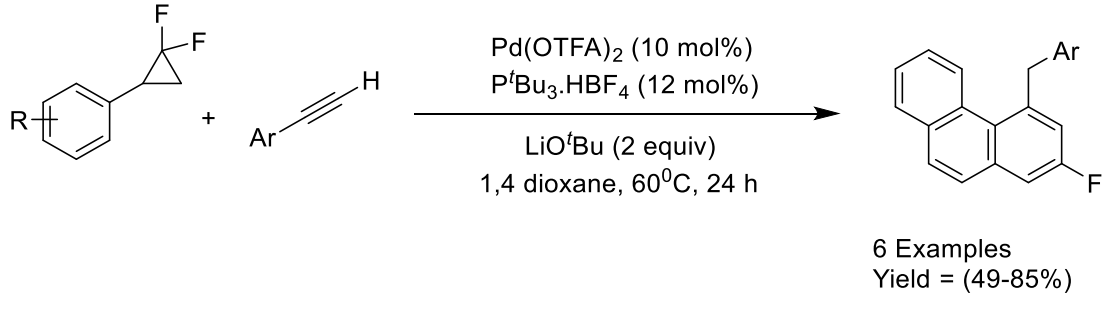
Scheme 31: Lewis acid catalyzed 1, 3-aminothiolation of Donor−Acceptor Cyclopropanes

Ebrahim *et al*. described[25] a new kind of palladium catalyzed C-C cross-coupling of gem-difluorinated cyclopropanes and alkynes showing admirable compatibility of the functional groups tolerating a number of terminal alkynes and gem-difluorinated cyclopropanes (Schemes 32 and 33). In addition to this, complex or modified gem-difluorinated cyclopropanes were also incorporated in this transformation.



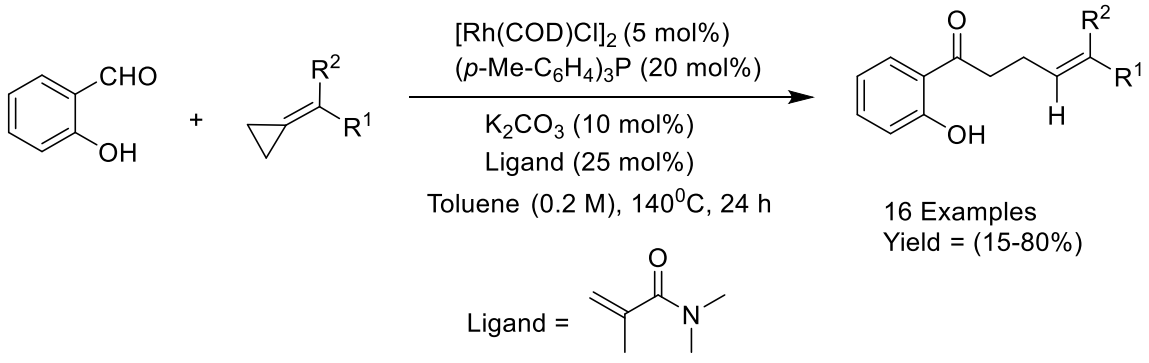
Scheme 32: Palladium-catalyzed ring-opening alkynylation of gem difluorinated cyclopropanes (I)

When aryl alkynes were used in this reaction, a variety of products were obtained by slightly modifying the reaction conditions. Even heteroaromatic alkynes also produced the corresponding products in good to high yields.



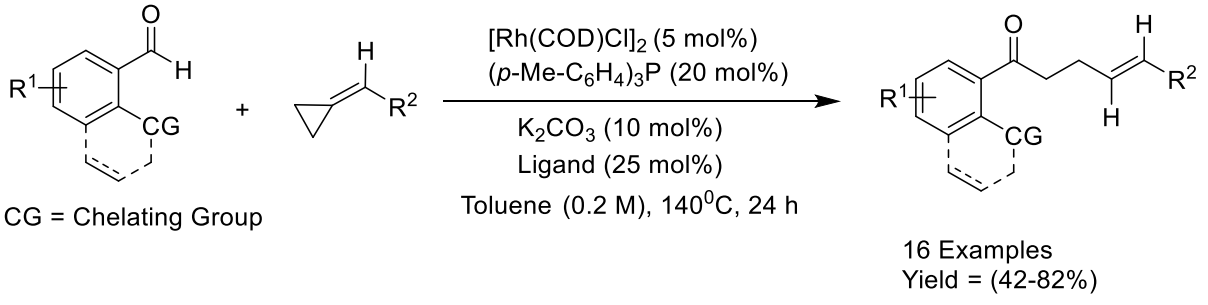
Scheme 33: Palladium-catalyzed ring-opening alkynylation of gem difluorinated cyclopropanes (II)

A Rh-catalyzed and chelation-assisted intermolecular ring-expanding hydroacylation of alkylidene cyclopropanes (ACPs) was reported[26] with O- and N-chelating aldehydes (Schemes 34 and 35). This reaction provided linear *trans*-γ, δ-unsaturated ketones through proximal selective C−C bond cleavage, using monosubstituted ACPs as the substrates.



Scheme 34: Rhodium-catalyzed Ring-Opening hydroacylation of alkylidene cyclopropanes (I)

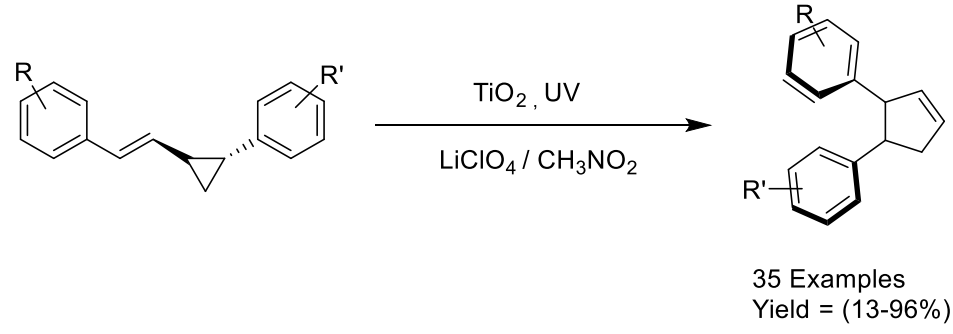
Mechanistic studies revealed that bidentate coordination of the N, N-dimethyl methacrylamide ligand to acyl-rhodium intermediates promoted the cyclopropane ring fragmentation followed by isomerization.



Scheme 35: Rhodium-catalyzed Ring-Opening hydroacylation of alkylidene cyclopropanes (II)

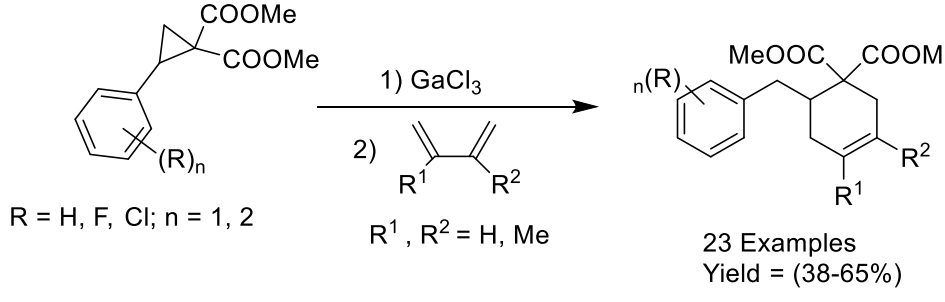
Another novel strategy in this field demonstrated[27] a radical cation mediated vinylcyclopropane rearrangement enabled by TiO_2 photocatalysis in $LiClO_4/CH_3NO_2$ medium (Scheme 36). The reactions were thought to be triggered by an oxidative single electron transfer, followed by direct ring-opening to provide radical cations.

SET combining with cyclopropyl ring-opening gave an excellent example of generating distonic radical ions, which have profound importance as reactive intermediates in synthetic organic chemistry. Moreover, this method was applied to vinyl cyclobutane for accessing six-membered rings, where a stepwise mechanism via radical cations was proposed based on the mechanistic studies and DFT calculations.



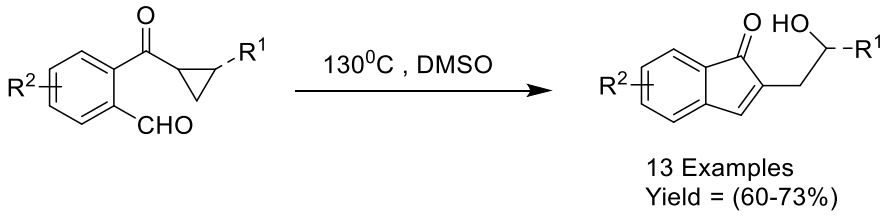
Scheme 36: Radical-cation mediated vinylcyclopropane rearrangements by TiO_2 photocatalysis

Belaya *et al*. introduced[28] a selective method for the formal [2+4] cycloaddition of DACs with conjugated dienes in the presence of $GaCl_3$ catalyst to generate cyclohex-3-ene-1, 1-dicarboxylates (Scheme 37). This process was governed by the formation of 1, 2-zwitterionic gallium complexes with the involvement of the carbocationic centre to terminal diene followed by 1, 6-cyclisation to the allyl position of the intermediate species.



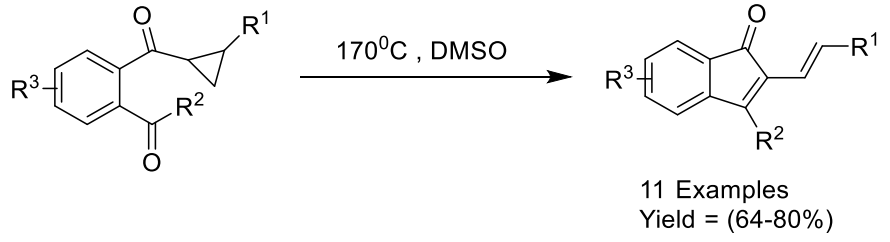
Scheme 37: $GaCl_3$ promoted formation of substituted cyclohexenes

An unprecedented metal-free and acid-free cascade ring opening followed by recyclization of cyclopropyl aryl ketones was established[29] by Ramasastry and his team (Schemes 38-39). This new strategy described the efficient and straightforward access to pentannulated aromatics and 2, 3-disubstituted fluorenones.



Scheme 38: Ring-opening of monoactivated cyclopropanes (I)

The mechanistic details elucidated the key advantages of this work including readily available starting materials, hassle-free procedural execution and good atom economy.



Scheme 39: Ring-opening of monoactivated cyclopropanes (II)

A comprehensive outline of recent protocols for cyclopropyl ring cleavage reactions has been presented here with different reagents, solvents and catalysts which fairly substantiate the essentiality and timeliness of the our investigation in this impressive field.

II.4.3. Present investigation:

II.4.3.1. Background of the investigation:

The rearrangement of cyclopropanes is considered to be a pivotal step in many important synthetic strategies. Cyclopropane ring cleavage reactions have been studied using a wide range of reactants using both thermal and photochemical ways with different electrophile, nucleophile and radical species. Aryl-substituted cyclopropylcarbinols (**I**) have been found to undergothe ring cleavage[7] on treatment with 2, 4, 6-trichloro-1, 3, 5-triazine (TCT) in combination with DMF to produce the homoallylic chloride or diene depending on the electronic nature and location of the substituents at the aromatic rings on the carbinol carbon as well as the cyclopropane ring. It was also be observed that the secondary benzylic alcoholic OH moiety was replaced with the acylamino moiety when treated with a nitrile in the presence of Amberlyst®-15(H) as the heterogeneous catalyst through the involvement of a carbocationic intermediate[30]. Therefore a curiosity was raised to note the effect of Amberlyst®-15(H) in acetonitrile towards the cleavage of cyclopropane ring system in aptly substituted cyclopropylcarbinols (**I**).

The probable outcomes have been delineated in Figure 1. Either **I** might undergo ipso-substitution to givethe product **II** (Step-A), although its possibility seems to be little becauseof the reluctance of the cyclopropane ring to undergo any cleavage in this case.Alternatively, **I** can undergo the ring scission to produce the diene (**III**) (Step-B) of homoallylic acetylamino substituted species (**IV**) (Step-C) depending on the electronic nature of the substituents along with their locations at the aromatic rings, analogous to theearlier observation[7] with TCT-DMF. One can also expecta mixture of (**III**) and (**IV**) depending on R and G.

Apart from the aforesaid issues, the importance of this study was also rested upon several factors. The proposed reaction utilizes a solid recyclable heterogeneous catalyst with water as the sole and innocuous by product. Thereby it minimizes the formation of waste and maximizes the atom economy in comparison to the earlier report[7] with TCT-DMF. Thus it seems to have the greater promise to be a better protocol in the light of sustainability for the construction of important molecular frameworks. So a detailed investigation has been undertaken in this direction.

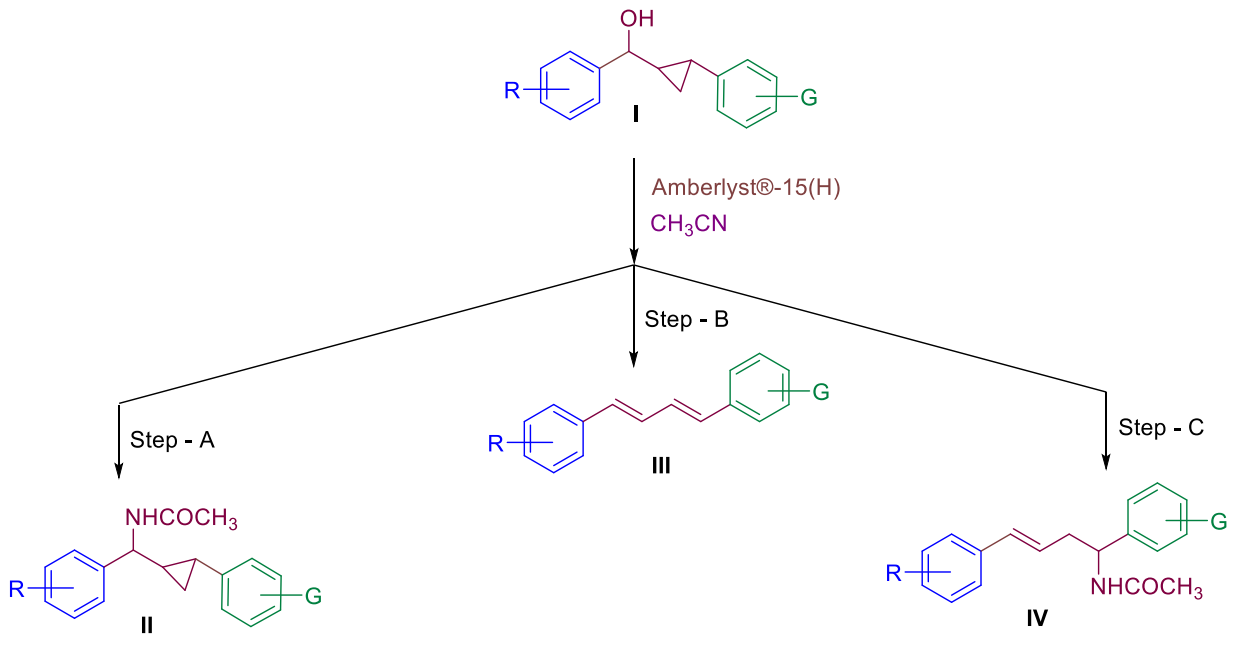
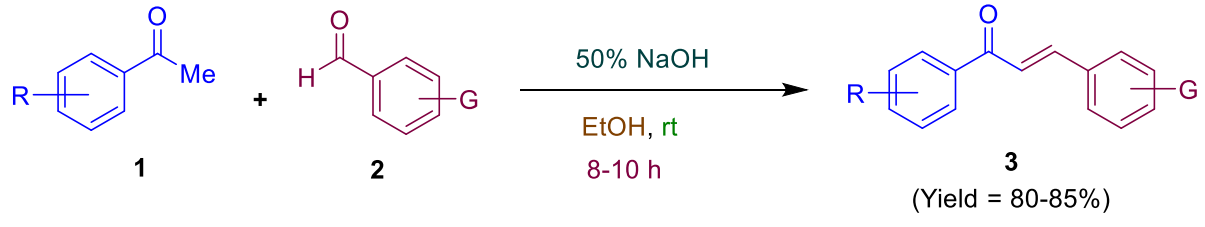


Figure 1: Possible outcomes of the effect of Amberlyst®-15(H) on cyclopropylcarbinols in acetonitrile

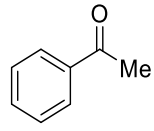
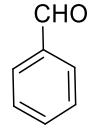
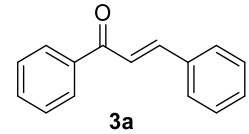
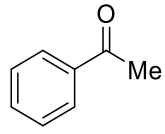
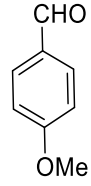
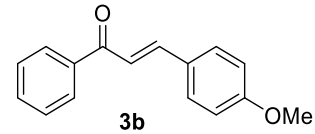
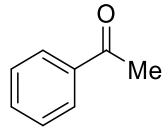
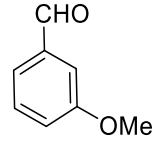
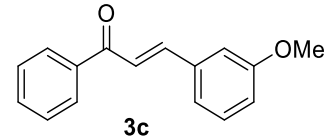
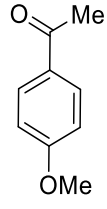
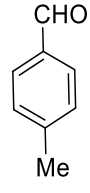
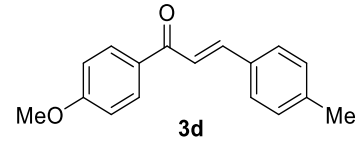
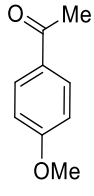
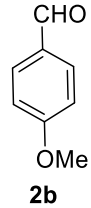
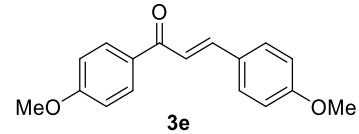
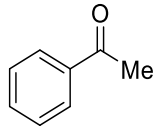
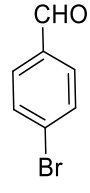
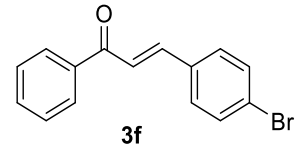
II.4.3.2. Results and Discussion:

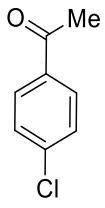
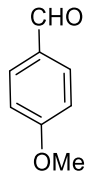
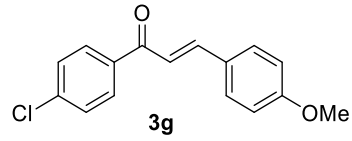
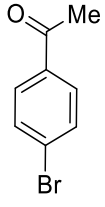
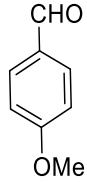
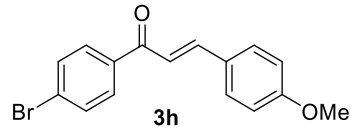
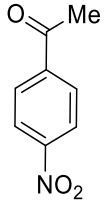
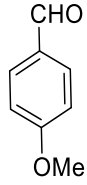
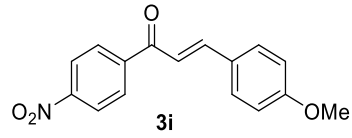
Chalcone is a simple and efficient scaffold found in many naturally occurring compounds, they are extensively used as an effective template for their convenient synthesis and capability to be converted into other beneficial structural motifs. For exploring the structural and reacting properties of cyclopropanes, first we prepared different chalcones; then sequentially converted them to our desired substrates. The preparation of chalcones (**3**) was carried out by taking different aromatic methylketones (**1**) and aromatic aldehydes (**2**) in presence of 50% NaOH and ethanol first at room temperature for 2-3 hours with occasional stirring then keeping the reaction mixture in refrigerator for 8 hours (Scheme 40).The results are furnished in Table 1.



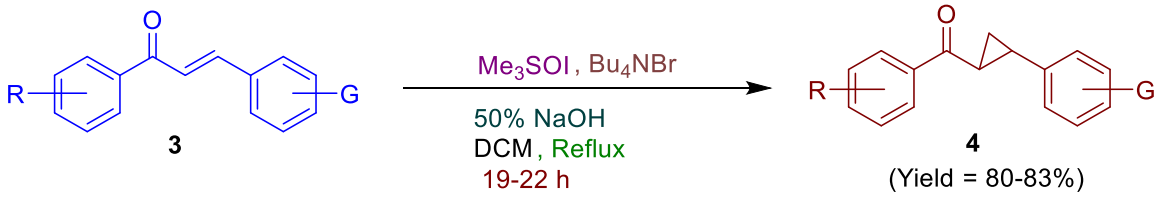
Scheme 40: Preparation of different chalcones (**3**)

Table 1: Reaction of different ketones (**1**) with aldehydes (**2**) to form chalcones (**3**) (as scheme 40)

Entry	Aromatic Ketone (1)	Aromatic Aldehyde (2)	Chalcone (3)	Time (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	9	83
2	 **1a**	 **2b**	 **3b**	8	83
3	 **1a**	 **2c**	 **3c**	8	82
4	 **1b**	 **2d**	 **3d**	8	84
5	 **1b**	 **2b**	 **3e**	8.5	85
6	 **1a**	 **2e**	 **3f**	8	82

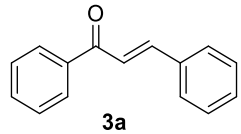
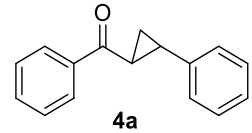
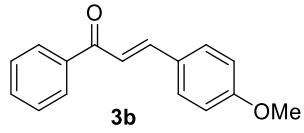
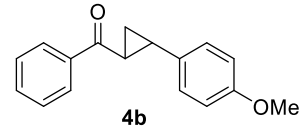
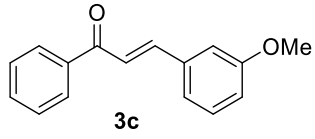
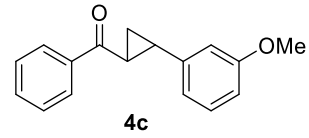
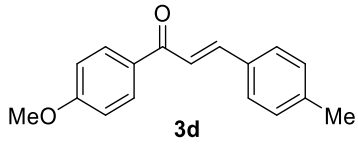
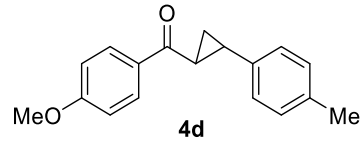
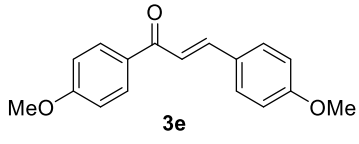
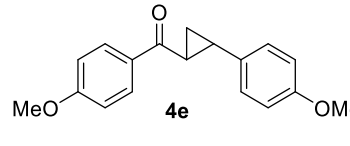
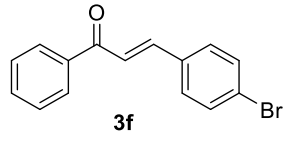
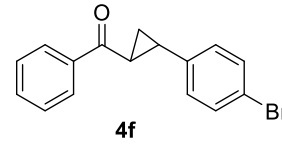
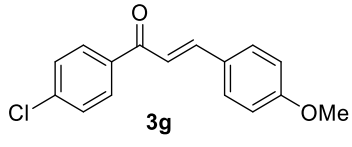
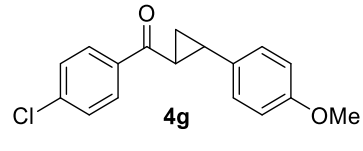
7	 **1c**	 **2b**	 **3g**	9	80
8	 **1d**	 **2b**	 **3h**	8.5	81
9	 **1e**	 **2b**	 **3i**	10	80

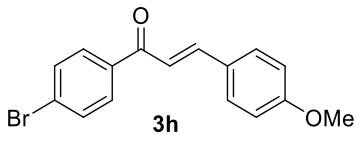
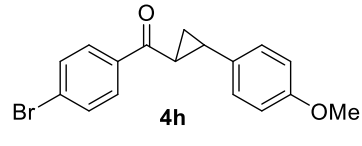
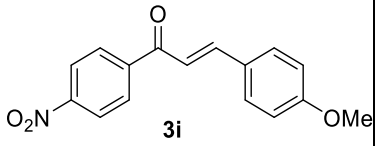
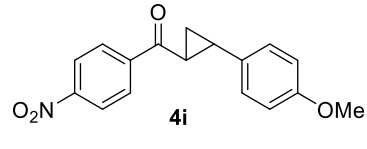
These chalcones (**3**) were then treated with trimethylsulfoxonium iodide and tetrabutylammonium bromide (TBAB) in dichloromethane (DCM) under refluxing condition with a few drops of 50% NaOH solution (Scheme 41) to obtain the cyclopropyl ketones **4**. The completion of cyclopropanation required long reaction time and the reaction was thoroughly monitored by thin layer chromatography (TLC). The results are presented in Table 2.



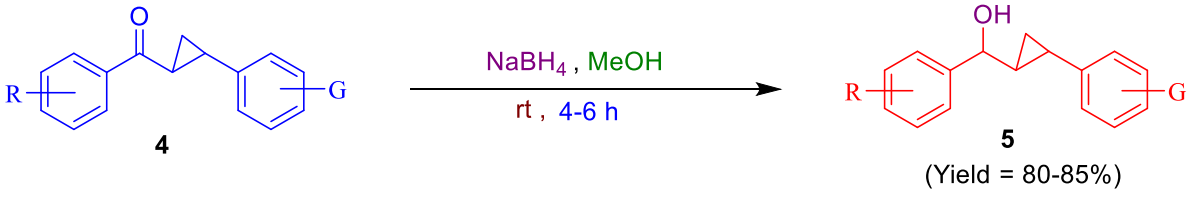
Scheme 41: Preparation of different cyclopropyl ketones (**4**)

Table 2: Reaction of chalcones (**3**) to form cyclopropyl ketones (**4**) (as Scheme 41)

Entry	Chalcone (3)	Cyclopropyl ketone (4)	Time (h)	Yield (%)
1	 **3a**	 **4a**	20	80
2	 **3b**	 **4b**	22	82
3	 **3c**	 **4c**	21	80
4	 **3d**	 **4d**	19	81
5	 **3e**	 **4e**	19	82
6	 **3f**	 **4f**	20	83
7	 **3g**	 **4g**	20	80

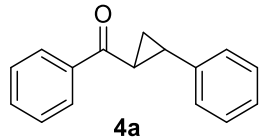
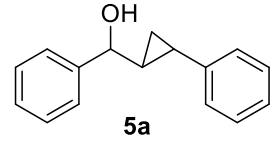
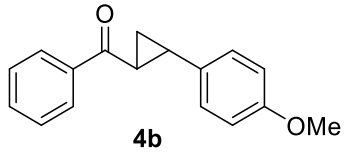
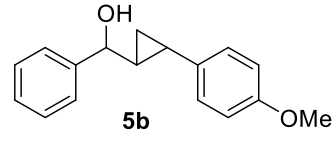
8	 **3h**	 **4h**	20	81
9	 **3i**	 **4i**	21	80

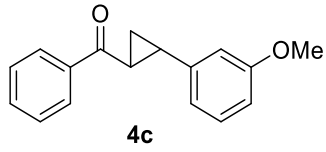
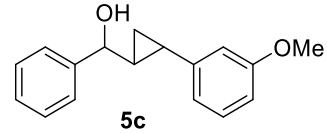
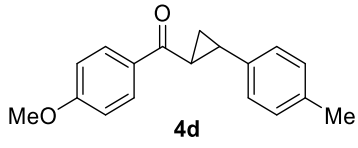
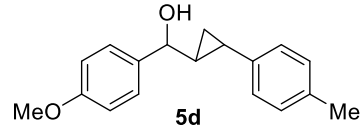
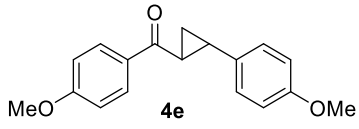
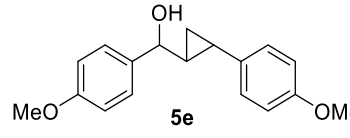
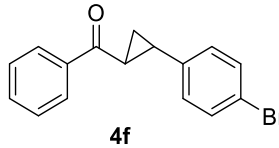
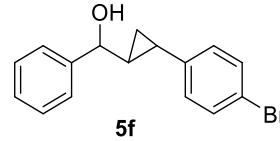
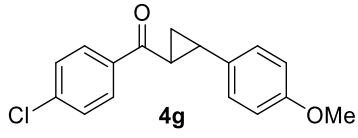
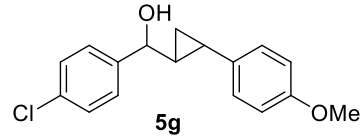
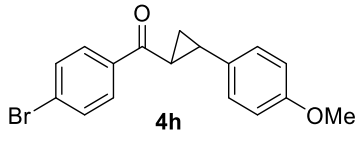
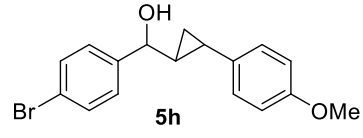
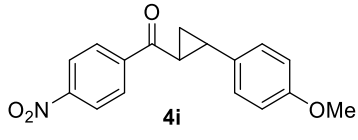
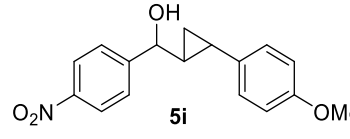
As shown in Table 2, a variety of cyclopropyl ketones (**4**) were prepared which were then subjected to reduction following the conventional $NaBH_4$/MeOH process for reducing the keto group to the corresponding alcohol moiety (Scheme 42). Thus a range of cyclopropyl carbinols (**5**) were obtained; the results are shown in Table 3.



Scheme 42: Reduction of different cyclopropyl ketones (**4**)

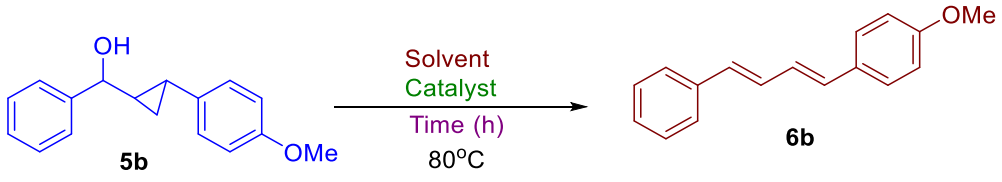
Table 3: Reduction of cyclopropyl ketones (**4**) to form cyclopropyl carbinols (**5**) (as Scheme 42)

Entry	Cyclopropyl ketone (4)	Cyclopropyl carbinol (5)	Time (h)	Yield (%)
1	 **4a**	 **5a**	5	82
2	 **4b**	 **5b**	5.5	83

3	 **4c**	 **5c**	5	81
4	 **4d**	 **5d**	4.5	84
5	 **4e**	 **5e**	4	85
6	 **4f**	 **5f**	5	84
7	 **4g**	 **5g**	6	80
8	 **4h**	 **5h**	5.5	81
9	 **4i**	 **5i**	6	80

These cyclopropylcarbinols (**5**) were the main substrates for further studies. Now it was aimed for the development of a synthetic protocol to provide exclusively the dienes from the cleavage of a cyclopropanol skeleton. The strategy was verified by reacting (2-(4-methoxyphenyl)cyclopropyl)(phenyl)methanol (**5b**) to obtain the corresponding conjugated

diene **6b** exclusively. To check the applicability of Amberlyst®-15(H) in this reaction, the reaction was carried out with **5b** (1 mmol) in presence of various catalysts along with different solvents at 80°C to produce 1-methoxy-4-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene(**6b**) (Scheme 43). The results are furnished in Table 4.



Scheme 43: Ring cleavage of (2-(4-methoxyphenyl)cyclopropyl)(phenyl)methanol (**5b**)

Table 4: Optimization of the reaction conditions[a] with **5b** (1 mmol) in different catalysts and solvents

Entry	Catalyst	Amount (mg)	Solvent	Time (h)	Yield of 6b (%)[b]
1	TCT	40	DMF	8	42
2	TCT	50	Toluene	8	21
3	Amberlite (IR-45)	40	DMF	6	trace
4	Dowex-50	50	DMF	8	12
5	Amberlyst®-15(H)	50	DMF	8	24
6	Amberlyst®-15(H)	40	Toluene	6	36
7	**Amberlyst®-15(H)**	**50**	**Acetonitrile**	**6**	**85**
8	Urea nitrate	50	Acetonitrile	6	14
9	Urea nitrate	80	Toluene	8	trace
10	Alumina (acidic)	70	Acetonitrile	6	trace
11	Ni-Alumina	70	Acetonitrile	6	20

[a]Reaction conditions: **5b** (1.0 mmol), catalyst and time (as indicated), solvent (3 ml)

[b]Yield of the isolated product.

As shown in Table 4, first we attempted the reaction with TCT, where the yield was only 42% using DMF (Entry 1, lower yield compared to earlier report[7] due to use of sub-stoichiometric amount of TCT) and 21% using toluene as the reaction medium (Entry 2). Then this reaction was performed with different solid acid resins, the well-known resins

Amberlite (IR-45) produced the desired diene in trace amount (Entry 3) and Dowex-50 gave only 12% of the product **6b** in DMF (Entry 4). Amberlyst®-15(H) was used in both DMF and toluene, it gave 24% yield of diene in DMF (Entry 5) and 36% of the diene in toluene (Entry 6). The reaction was optimized with 50 mg Amberlyst®-15(H) in acetonitrile solvent at 80°C for 6h affording 85% of the diene **6b** (Entry 7). Urea nitrate was chosen as a possible alternative of Amberlyst®-15(H) and the reaction was carried out in both acetonitrile and toluene giving 14% of the product in acetonitrile (Entry 8) and only trace amount in toluene (Entry 9). Other supports such as alumina (acidic) and Ni-alumina were also unsuccessful to provide the desired product with satisfactory yield (entries 10 and 11).

This reaction thus came out as an efficient method for converting cyclopropyl carbinols to the corresponding dienes using Amberlyst®-15(H). The catalyst used in this process was recovered by normal filtration, repetitively washed with ethyl acetate, dried and further reused upto 5 times with marginal loss of its catalytic activity (Figure 2).

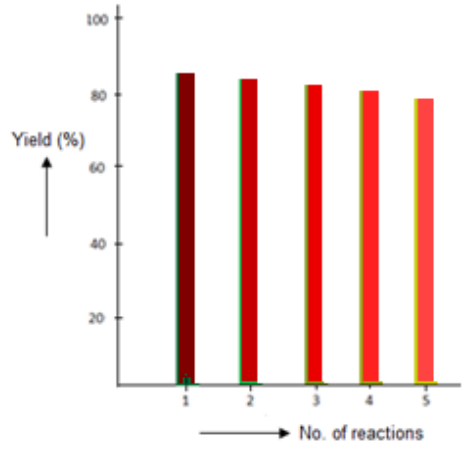
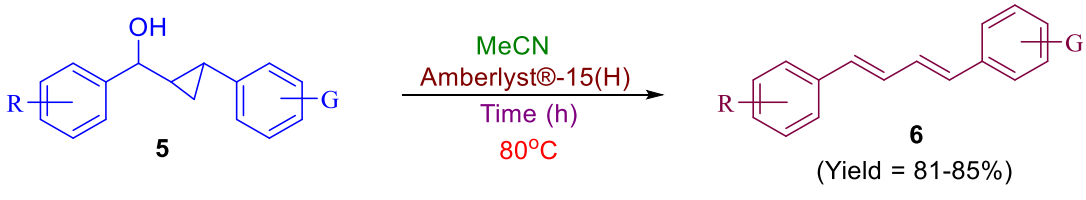


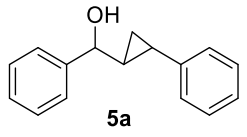
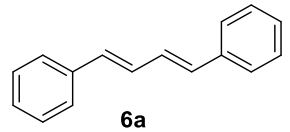
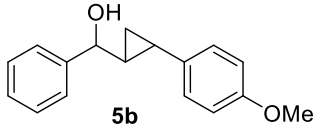
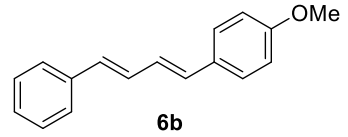
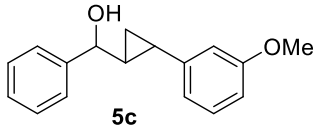
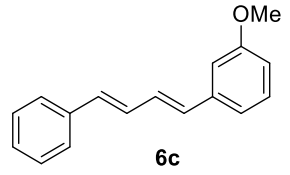
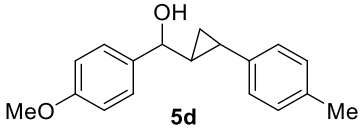
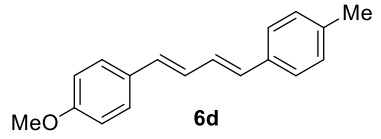
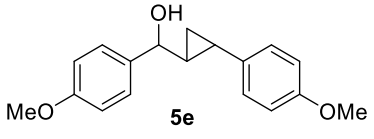
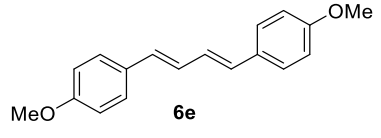
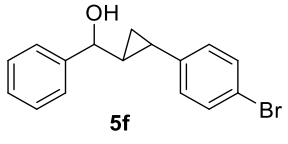
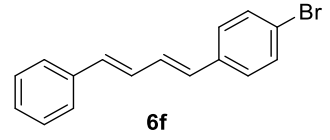
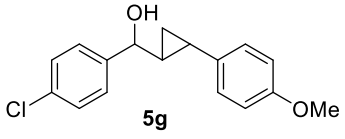
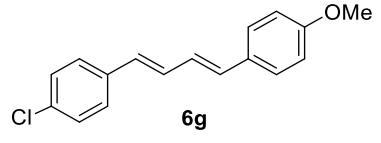
Figure 2: Recycling of Amberlyst®-15(H) using **5b** in MeCN at 80°C for 6 hours; % of yield was the isolated yield of **6b**

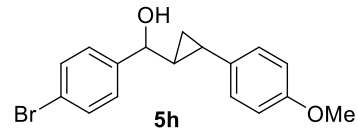
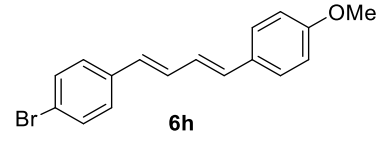
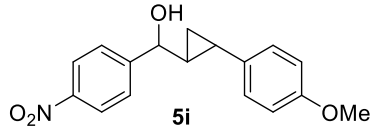
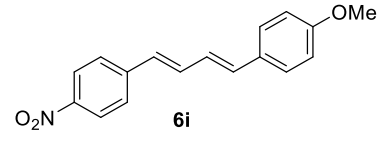
A wide range of dienes (**6**) were prepared with good to high yields using this method (Scheme 44) by changing the substituents at both the phenyl rings. The results are shown in Table 5.



Scheme 44: Synthesis of dienes (**6**) from cyclopropyl carbinols (**5**) using Amberlyst®-15(H)

Table 5: Reaction of cyclopropylcarbinols (**5**) to form corresponding dienes (**6**) (as Scheme 44)

Entry	Cyclopropyl carbinol (5)	Diene (6)	Time (h)	Yield (%)
1	 **5a**	 **6a**	7	83
2	 **5b**	 **6b**	6	85
3	 **5c**	 **6c**	8	81
4	 **5d**	 **6d**	6	84
5	 **5e**	 **6e**	5.5	85
6	 **5f**	 **6f**	6	82
7	 **5g**	 **6g**	8	81

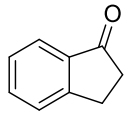
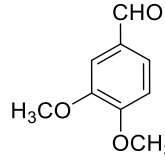
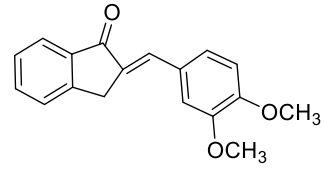
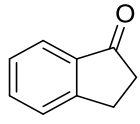
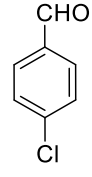
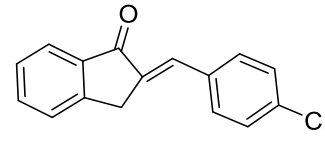
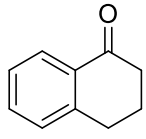
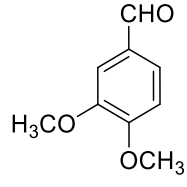
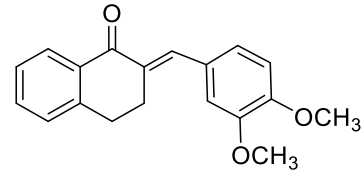
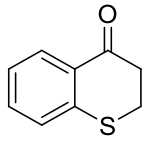
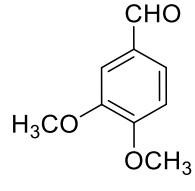
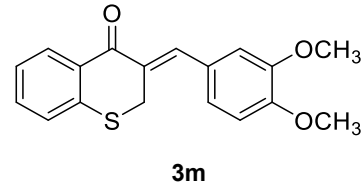
8	 **5h**	 **6h**	7.5	85
9	 **5i**	 **6i**	9	82

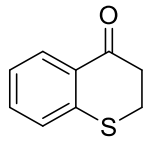
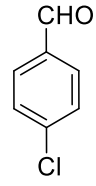
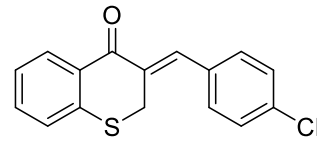
Following the present protocol, conjugated dienes were prepared exclusively by the ring opening of strained cyclopropane system. The yields refer to those of purified products obtained after isolation. Using the optimized reaction condition cyclopropanes havingun substituted phenyl ring or alkyl substituted phenyl rings were converted successfully to their corresponding dienes (**6a-6e**) with high yield. The occurrence of **6b** was confirmed by only one singlet at δ 3.83 in ^{1}H NMR (δ 55.3 in ^{13}C NMR) due to the –OMe group and the doublet at δ 6.63 further substantiated the presence of conjugated double bond. The non-occurrence of any product bearing the acetylamino (-$NHCOCH_3$) moiety was confirmed by the absence of any singlet around δ 2.20 in ^{1}H NMR spectra of all the compounds. Especially when **5c** was previously treated with TCT-DMF combination[7] to cleave the cyclopropane ring, homoallylic chloride was the final product instead of the diene, but under the present strategy thedesired diene **6c** was obtained as the exclusive product. Even the absence of any other peak in the aliphatic region suggested the exclusive cleavage of cyclopropyl ring. For **5d** where *p*-Me group was present as G, homoallylic chloride was found as the major product with minor formation of the diene in another earlier report,[35] but in our study the diene **6d** was formed exclusively. The merit of the reaction was judged by switching over the groups present on the two phenyl rings for observing the electronic effect on the substrate scope. Previously prepared **5f** having bromo group present at the *para* position of distant phenyl ring was checked under the reaction condition, and the reaction went successfully to give the diene **6f** as the exclusive product with 82% yield. Then the substrates were prepared by taking halogen and methoxy groups at the two phenyl rings, when –Cl and –Br were present at the *para* position of near phenyl group and –OMe was present at the *para* position of distant phenyl ring, the reactions went smoothly giving the products **6g** and **6h** with 81% and 85% yields respectively. But when the substrates having –OMe group at the *para* position of near phenyl group and –Cl or –Br at the *para* position of distant phenyl ring were reacted

under this present protocol, the desired dienes were in very low amount along with several unwanted by-products. Similar case happened when $–NO_2$ and –OMe were chosen as the substitutes. While **5i** gave the diene **6i** with 82% yield, the other isomeric substrate, having the positions of $–NO_2$ and –OMe groups interchanged, failed to react under this protocol.

Further exploration of this protocol was attempted with a thought of combining cyclic ketones with different aldehydes to generate some structurally beneficial chalcone molecules. The condensation was done in a basic medium for indanone (**1f)** and tetralone (**1g)**.But for thiochromanone (**1h)** the condensation was performed in acidic medium as the basic medium promotes the opening the heterocyclic ring to the precursor components. Results are presented in Table 6.

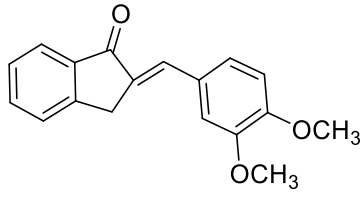
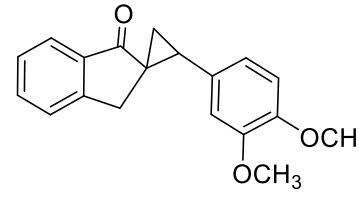
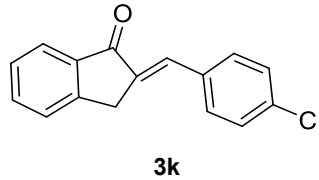
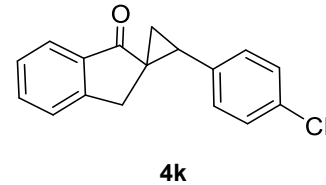
Table 6: Reaction of cyclicketones (**1**) with aldehydes (**2**) to form chalcones (**3**)

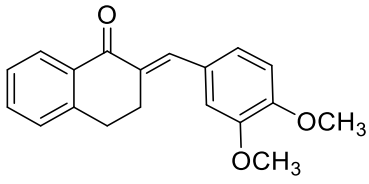
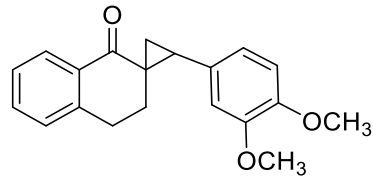
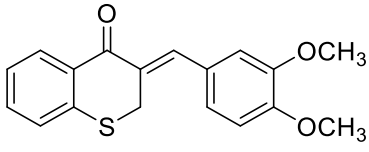
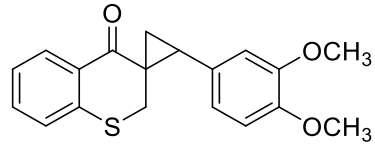
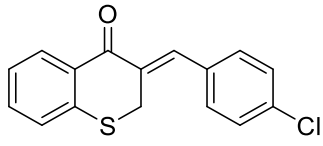
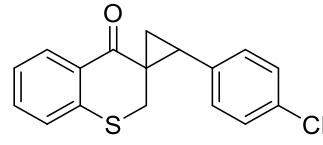
Entry	Cyclic Ketone (1)	Aromatic Aldehyde (2)	Chalcone (3)	Time (h)	Yield (%)
1	 **1f**	 **2f**	 **3j**	4	87
2	 **1f**	 **2g**	 **3k**	5	84
3	 **1g**	 **2f**	 **3l**	4	85
4	 **1h**	 **2f**	 **3m**	12	65

5	 **1h**	 **2g**	 **3n**	12	72

Chalcones **3j** and **3k** were prepared by taking equimolecular amounts of **1f** with **2f** and **2g** respectively in a mortar; they were mixed and crushed together with a pestle until it turned into brown oil. Finely ground solid NaOH was further added to the reaction mixture and it was continuously mixed in the absence of any solvent until it became solid. Then the mixture was allowed to stand for 15 minutes and then acidified with 10% aqueous HCl. Next the solid product chalcones were filtered, washed with water and dried to come out with 87% and 84% yield respectively. Chalcone **3l** was formed with 85% yield from **1g** and **2f** following the aforesaid process. Chalcones **3m** and **3n** were prepared by the aldol condensation of **1h** with **2f** and **2g** respectively followed by dehydration in the presence of conc. HCl and methanol under refluxing condition for 12 hours. The products were filtered out and washed cautiously with small amount of cold methanol. Yields were 65% and 72% respectively. These chalcones (**3j**-**3n**) were then cyclopropanated using previously mentioned protocol and all of them gave their corresponding cyclopropyl ketones (**4j**-**4n**) in high yields. The results are presented in Table 7.

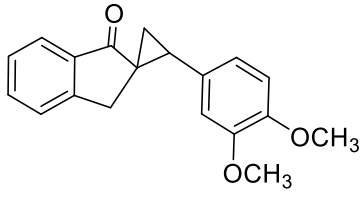
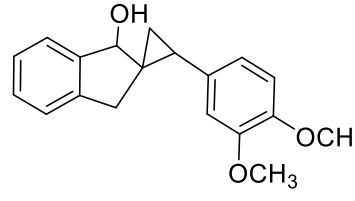
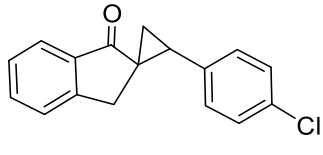
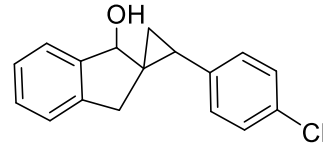
Table 7: Reaction of chalcone (**3j-3n**) to form cyclopropyl ketones (**4j-4n**)

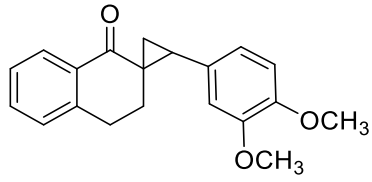
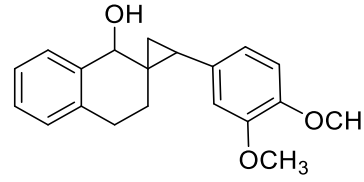
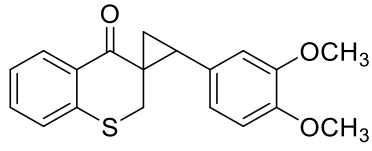
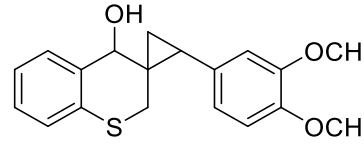
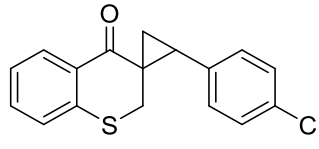
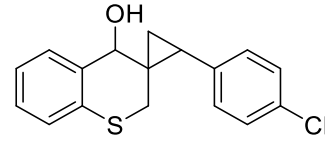
Entry	Chalcone (3)	Cyclopropyl ketone (4)	Time (h)	Yield (%)
1	 **3j**	 **4j**	27	88
2	 **3k**	 **4k**	25	83

3	 **3l**	 **4l**	27	85
4	 **3m**	 **4m**	28	84
5	 **3n**	 **4n**	25	82

These cyclopropyl ketones (**4j-4n**) were then subjected to reduction under the conventional $NaBH_4$/MeOH system at room temperature, where they produced the corresponding cyclopropyl carbinols (**5j-5n**) as the sole product with around 85% yield. The detailed results are presented in Table 8.

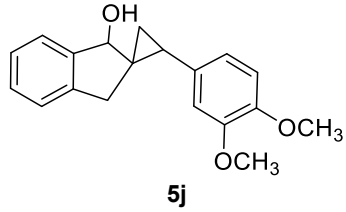
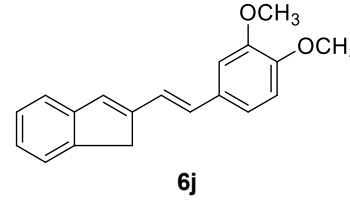
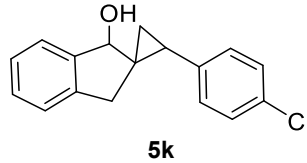
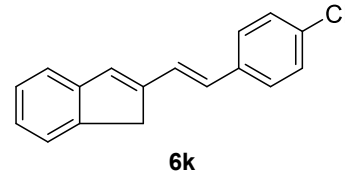
Table 8: Reduction of cyclopropyl ketones (**4j-4n**) to form cyclopropyl carbinols (**5j-5n**)

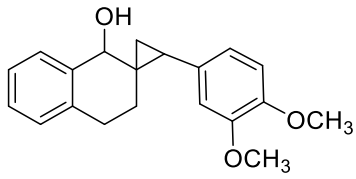
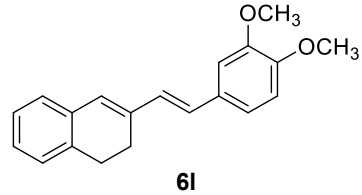
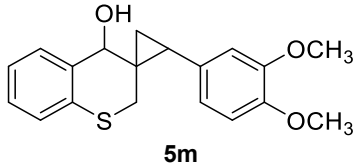
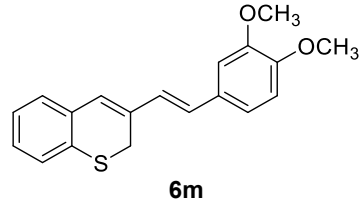
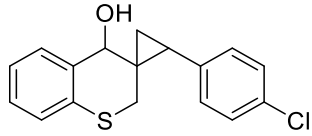
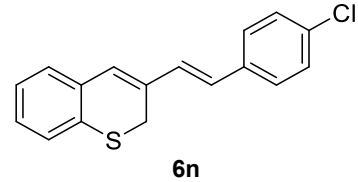
Entry	Cyclopropyl ketone (4)	Cyclopropyl carbinol (5)	Time (h)	Yield (%)
1	 **4j**	 **5j**	5.5	87
2	 **4k**	 **5k**	6	85

3	 **4l**	 **5l**	5.5	83
4	 **4m**	 **5m**	6	84
5	 **4n**	 **5n**	6	86

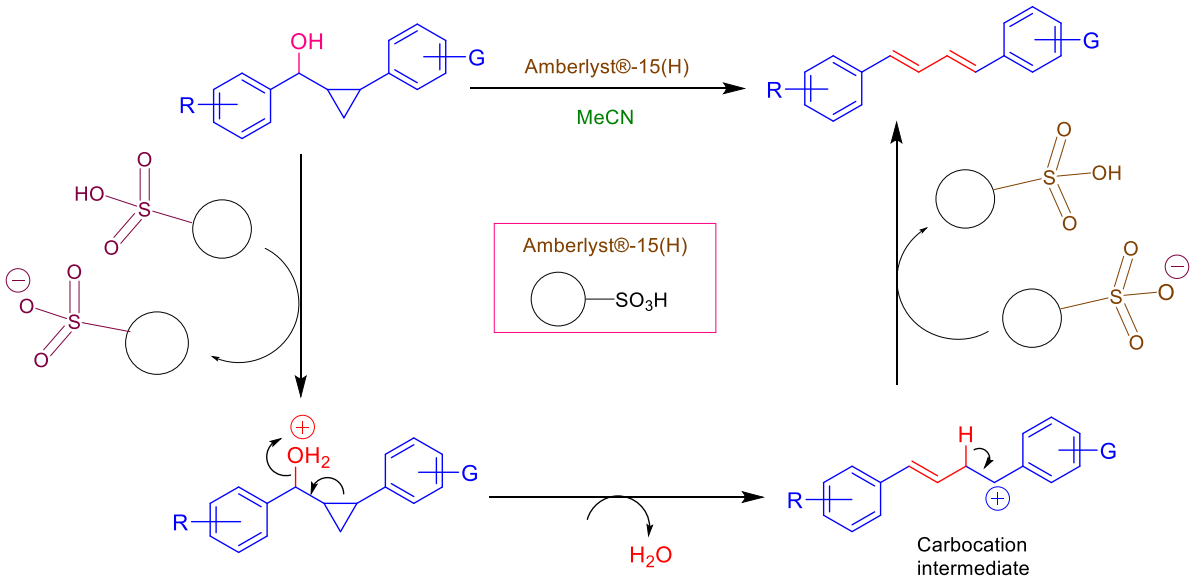
Thus the main substrate cyclopropylcarbinols (**5j-5n**) were prepared having a cyclic or heterocyclic ring present adjacent to it and were reacted with Amberlyst in MeCN as discussed before to discover the fate of the cyclopropane ring. As expected, after the reaction the cyclopropane ring was cleaved to produce the dienes (**6j-6n**). The results are presented in Table 9.

Table 9: Reaction of cyclopropylcarbinols (**5j-5n**) to form corresponding dienes (**6j-6n**)

Entry	Cyclopropyl carbinol (5)	Diene (6)	Time (h)	Yield (%)
1	 **5j**	 **6j**	6.5	87
2	 **5k**	 **6k**	7	85

3	 **5l**	 **6l**	5.5	86
4	 **5m**	 **6m**	6	85
5	 **5n**	 **6n**	6	83

Using the optimum reaction condition the cyclopropylcarbinols (**5j-5l**) were successfully converted to their corresponding conjugated dienes (**6j-6l**) with good yield. The occurrence of diene moiety was confirmed, for example, by the singlet at δ 6.56 (due to the olefinic hydrogen of the diene moiety) along with a doublet at δ 6.65 with J = 15.9 Hz (due to olefinic hydrogen adjacent to the aromatic ring of the substituent's *trans*-double bond) in the ^{1}H NMR spectrum of **6l**. Even cyclopropanes having a heterocyclic ring present nearby were also converted to their corresponding dienes (**6m-6n**) with good yield. It is important to note that the substrates **5k** and **5n**, when treated with Amberlyst®-15(H) in acetonitrile, produced the dienes **6k** and **6n** exclusively with 85% and 83% yields respectively. This is contrary to the earlier reports[7, 35] where dienes were not obtained, rather the homoallylic chlorides were obtained as the major products. Thus after extending the substrate scope to a satisfactory extent we came up with a reaction pathway where conjugated dienes are prepared exclusively by the ring opening of highly strained cyclopropane moiety. Based on the reaction outcomes, a plausible mechanism has been suggested (Scheme 45).The reaction is believed to be initiated by the solid acid-catalysed dehydration of cyclopropyl carbinol with concomitant cleavage of the cyclopropane ring and subsequent deprotonation of the ultimate carbocationic species where the gain of stabilization through extended conjugation seems to be the driving force to yield the products as conjugated dienes.



Scheme 45: Plausible mechanismof forming dienes from cyclopropanols using Amberlyst®- 15(H)

This given mechanism also supported the catalytic role of Amberlyst®-15(H) in terms of its Bronsted acidity and recyclability.

II.4.3.3. Conclusion:

In this mild and efficient protocol, readily available, air-stable, inexpensive and recyclable heterogeneous solid acid catalyst Amberlyst®-15(H) was successfully utilized for the formation of structurally and functionally important conjugated dienes utilizing the cleavage of properly substituted cyclopropyl carbinols. This reaction has high atom-economy and generates water as the sole and innocuous by-product. Thus it minimizes the release of deleterious waste to the surroundings and maximizes the reuse of renewable resource. Thus it bodes for eco-compatibility compared to many earlier reports. Presently works are going on to extend this method towards the construction of unique molecular skeletons having one cyclopropane ring intact through the discriminatory cleavage of symmetrical bis-cyclopropylcarbinols. Moreover, further investigations are needed to establish the effects of alkyl and vinylogous substituents in place of aryl moieties.

II.4.3.4. Experimental

General:

All organic solvents used for the reaction were purchased from Merck and SRL, and were distilled before use. Melting points were recorded in open capillary on electrical bath which are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker–300 (300 MHz) and Bruker–400 (400 MHz) spectrometer in $CDCl_3$ solvent with TMS as internal reference. Column chromatography were performed on silica gel (60–120 mesh) supplied by SRL, India. Thin layer chromatographic separations were performed on pre-coated glass plates using silica gel G for TLC (E. Merck).

(iii) <u>Representative procedure for the reaction</u>:

To a mixture of (2-(4-methoxyphenyl)cyclopropyl)(phenyl)methanol (**5b**, 254 mg, 1.0 mmol) and MeCN (3 ml) the catalyst Amberlyst®-15(H) (50 mg) was added. The reaction mixture was stirred for the required period of time at 80°C till the reaction was completed (monitored with TLC). Then the reaction mixture was cooled to room temperature, excess MeCN was removed under reduced pressure, keeping a cotton plug on a funnel the catalyst were filtered out and washed repeatedly by ethyl acetate (20 ml) to dissolve and collect the product. The organic extract was then thoroughly washed with water (3×10 ml) to remove remaining MeCN and dried over anhydrous Na_2SO_4. The crude product was obtained by removal of the solvent under reduced pressure and purified by filtration chromatography on a short column of silica gel using 1-4% ethyl acetate-hexane as eluent to afford 1-methoxy-4-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene (**6b**, 200 mg, Yield 85%).

(iv) <u>Spectral and analytical data of the compounds</u>:

1. **(1*E*, 3*E*)-1,4-diphenylbuta-1, 3-diene** (**6a**)[31] White solid (Yield 83%, mp 150-151°C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.77 (2H, d, *J* = 6.0 Hz), 8.02 (2H, d, *J* = 15 Hz), 7.14-7.41 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 126.7, 128.5, 130.4, 134.2, 136.1

2. **1-methoxy-4-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene** (**6b**)[31] Yellowish solid (Yield 85%, mp 164-165°C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.83 (3H, s), 6.62 (2H, d, *J* = 9.0 Hz), 6.81-6.97 (4H, m), 7.21-7.44 (7H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 55.3, 114.1, 126.3, 127.3, 127.6, 128.6, 129.5, 130.2, 131.7, 132.5, 137.6, 159.3

3. **1-methoxy-3-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene (6c)**[32] White solid (Yield 81%, mp 69-70^{o}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.87 (3H, s), 6.63-6.76 (2H, m), 6.81-6.97 (4H, m), 6.84-7.08 (3H, m), 7.24-7.31 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 55.2, 111.6, 113.4, 119.2, 126.4, 127.6, 128.7, 129.2, 129.6, 132.7, 133.0, 137.4, 138.8, 159.9

4. **1-methoxy-4-((1*E*, 3*E*)-4-(p-tolyl)buta-1, 3-dien-1-yl)benzene (6d)**[33] Colourless semisolid (Yield 84%,); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.35 (3H, s), 3.82 (3H, s), 6.62 (2H, d, *J* = 10.8 Hz), 6.79-6.93 (4H, m), 7.13-7.17 (2H, m), 7.26-7.39 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.2, 55.3, 114.2, 126.2, 127.5, 128.6, 129.1, 130.4, 131.8, 134.8, 137.2, 159.2

5. **(1*E*, 3*E*)-1, 4-bis(4-methoxyphenyl)buta-1, 3-diene (6e)**[31] Yellowish solid (Yield 85%, mp 165-166^{0}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.79 (6H, s), 6.56-6.59 (2H, m), 6.73-7.26 (6H, m), 7.36 (4H, d, *J* = 6.3 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 56.1, 114.4, 127.3, 130.5, 133.9, 158.9

6. **1-bromo-4-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene (6f)**[33] Yellow semisolid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.58-6.70 (2H, m), 6.92-6.99 (2H, m), 7.28-7.46 (9H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 122.1, 128.2, 128.7, 129.8, 131.7, 133.9, 134.3 135.4

7. **1-chloro-4-((1*E*, 3*E*)-4-(4-methoxyphenyl)buta-1, 3-dien-1-yl)benzene (6g)**[7] Yellow solid (Yield 81%, 191-192^{0}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.82 (3H, s), 6.54-6.66 (2H, m), 6.77-6.95 (4H, m), 7.26-7.39 (6H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 55.7, 114.4, 127.7, 128.8, 130.5, 133.3, 133.8, 159.2

8. **1-bromo-4-((1*E*, 3*E*)-4-(4-methoxyphenyl)buta-1, 3-dien-1-yl)benzene (6h)**[34] Yellow semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.81 (3H, s), 6.56-6.76 (2H, m), 6.82-6.92 (4H, m), 7.21-7.47 (6H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 55.2, 114.1, 120.8, 126.8, 127.6, 130.2, 131.7, 133.1, 136.5, 159.4

9. **1-methoxy-4-((1*E*, 3*E*)-4-(4-nitrophenyl)buta-1, 3-dien-1-yl)benzene(6i)**[7] Yellowish solid (Yield 82%, mp 242-244^{0}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.83 (3H, s), 6.61-7.13 (6H, m), 7.41 (2H, d, *J* = 8.5 Hz), 7.52 (2H, d, *J* = 7.6 Hz), 8.17 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 55.9, 114.3, 123.8, 127.7, 129.2, 130.4, 133.7, 141.1, 146.7, 159.8

10. **(*E*)-2-(3, 4-dimethoxystyryl)-1H-indene (6j)** Yellowish semisolid (Yield 87%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.66 (1H, s), 3.91 (3H, s), 3.98 (3H, s), 6.70-7.43 (10H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 37.8, 55.9, 108.6, 111.3, 119.8, 120.8, 123.2, 123.6, 124.8, 126.2, 126.6, 128.0, 129.3, 130.5, 142.7, 145.3, 146.5, 147.5

11. **(*E*)-2-(4-chlorostyryl)-1H-indene** (**6k**) Brown semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.67 (2H, s), 6.58 (1H, s), 6.88-6.90 (2H, m), 6.91-6.97 (2H, m), 7.28-7.35 (3H, m), 7.44-7.54 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 42.5, 121.4, 125.3, 125.6, 126.3, 127.3, 127.8, 128.7, 129.0, 133.5, 134.5, 135.3, 143.0, 145.1

12. **(*E*)-3-(3, 4-dimethoxystyryl)-1, 2-dihydronaphthalene** (**6l**) Colourless semisolid (Yield 86%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.61 (2H, t, J = 8.1 Hz), 2.92 (2H, t, J = 7.8 Hz), 3.92 (3H, s), 3.94 (3H, s), 6.56 (1H, s), 6.63 (1H, s), 6.68 (1H, s), 6.76-7.26 (7H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 23.2, 27.9, 55.9, 108.6, 111.3, 119.8, 126.4, 126.6, 127.3, 127.9, 128.9, 130.7, 134.9, 135.5, 137.7, 148.8, 149.1

13. **(*E*)-3-(3, 4-dimethoxystyryl)-2H-thiochromene** (**6m**)[35] Colourless semisolid (Yield 85%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.71 (1H, s), 3.92 (3H, s), 3.98 (3H, s), 3.94 (3H, s), 6.56 (1H, s), 6.63 (1H, s), 6.75-7.28 (7H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.0, 55.9, 108.7, 110.4, 120.5, 124.3, 126.7, 128.5, 129.3, 130.7, 131.3, 132.8, 133.2, 149.1

14. **(*E*)-3-(4-chlorostyryl)-2H-thiochromene** (**6n**)[35] Brownish semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.46 (1H, s), 6.70 (1H, s), 6.81-6.84 (2H, m), 7.13-7.21 (2H, m), 7.36-7.43 (2H, m), 7.62-7.68 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 41.3, 124.1, 125.0, 125.4, 126.7, 127.4, 128.2, 128.7, 129.1, 129.9, 133.3, 133.5, 134.5, 135.3, 138.7

^{1}H NMR, ^{13}C NMR and DEPT Spectra of some representative compounds

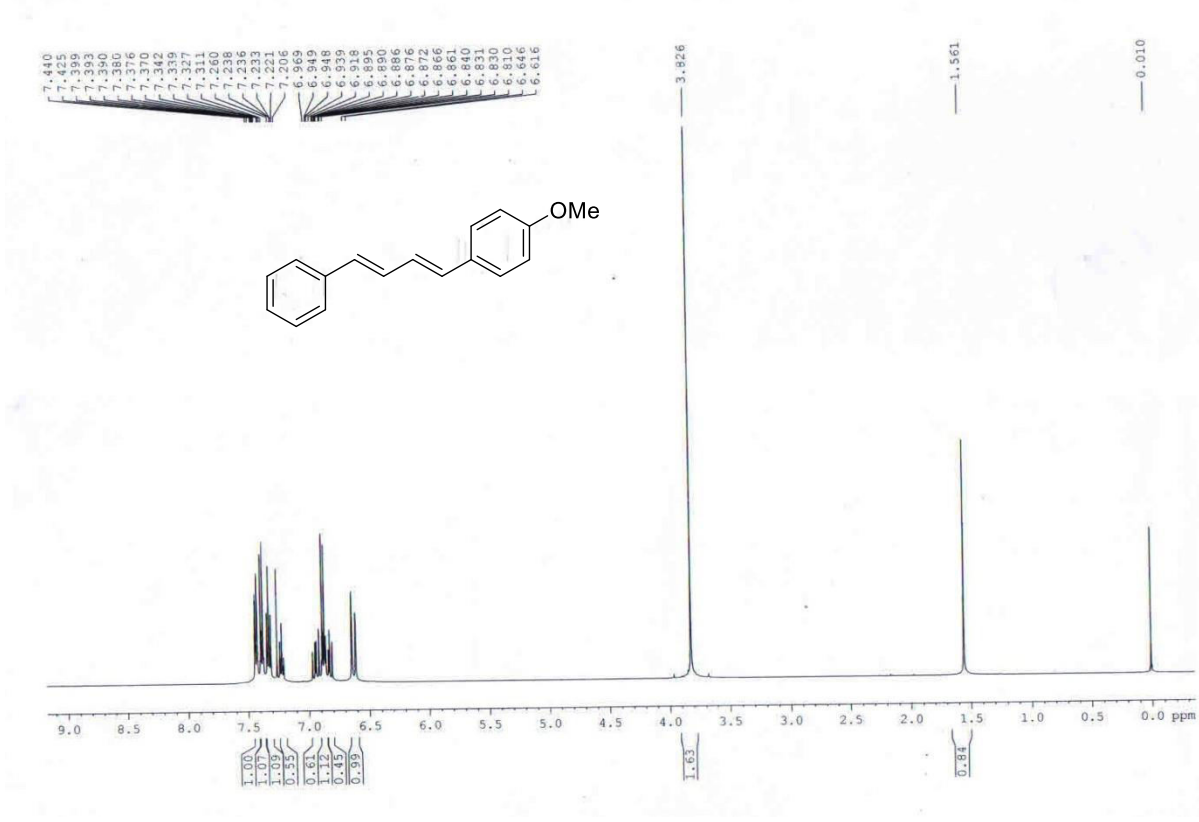


Figure 1: [1]H NMR of 1-methoxy-4-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene (**6b**)

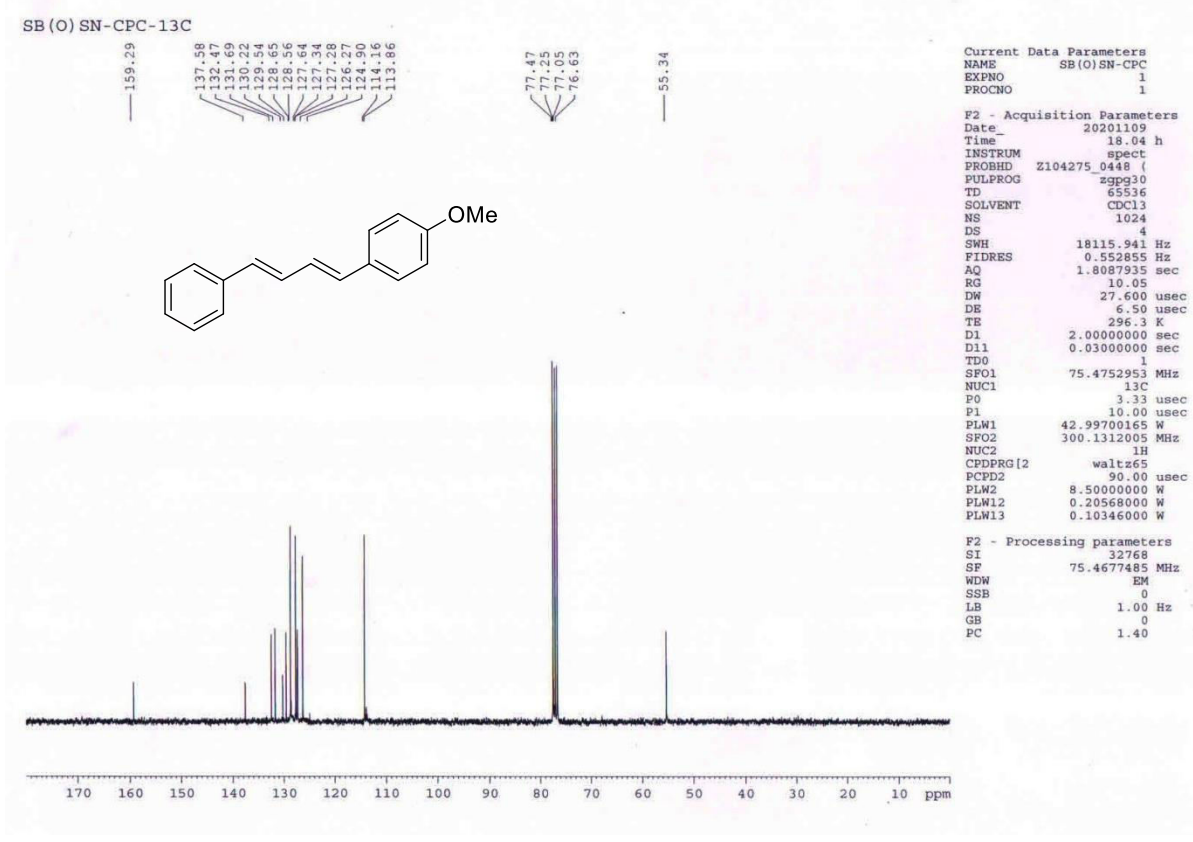


Figure 2: [13]C NMR of 1-methoxy-4-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene (**6b**)

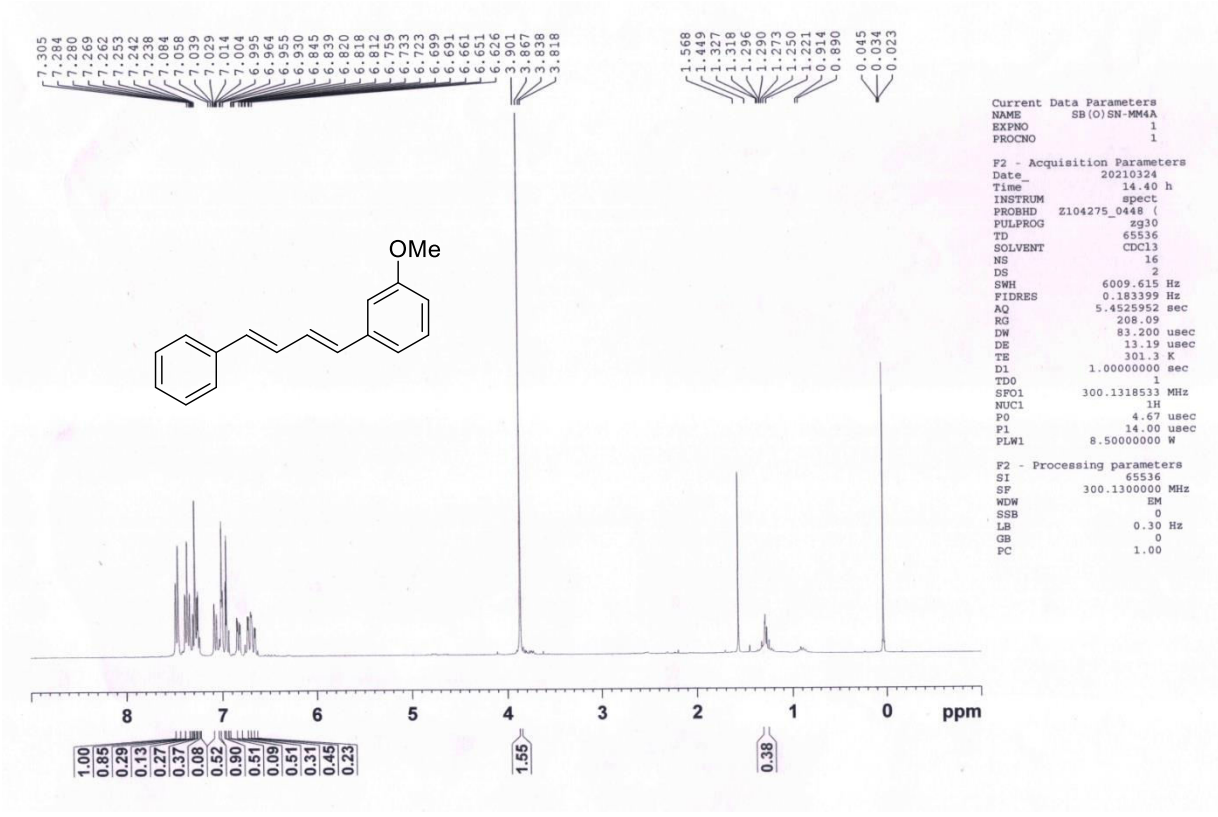


Figure 3: [1]H NMR of 1-methoxy-3-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene (**6c**)

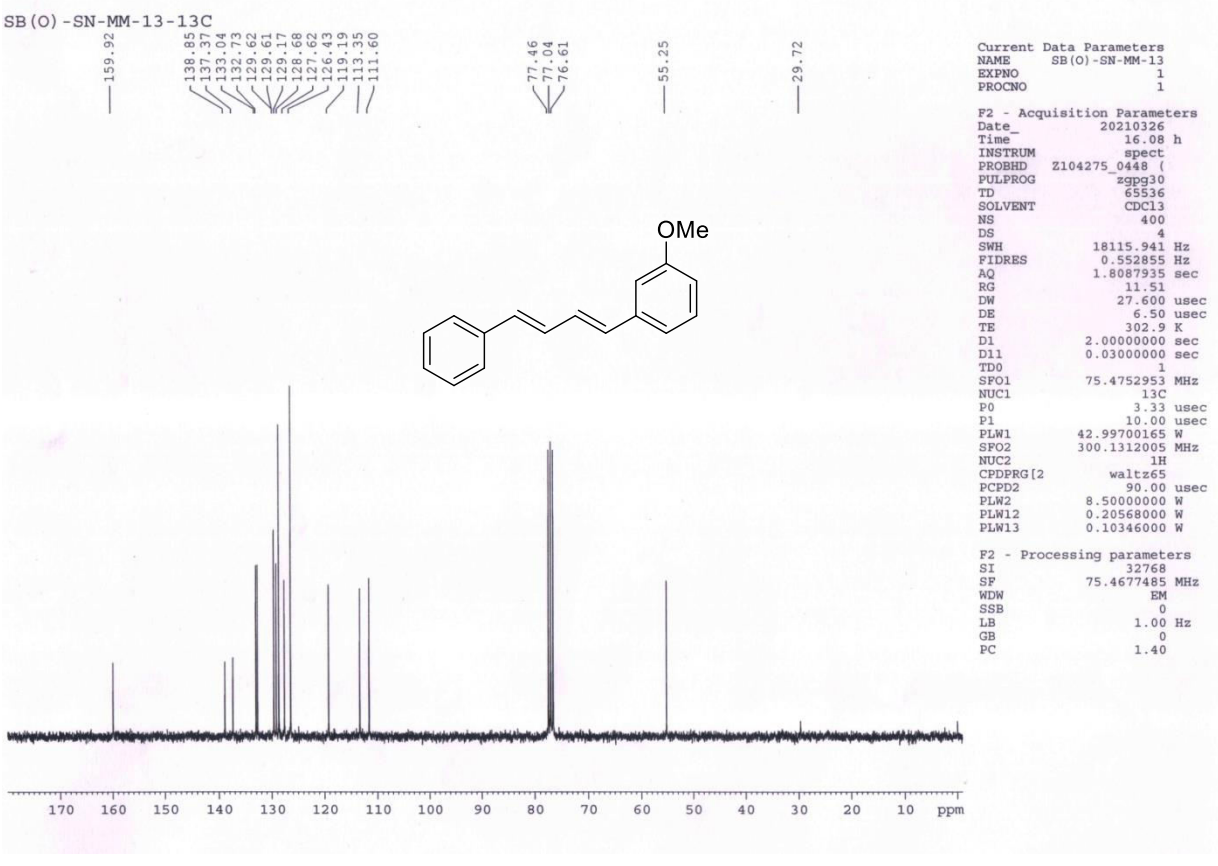


Figure 4: [13]C NMR of 1-methoxy-3-((1*E*, 3*E*)-4-phenylbuta-1, 3-dien-1-yl)benzene (**6c**)

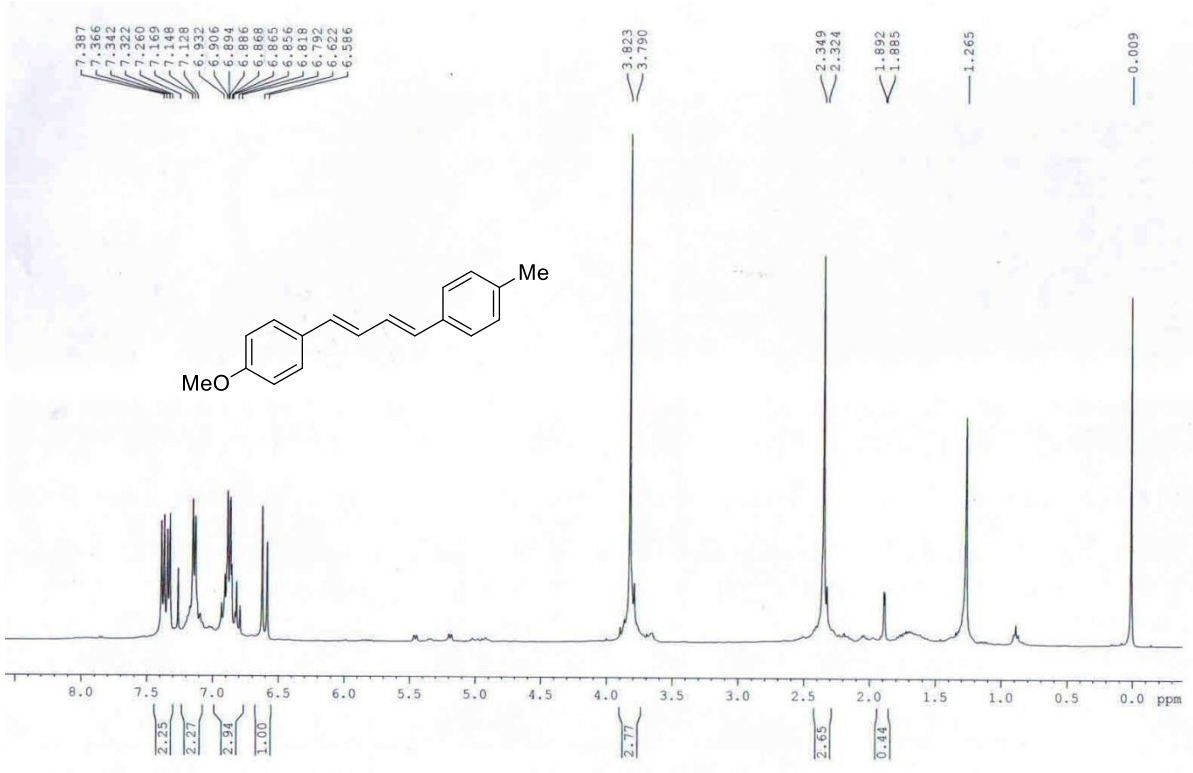


Figure 5: [1]H NMR of 1-methoxy-4-((1*E*, 3*E*)-4-(p-tolyl)buta-1, 3-dien-1-yl)benzene (**6d**)

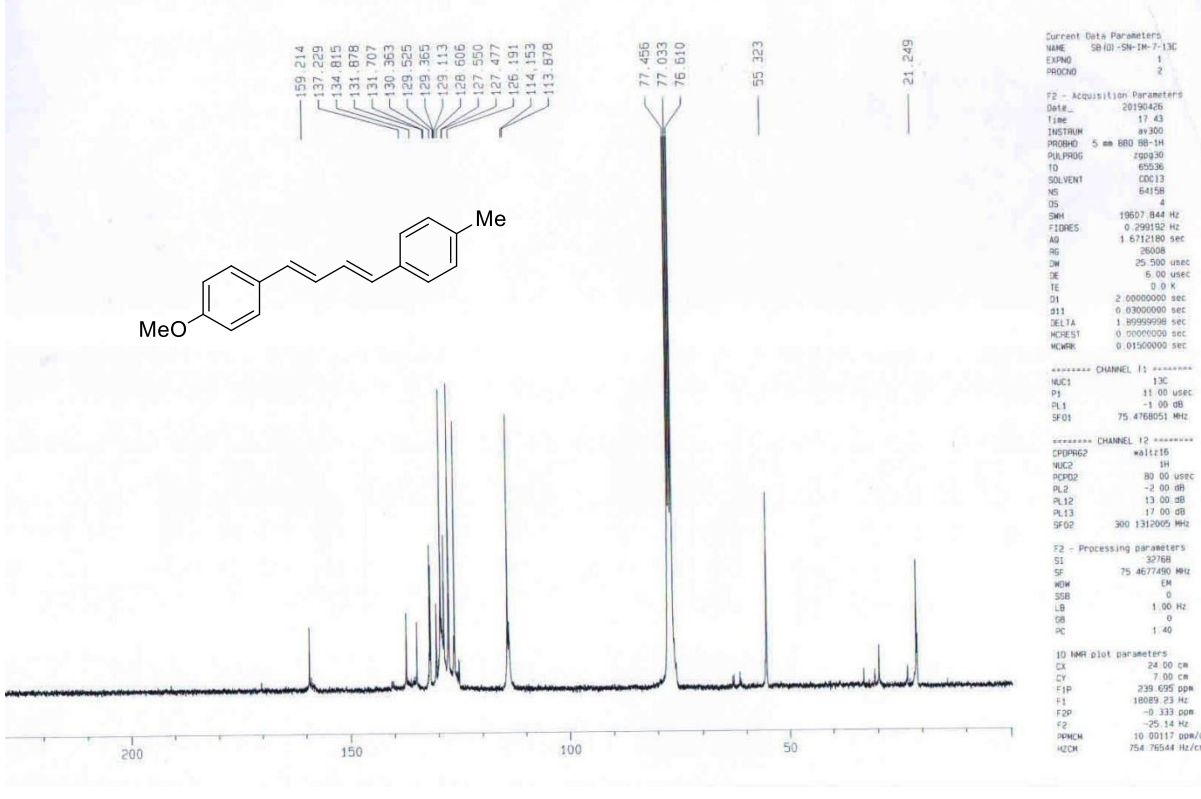


Figure 6: [13]C NMR of 1-methoxy-4-((1*E*, 3*E*)-4-(p-tolyl)buta-1, 3-dien-1-yl)benzene (**6d**)

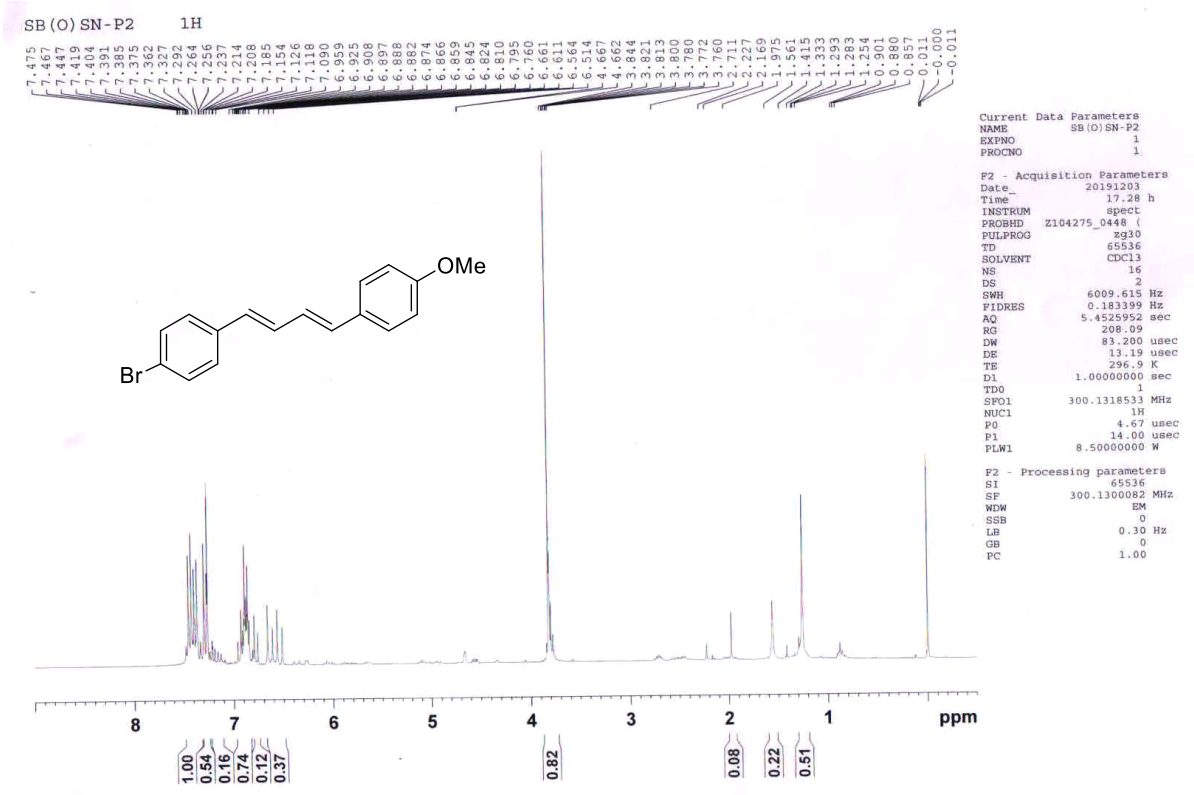


Figure 7: [1]H NMR of 1-bromo-4-((1*E*, 3*E*)-4-(4-methoxyphenyl)buta-1, 3-dien-1-yl)benzene (**6h**)

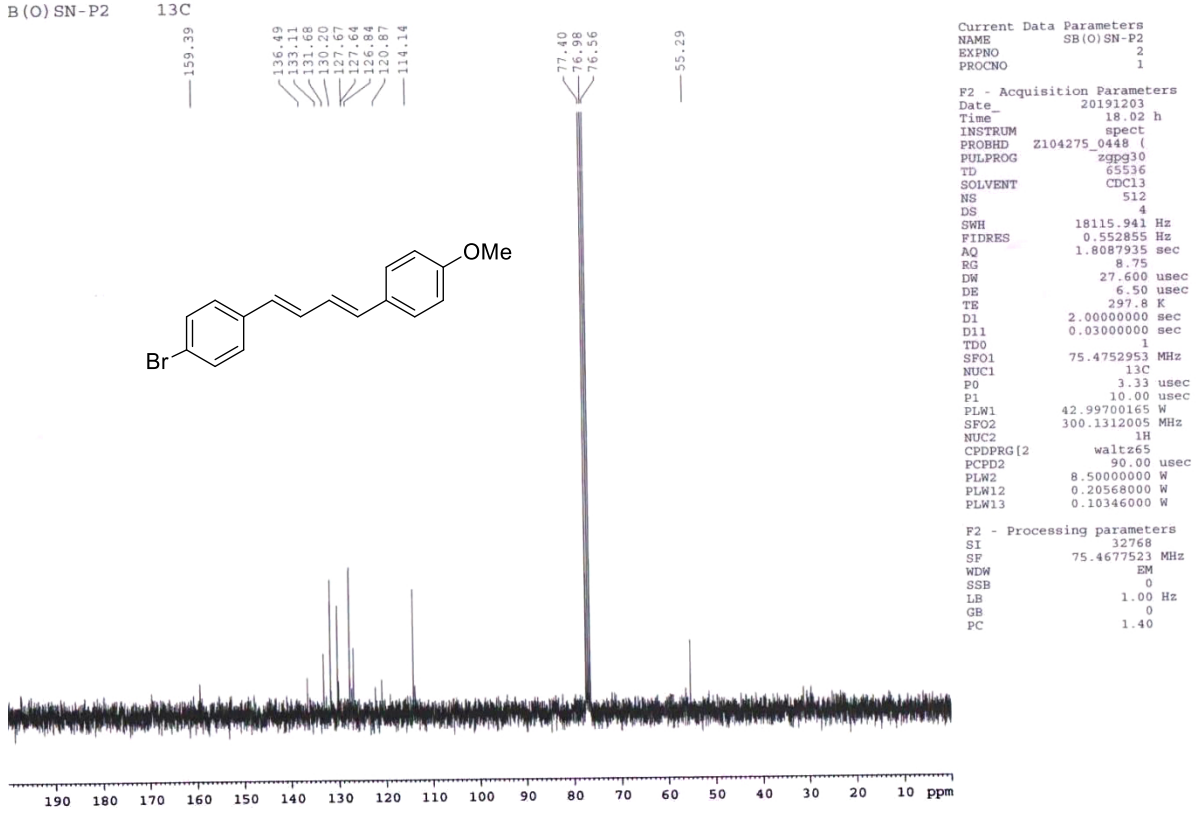


Figure 8: [13]H NMR of 1-bromo-4-((1*E*, 3*E*)-4-(4-methoxyphenyl)buta-1, 3-dien-1-yl)benzene (**6h**)

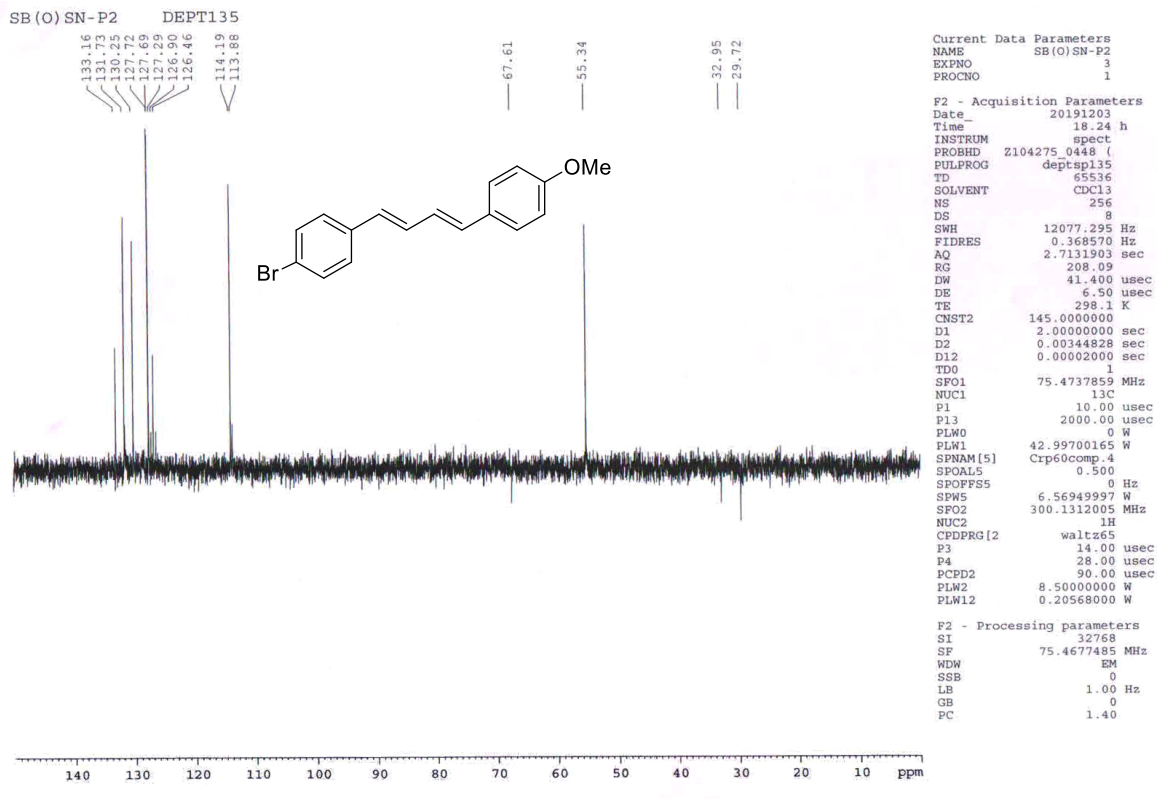


Figure 9: DEPT-135 of 1-bromo-4-((1*E*, 3*E*)-4-(4-methoxyphenyl)buta-1, 3-dien-1-yl)benzene (**6h**)

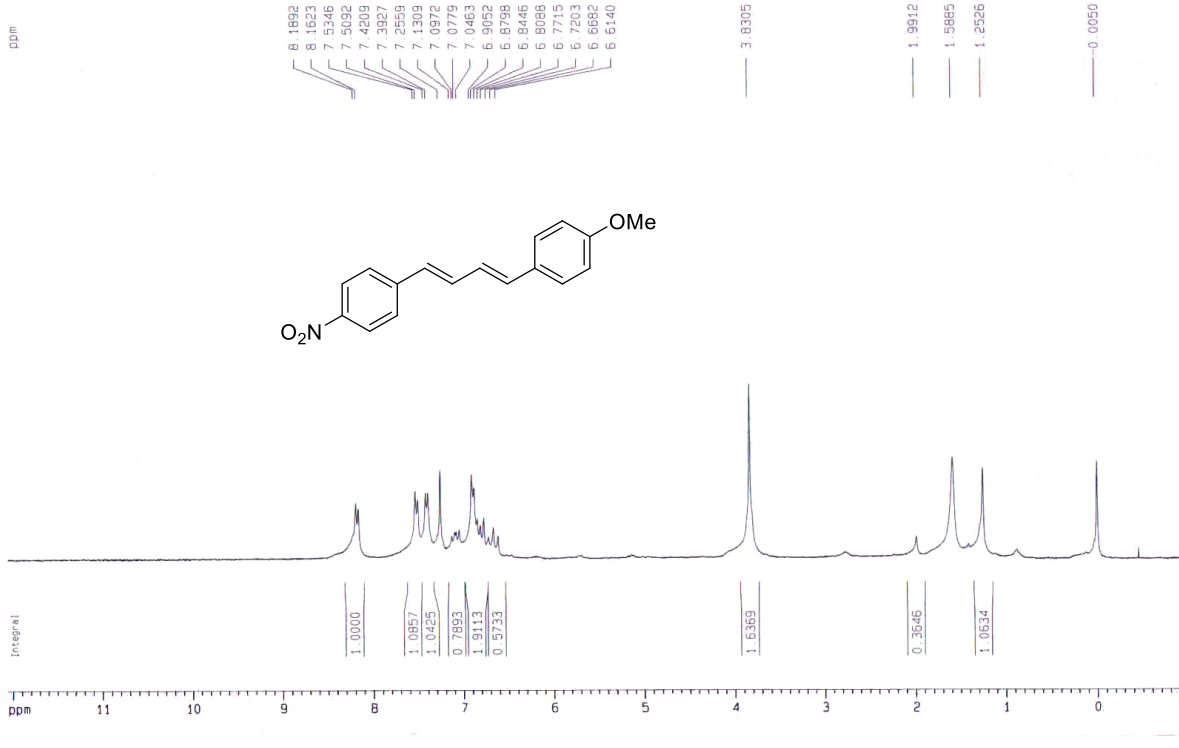


Figure 10: ^{1}H NMR of 1-methoxy-4-((1*E*, 3*E*)-4-(4-nitrophenyl)buta-1, 3-dien-1-yl)benzene (**6i**)

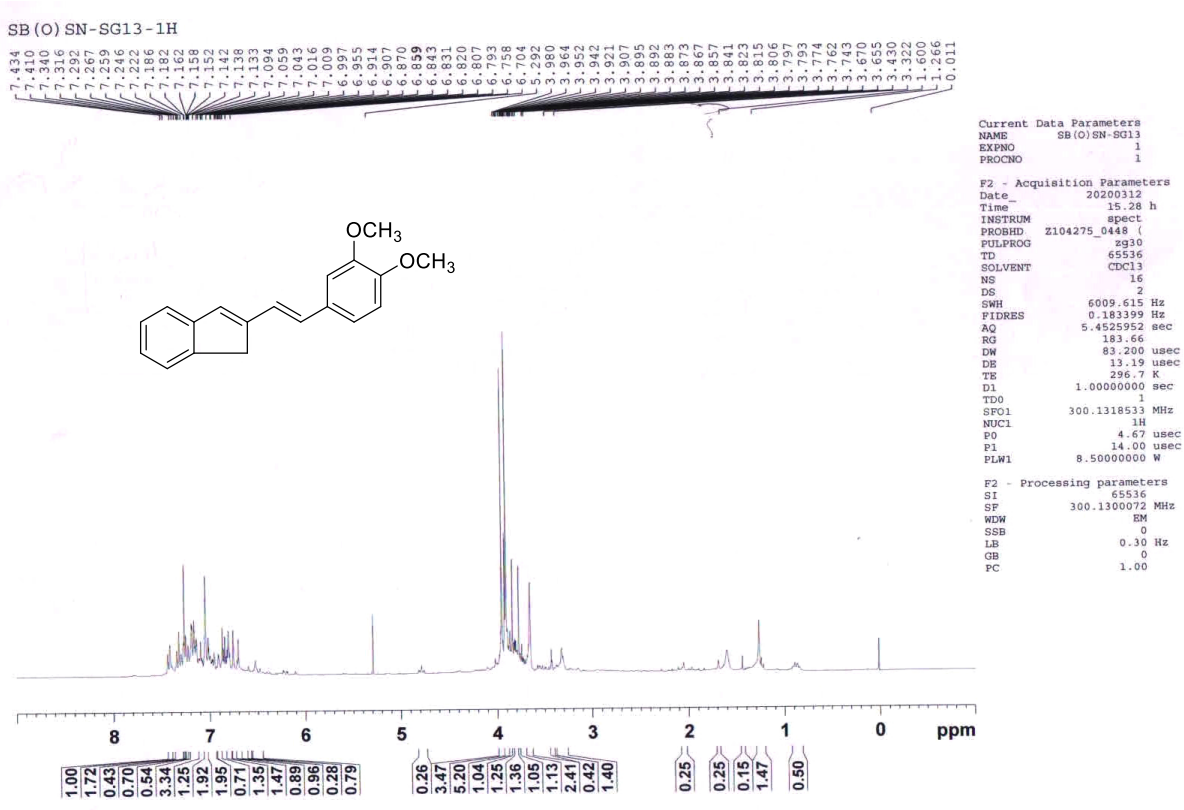


Figure 11: ^{1}H NMR of (*E*)-2-(3, 4-dimethoxystyryl)-1H-indene (**6j**)

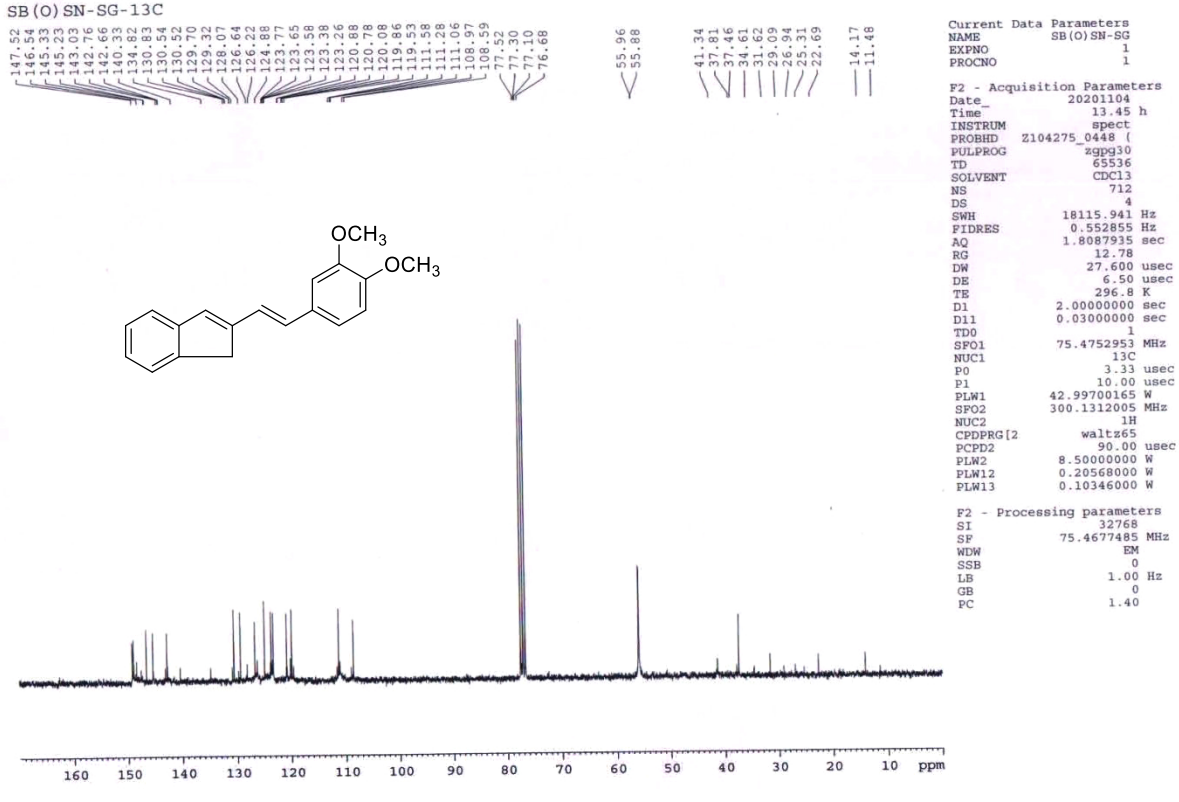


Figure 12: ^{13}C NMR of (*E*)-2-(3, 4-dimethoxystyryl)-1H-indene (**6j**)

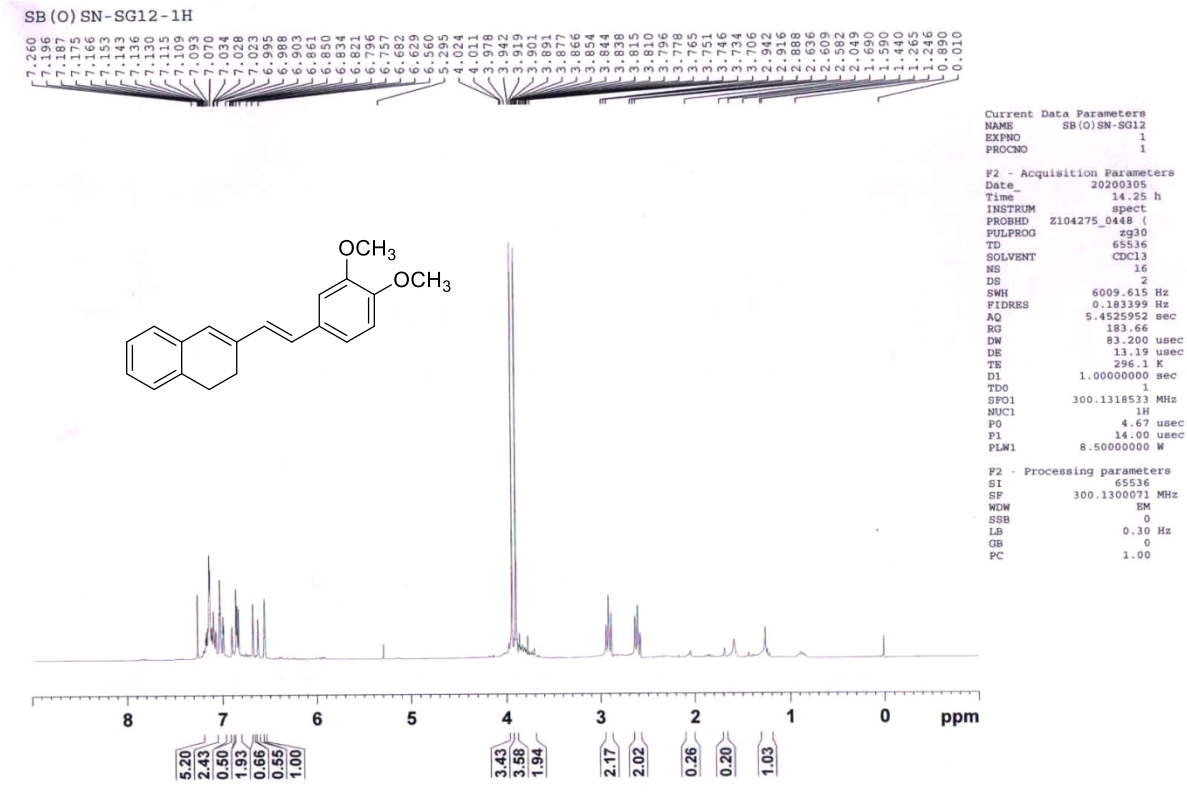


Figure 13: ^{1}H NMR of (*E*)-3-(3, 4-dimethoxystyryl)-1, 2-dihydronaphthalene (**6l**)

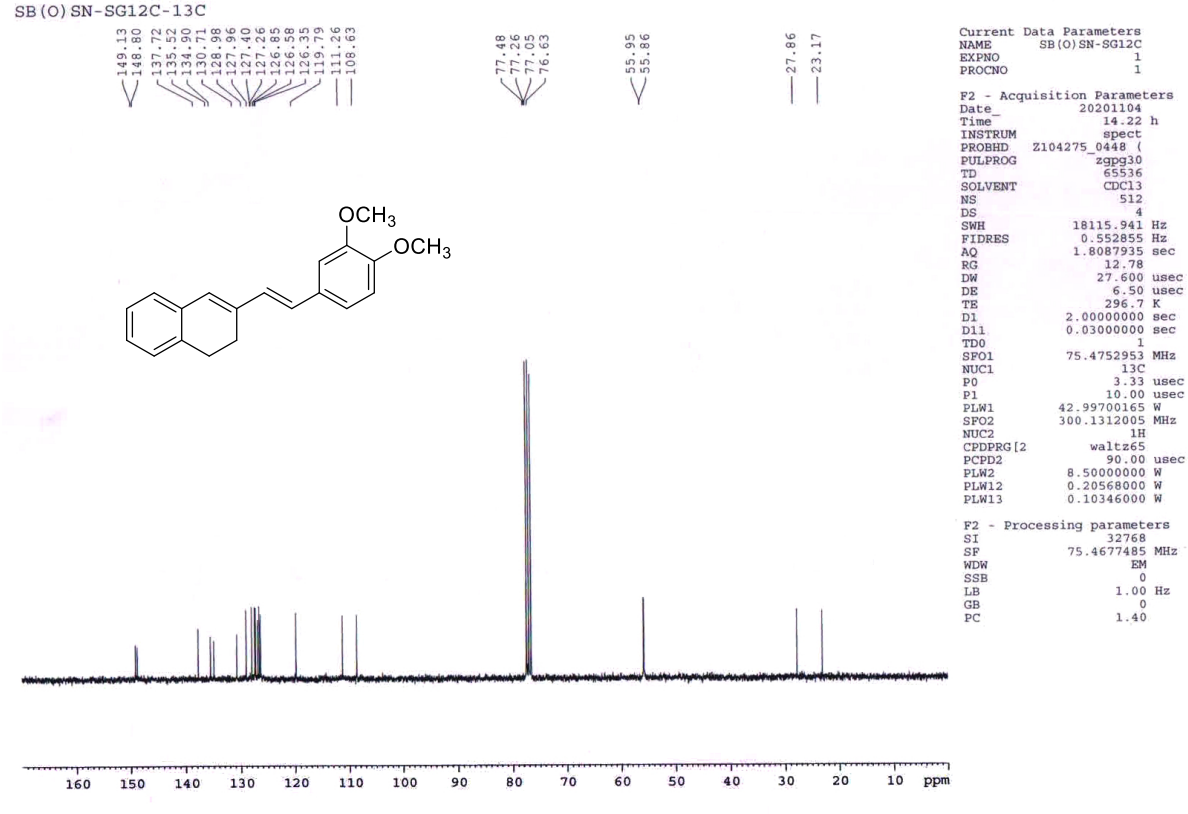


Figure 14: ^{13}C NMR of (*E*)-3-(3, 4-dimethoxystyryl)-1, 2-dihydronaphthalene (**6l**)

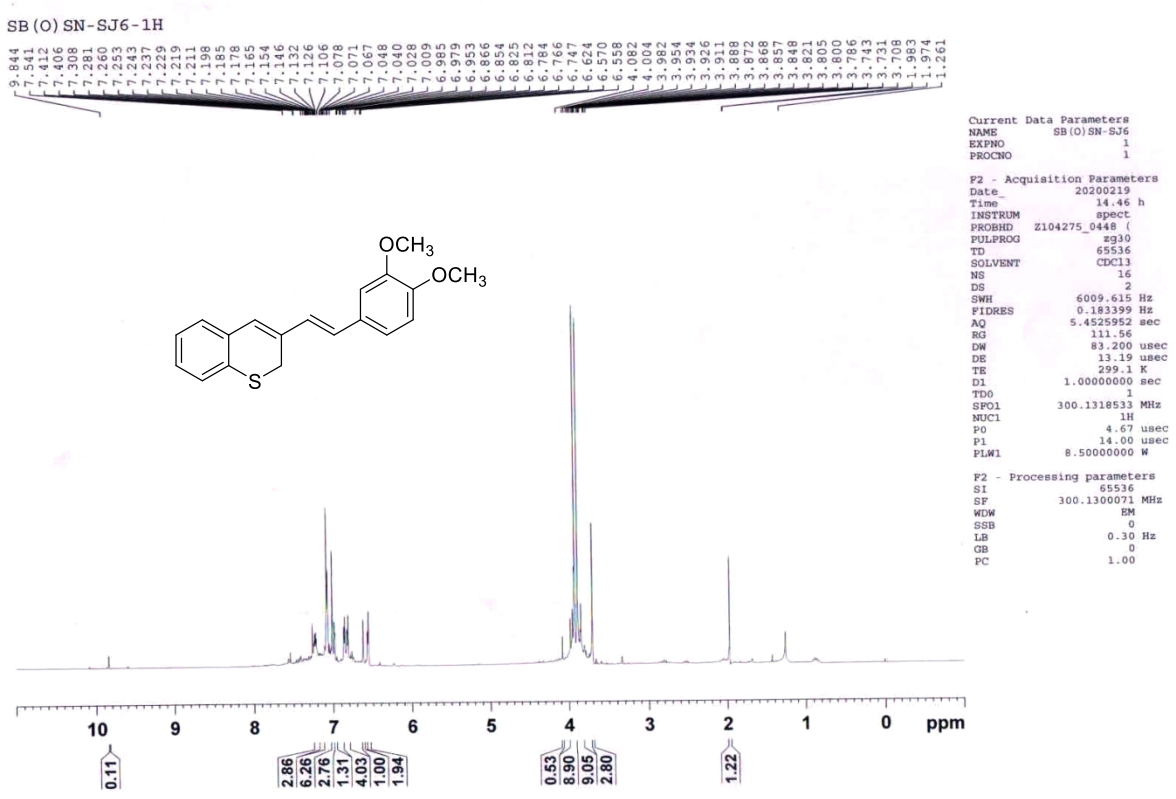


Figure 15: [1]H NMR of (*E*)-3-(3, 4-dimethoxystyryl)-2H-thiochromene (**6m**)

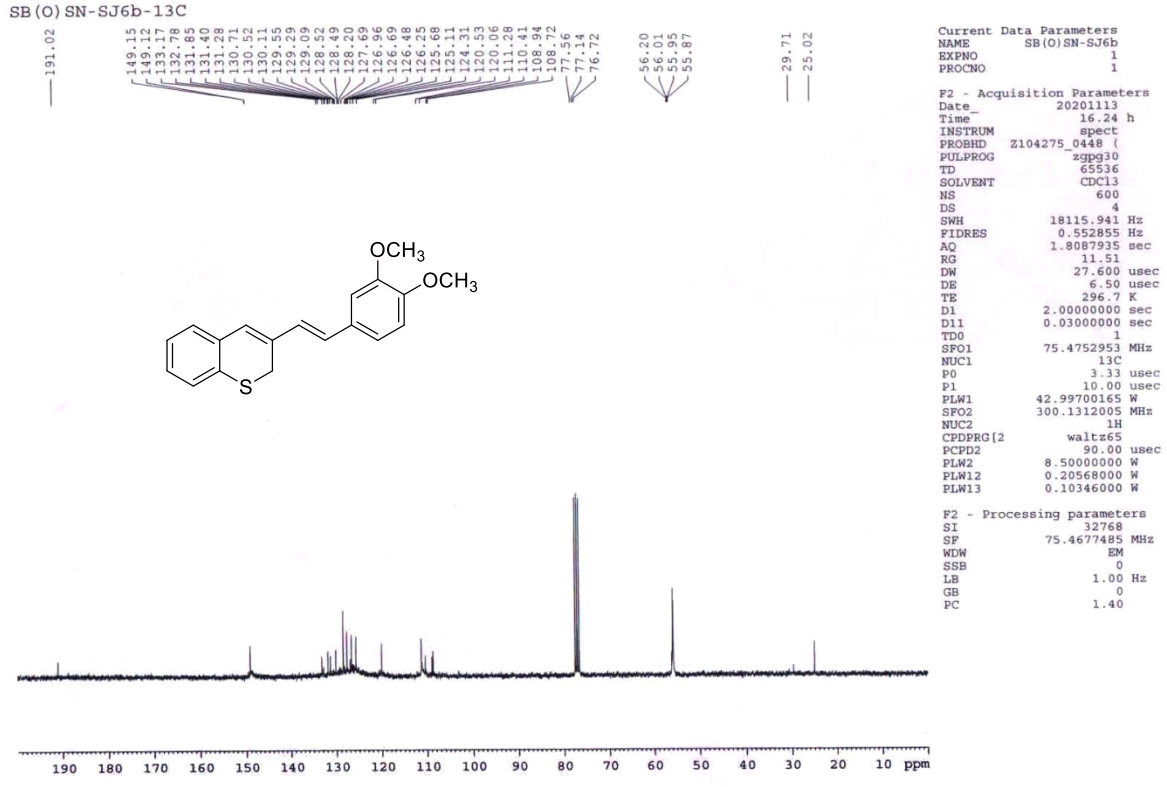


Figure 16: [13]C NMR of (*E*)-3-(3, 4-dimethoxystyryl)-2H-thiochromene (**6m**)

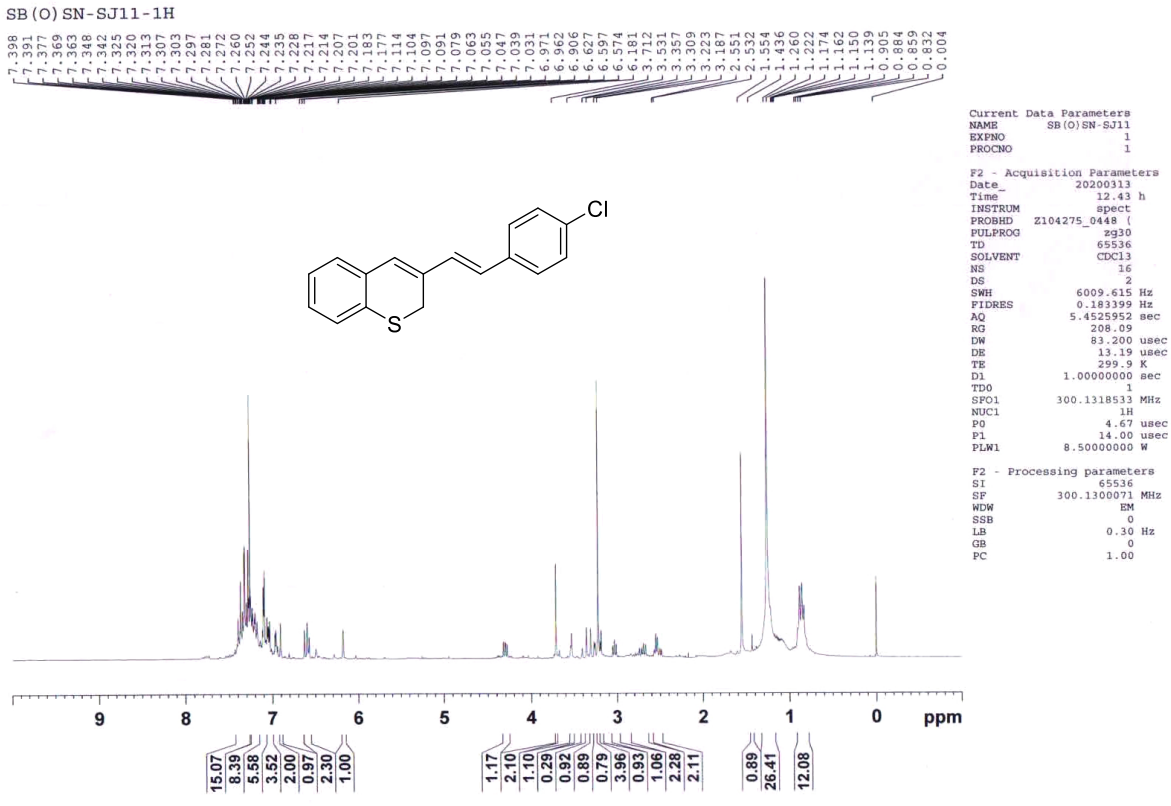


Figure 17: ^{1}H NMR of (*E*)-3-(4-chlorostyryl)-2H-thiochromene (**6n**)

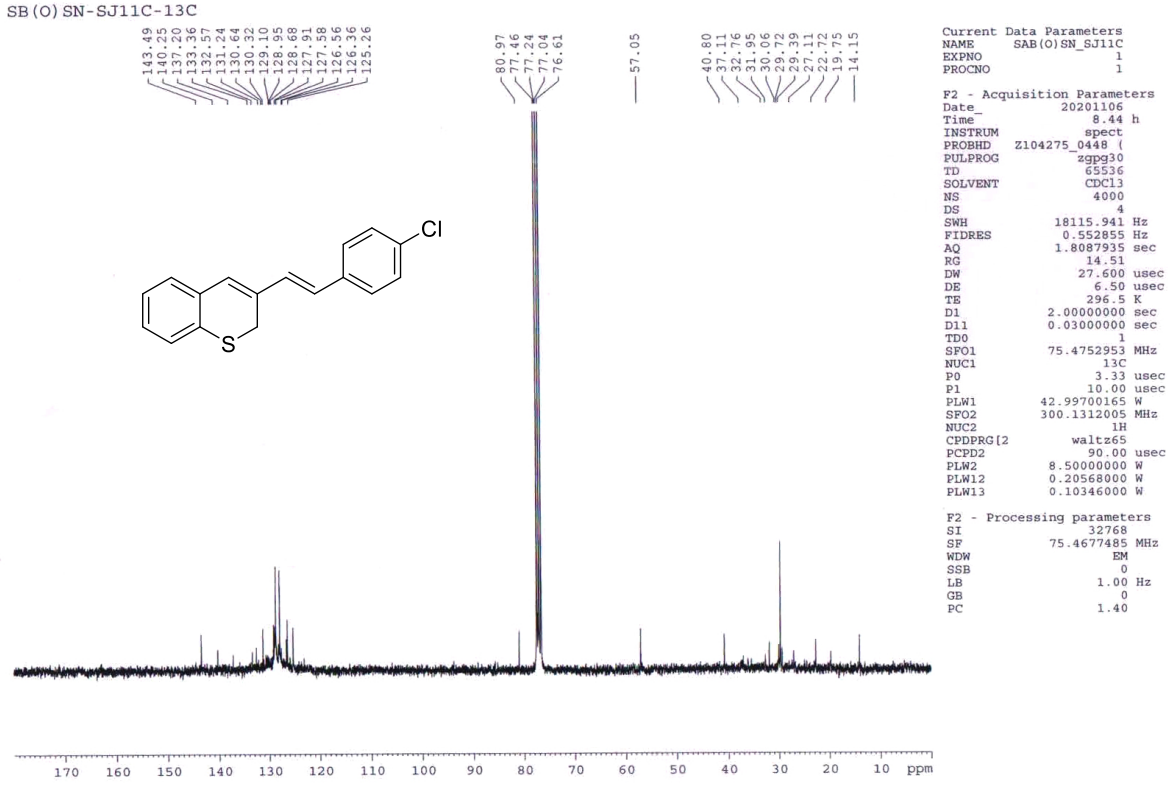


Figure 18: ^{13}C NMR of (*E*)-3-(4-chlorostyryl)-2H-thiochromene (**6n**)

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CHAPTER-III

Reduction of α-heteroatomic esters with $NaBH_4$ in MeOH

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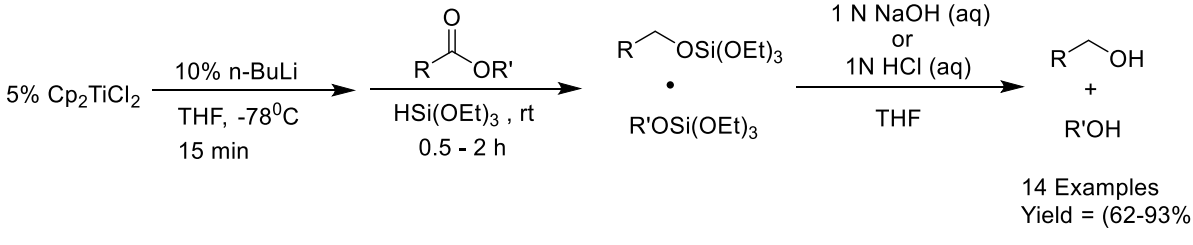
Reduction of α-heteroatomic esters with $NaBH_4$ in MeOH

III.1. Introduction:

Primary alcohols serve as important building blocks in chemical synthesis and largely used as bulk industrial feedstock. They are mostly used for the preparation of cosmetics, agrochemicals, several bioactive molecules and also in different ways for pharmaceutical industry. For preparing primary alcohols, reduction of carboxylic acid esters with hydride reagents such as $LiAlH_4$ is considered to be one of the main synthetic methods. But such synthetic approach suffers from non-compatibility with other functional groups, sensitivity of pyrophoric reagents and also lack of chemoselectivity. Primary alcohols can also be prepared from the hydrogenation of esters in other suitable ways where a lot of modifications are developed through time.

III.2. Recent methods for reducing esters to primary alcohols: A Review

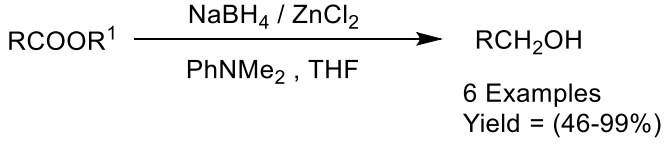
Buchwald and his team developed[1] a catalytic hydrosilylation system for the conversion of different esters to their corresponding primary alcohols utilizing inexpensive silanes as the stoichiometric reducing agent (Scheme 1). This protocol was very efficient and substrate selective, representing a safe and convenient alternative to the use of other reducing agents such as DIBAL or $LiAlH_4$ in large scale.



Scheme 1: Catalytic method for the reduction of esters to alcohols

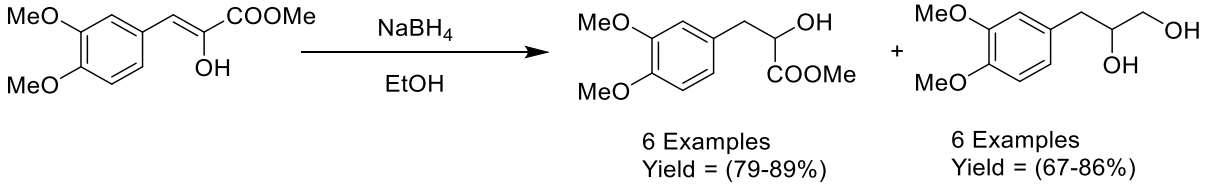
Yamakawa *et al*. designed[2] a process where carboxylic esters were smoothly reduced to their corresponding alcohols by using $NaBH_4$ and $ZnCl_2$ in presence of a tertiary amine, where THF was used as a solvent (Scheme 2).

Even utilising this technique amino-benzoates such as anthranilic esters were also reduced to corresponding amino-benzyl alcohols with moderate to good yields without the addition of tertiary amine.



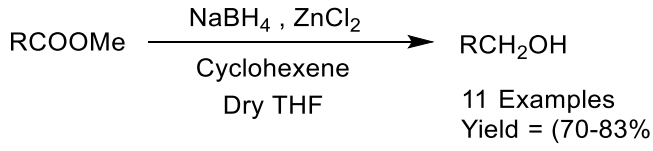
Scheme 2: Reduction of carboxylic esters by $NaBH_4/ZnCl_2$

Another similar type of process[3] showed that aromatic keto-esters were smoothly reduced using $NaBH_4$ under proper conditions (Scheme 3). Using one equivalent of reagent in methanol, α-hydroxyesters were obtained in very short time with good yield without giving any unnecessary byproduct. Moreover, they demonstrated that the second reduction of ester functional group occurred in an intramolecular way and was governed only by $NaBH_4$ itself. In addition, the reaction occurred readily when it was performed in such solvents that were inert towards the reducing system, providing a convenient access to structurally important diols.



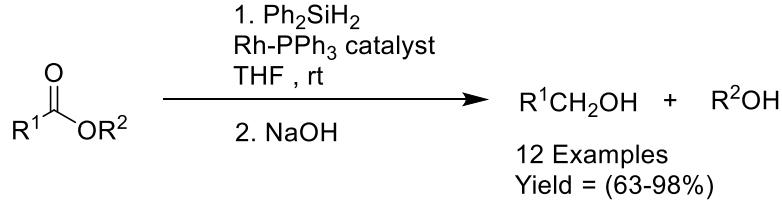
Scheme 3: Chemocontrolled reduction of aromatic α -ketoesters by $NaBH_4$

Narasimhan *et al*. modified[4] the reactivity of $NaBH_4/ZnCl_2$ combination by adding cyclohexene to the system, this addition facilitated the reduction of aromatic esters to primary alcohols which was not possible otherwise using only the mild reducing agent (Scheme 4). In this protocol good substrate compatibility was provided towards the ester reduction. Unsaturated compounds which underwent hydroboration were also utilized for the conversions where both reduction and hydroboration were required. This method increased the adaptability and application of $Zn(BH_4)_2$ in applied synthetic chemistry.



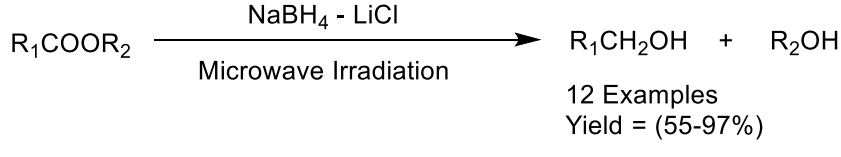
Scheme 4: Alkene catalyzed reduction of aromatic esters to alcohols

Carboxylic esters were reduced[5] to primary alcohols using diphenylsilane catalyzed by ruthenium complex at room temperature (Scheme 5). Even ethyl decanoate and ethyl phenylacetate were transformed to decanol and 2-phenylethanol by $[RhCl(cod)]_2/4PPh_3$ in excellent yields. This was one of the pioneering examples of the reduction of esters using silanes in presence of a transition metal catalyst. Moreover this process needed no pressurization, no heating and no activation by any of the reducing reagent and the catalyst was stable in air and moisture.



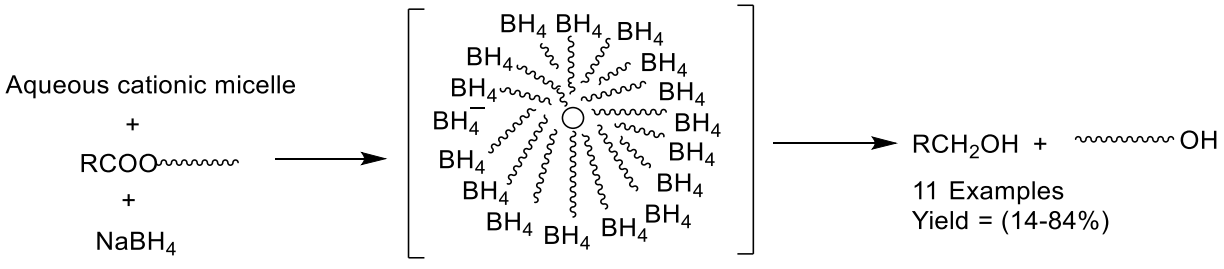
Scheme 5: Rhodium-catalyzed reduction of esters to alcohols

Tu and his team proposed[6] an interesting method of reducing the esters to corresponding alcohols with borohydride and lithium chloride under microwave irradiation without any solvent (Scheme 6). Complete conversion of substrates took place rapidly with yields in the range of 55% to 95%. The application of microwave irradiation in solid phase offered a very efficient and environment friendly method for the reduction of esters. Operational simplicity, good yields in short reaction time made this procedure a very attractive and practical method.



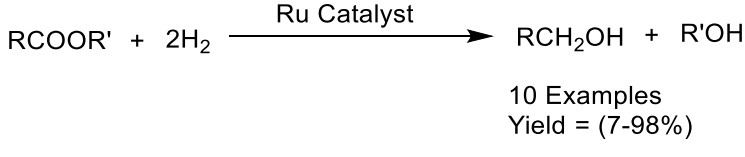
Scheme 6: Microwave assisted reduction of esters to alcohols

Das *et al*. developed[7] a proficient and simple system of reducing esters under ambient reaction conditions using $NaBH_4$in aqueous self-aggregates of cationic surfactants (Scheme 7). Here the presence of long chain provided good flexibility to the molecule, allowing more accessibility of the ester group for coming close to BH_4^- ions. They suggested that absence of any hydrophilic moiety in the n-hexylbenzoate apparently led to more penetration of ester in the hydrocarbon-like centre of micelles. Besides being applicable for reducing aromatic or aliphatic esters; this method proved its efficacy for enormous use in selective functional group reduction and stereocontrolled synthesis of alcohols.



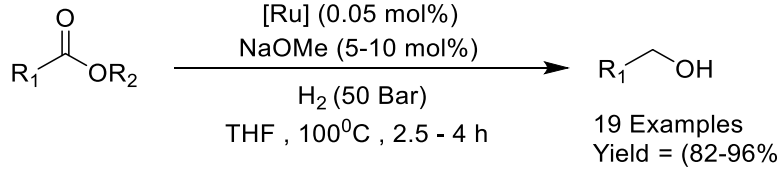
Scheme 7: $NaBH_4$ reduction of esters at cationic micellar surface

Non-activated aromatic and aliphatic esters were effectively hydrogenated[8] to corresponding alcohols under mild and neutral conditions using a ruthenium-hydride complex as catalyst (Scheme 8). The catalyst exhibited a comparable reactivity with dihydrogen and catalysed the dehydrogenation of esters. This reaction followed an unusual aromatization-dearomatization pathway where ananalogous complex was less active, suggesting hemilability of the pincer ligand PNN (2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine) and subsequent ester coordination. This reaction pathway differed from the traditional ones where mainly the binding of substrate to the metal was not required and the hydrogenation took place in a concerted hydride or proton transfer.



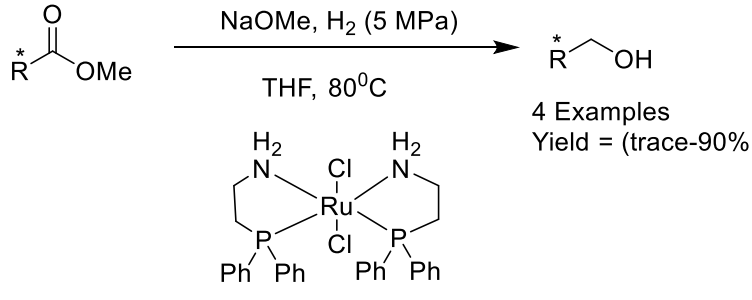
Scheme 8: Efficient homogeneous catalytic hydrogenation of esters to alcohols

Saudan *et al*. developed[9] a process to reduce aliphatic and aromatic carboxylic esters to primary alcohols with H_2 and highly efficient homogeneous ruthenium complexes with N, P ligands as catalyst (Scheme 9). The best yield in this process was observed with THF, so it was chosen as the reaction medium whereas almost all the optimization reactions gave poor yield of the desired products when MeOH was used. Here the active catalyst was supposed to be a *trans*-dihydride complex generated from the dichloride complex on reaction with an alkoxide base in presence of H_2. The reaction occurred under relatively mild conditions and esters with a di- or tri- substituted C=C bond were readily reduced to corresponding unsaturated alcohols with excellent chemoselectivity. This process proved its superiority over the waste generating reduction techniques with metal-hydride reagents.



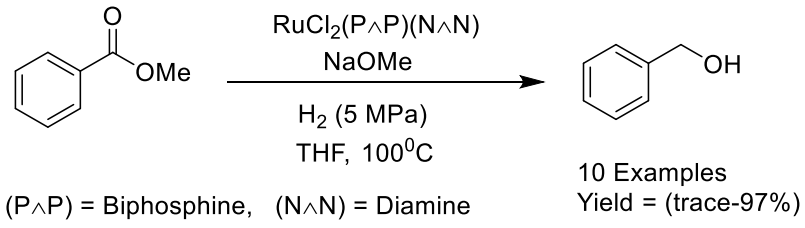
Scheme 9: Dihydrogen reduction of carboxylic esters to alcohols

Another novel method was reported[10] using ruthenium catalyzed hydrogen reduction which provided various types of optically active esters to their corresponding chiral alcohols with retention of optical purity (Scheme 10-11). Here unprotected β-hydroxy and β-amino esters were reduced to corresponding diols and amino alcohols.



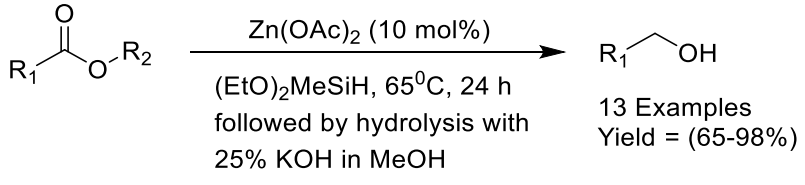
Scheme 10: Reduction of chiral esters to the corresponding chiral alcohols

Even a wide variety of N-phenylalanine esters and Boc-protected α-amino acid esters were reduced in this process, protected lactic acid ester also gave the mono protected diol without hydrogenolysis of remaining benzyl moiety.



Scheme 11: Reduction of methyl benzoates with $RuCl_2$(bisphosphine)(diamine) and base

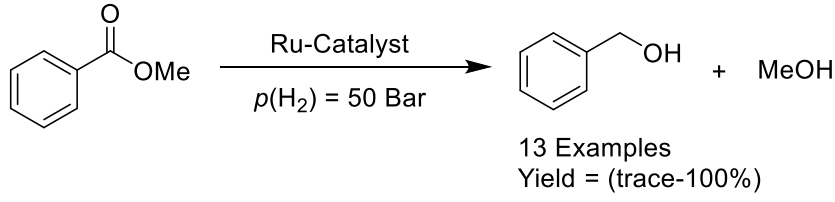
Das *et al*. reported[11] an improved method for catalytic hydrosilylation of esters to generate primary alcohols. Esters were reduced in presence ofnitrile, nitro as well as triple bonds and isolated or conjugated double bonds, where none of these functional groups were reduced (Scheme 12). Additionally, methyl perilate also underwent ester reduction in the presence of anisolated and conjugated double bond providing perillyl alcohol in excellent yield. Especially, high chemoselectivity was one of the best features in this reaction where selective reduction was achieved in presence of different reducible functional groups.



Scheme 12: Zinc-catalyzed chemoselective reduction of esters to alcohols

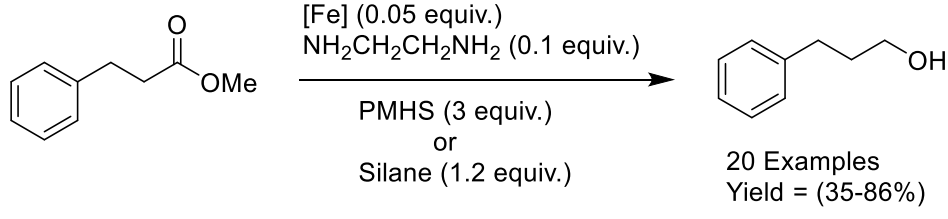
Gusev and his team presented[12] a versatile catalyst system for the reduction of esters followed by dehydrogenative coupling of alcohols (Scheme 13). Ruthenium dimer here showed an excellent efficiency under neutral conditions while osmium dimer proved to be predominantly useful for hydrogenation of esters in the presence of C=C bonds. Hydrogenation of α, β-unsaturated methyl 2-nonenoate successfully afforded nonanol, but the selectivity was not very appreciable for methyl cinnamate.

This homogenous catalyst system was applicable for hydrogenation of triglycerides, which gave rise to useful fatty alcohols directly from olive oil.



Scheme 13: Reduction esters to alcohols with ruthenium catalyst

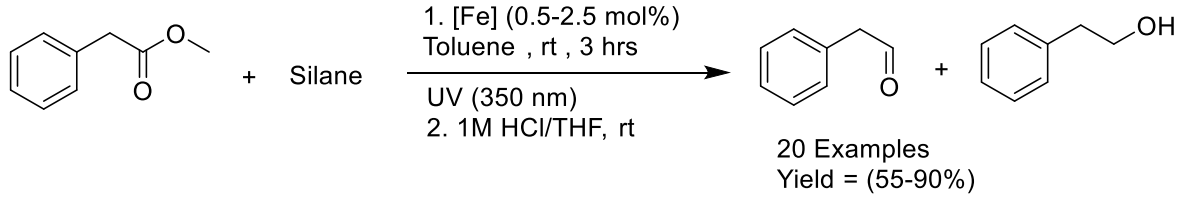
Iron-catalyzed hydrosilylation of carboxylic acid esters to primary alcohols was demonstrated[13] by Junge *et al.* using a combination of a Fe-stearate complex and polymethylhydrosiloxane (PMHS) (Scheme 14).This method showcased broad substrate scope with a number of aromatic, aliphatic and heterocyclic substrates which produced their corresponding primary alcohols in high yields. Interestingly both, electron-donating and electron-withdrawing groups present in the substrates increased the product yield.



Scheme 14: Iron-catalyzed reduction of carboxylic esters to alcohols

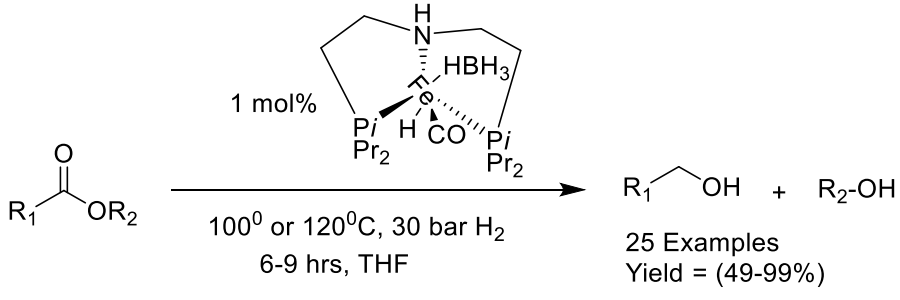
Darcel and his team developed[14] a simple and effective methodology for chemoselective reduction of esters to aldehydes and alcohols using N-heterocyclic carbene–iron complex as the catalyst in the presence of diethylsilane or diphenylsilane as the reducing agent (Scheme 15). This reaction was carried out at room temperature under UV irradiation in case of both aromatic and aliphatic esters. Under this condition, alkyl and benzyl esters were converted selectively into corresponding aldehydes, where the full conversion was observed after only 3 hours with satisfactory yields. The reaction proceeded really well with methyl acetates substituted with *ortho*, *meta*-, and *para*- tolyl groups, even though substitution at the *ortho* position probably inhibited the reactivity to some extent.

Particularly, this catalytic system allowed selective reduction of lactones to lactols. They also provided evidence showing that the hydrosilylation occurredvia an oxidative addition of the hydrosilane to the unsaturated NHC–Fe species forming a silyl iron hydride complex.



Scheme 15: Selective reduction of esters under NHC–Iron complexes

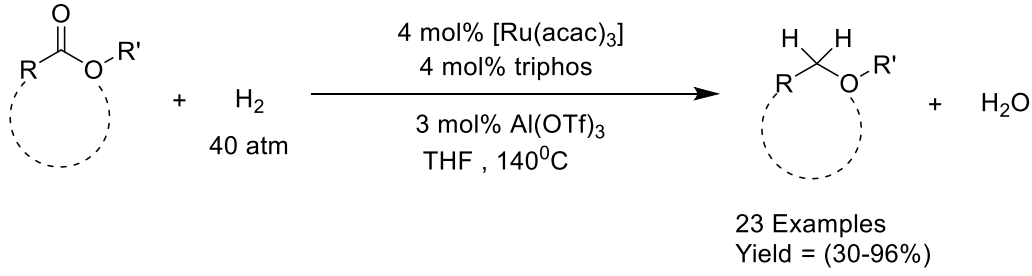
Beller and his team introduced[15] the first base-free iron-mediated catalysis for the hydrogenation of several carboxylic acid esters and lactones showing high efficiency (Scheme 16). The practical importance of the aforesaid catalyst system was demonstrated in the reduction of pharmaceutical intermediates. Based on studies, an outer-sphere mechanism was anticipated involving simultaneous hydrogen transfer from the metal centre and the ligand where the assumption was also supported by NMR experiments.



Scheme 16: Hydrogenation of esters to alcohols with Iron complex

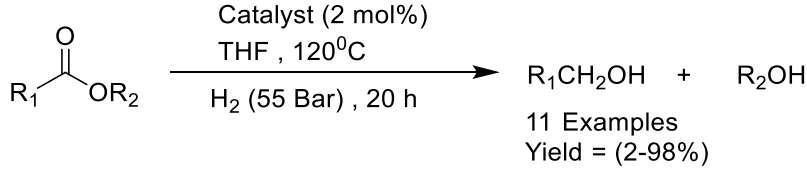
An excellent methodology further demonstrated[16] a general and effective deoxygenative hydrogenation of ester molecules in the presence of easily available ruthenium pre-catalysts. Using this method various aromatic and aliphatic lactones were transformed into cyclic ethers with high yields (Scheme 17). In addition to the reduction, linear esters provided the corresponding ethers with this dual catalyst system. Preliminary mechanistic studies disclosed that the Lewis acid and water played a crucial role for activating the catalyst in toluene and cleaving the selective C-OH bond of hemiacetal intermediates.

The applicability of this etherification technique was demonstrated by recycling the in situ formed catalyst without much loss of catalytic activity. However, the reaction pathway taking place through intramolecular condensation forming the corresponding ether was not accurately understood based on the reports of control experiments.



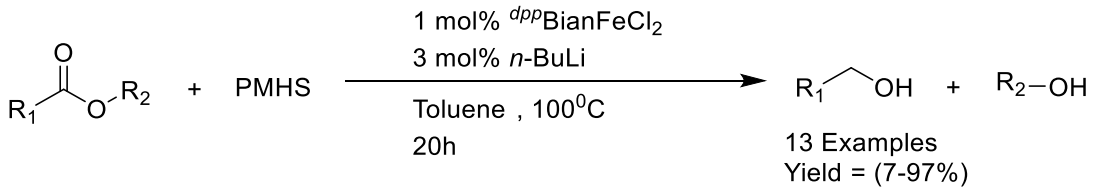
Scheme 17: Ruthenium (II) catalyzed etherifications of carboxylic acid esters

Yuwen *et al*. reported[17] a cobalt mediated additive-free catalytic system for the reduction of carboxylic acid esters to primary alcohols (Scheme 18). A variety of substrates including methyl, ethyl and benzyl esters were subjected under hydrogenation conditions, but, methyl esters exhibited low reactivity compared to corresponding ethyl and benzyl esters. Metal-ligand cooperativity was proved with an important derivative of the utilized cobalt catalyst and the results directed to a non bifunctional hydrogenation mechanism.



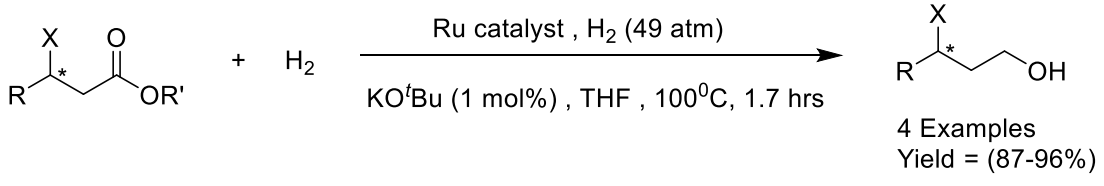
Scheme 18: Cobalt catalyzed hydrogenation of esters to alcohols

Tamang *et al*. proposed[18] a hydrosilylation process of esters achieved through the activation of ^{dpp}BIAN $FeCl_2$ (BIAN = 1, 2-((bis-2, 6-diisopropylphenyl)imino)acenaphthene) with *n*-BuLi (Scheme 19). In this reaction pathway electron donating, electron withdrawing, alicyclic and aliphatic esters were proved to be successful as substrates and the corresponding products were formed in good to excellent yields. Experimental works in this field suggested the possibility of radical transfer mechanism.



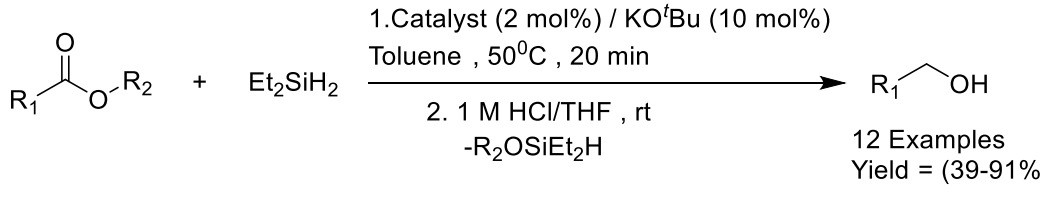
Scheme 19: Iron catalysed selective reduction of esters to alcohols

Ru-catalyzed hydrogenation[19] of esters to primary alcohols was reported by hydrosilylation using Ru-Triphos. A well-defined ruthenium pincer complex helped to overcome the limitation of low substrate scope (Scheme 20). Even Ru-catalysts with tri- and tetradentate ligands were also implemented for the reduction of esters where the transfer of hydrogen was achieved using alcohols as the hydrogen source under mild conditions.



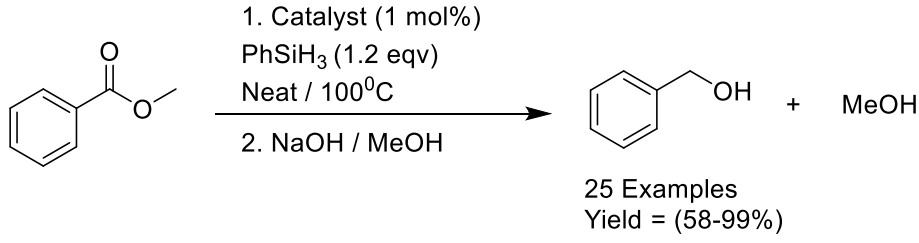
Scheme 20: Ruthenium catalyzed selective reduction of carboxylic esters

Gunanathan and his team developed[20] a simple and effective catalytic system for selective reduction of esters to alcohols utilizing diethylsilane as a reductant (Scheme 21). Specially, only a single cobalt pincer complex catalysed the transformations with complete selectivity without any additives. The diethylsilane mediated selective reduction of esters and the subsequent workup provided the product alcohols in high yields. Appreciable substrate scope with different functional group tolerance was achieved in the synthesis of alcohols starting from the esters. The hydrosilylation step was proposed to proceed via a Si-H bond activation initiated by cobalt, facilitated by metal–ligand.



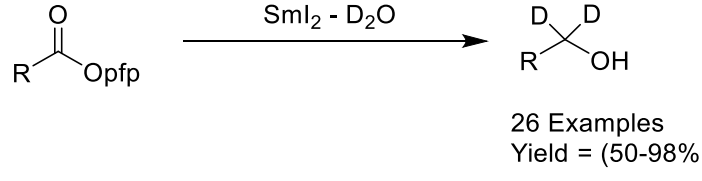
Scheme 21: Cobalt catalysed selective synthesis of alcohols from esters

Another novel work in this field described[21] a manganese catalyzed reduction of esters to alcohols using inexpensive and readily available PMHS as a reducing agent (Scheme 22). This reduction worked well with a variety of esters giving rise to their corresponding alcohols in high yields. The formation of Mn(I) intermediate as the active species in the catalytic reaction was detected using ^{55}Mn NMR spectroscopy.



Scheme 22: N-heterocyclic carbene (NHC) complex mediated reduction of esters to alcohols

Recently Li *et* al. reported[22] a chemoselective synthesis of α, α-dideuterio alcohols with the incorporation of deuterium by using pentafluorophenyl (pfp) esters as ketyl radical precursor and SmI_2 as a source of single electron (Scheme 23). They demonstrated the efficacy of the reaction to selectively form ketyl radicals from pfp esters and around 98% D_2 incorporation. The reaction accommodated a range of functional groups like nitrile, chloride, bromide, iodide and sulfonyls. Other functional groups like methoxy, phenolic hydroxyl, thiomethyl and sulphonamides also gave products with high yield under the reaction conditions.



Scheme 23: SmI_2-D_2O mediated reduction of esters to alcohols with D_2 incorporation

Thus, an overview of recent protocols for hydrogenation of esters involving several reagents and catalysts has been presented here to substantiate the importance of the current investigation going to be described in the next part.

III.3. Present investigation:

III.3.1. Background of the investigation:

Lithium aluminum hydride (LAH) is widelyused as a traditional reducing reagent for the reduction of carboxylic acid esters and sodium borohydride ($NaBH_4$) is used for the reduction of aldehydes and ketones chemoselectively in the presence of esters. In connection of another study, we targeted a chemoselective reduction starting with α-heteroatomic ester (**I**) having ketomethyl group present at the *para*- position. The reduction was attempted with $NaBH_4$ in methanol and it was expected that the reagent will selectively reduce the ketomethyl group to the corresponding secondary alcohol (**II**) without affecting the ester. But after the reduction the result was quite surprising, it was observed that both the α-heteroatomic ester and the ketomethyl group were reduced (**III**) under the reaction condition (Figure 1).

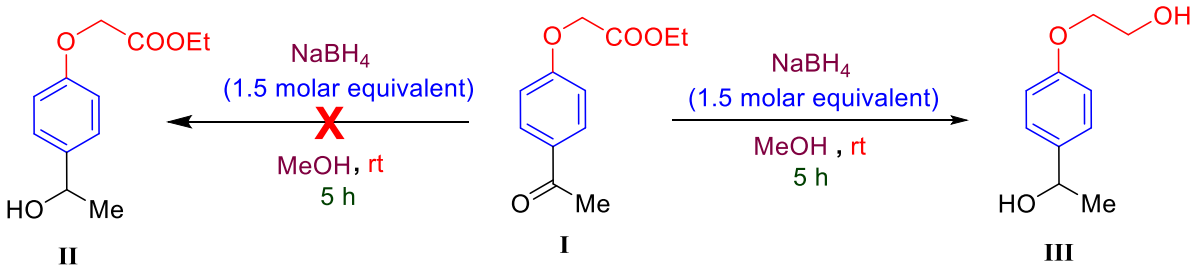


Figure 1: Reduction of both α-heteroatomic ester and ketomethyl groups with $NaBH_4$

To establish this experimental result further and to be sure of the role of α-heteroatom, the reduction was performed with ethyl 3-phenylpropanoate (**IV**) and the reaction failed (Figure 2) to give any reduced product. This result substantially proved that the presence of α-heteroatom in the ester is necessary for this reduction to occur with sodium borohydride. Ester reduction with $NaBH_4$ traditionally requires other additives,[2, 4, 6] being a mild hydride donor it, in general, cannot carry out the reduction of esters. But our detailed research based on the aforesaid experimental findings introduced such a unique additive-free reduction protocol; where α-heteroatomic esters were completely reduced to primary alcohols with excellent yield in the presence of $NaBH_4$ and methanol at room temperature.

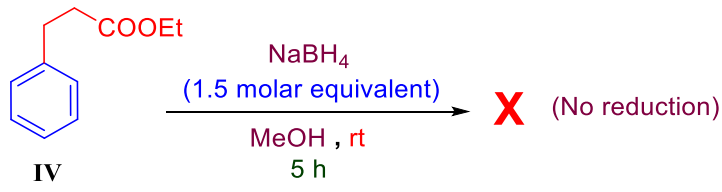
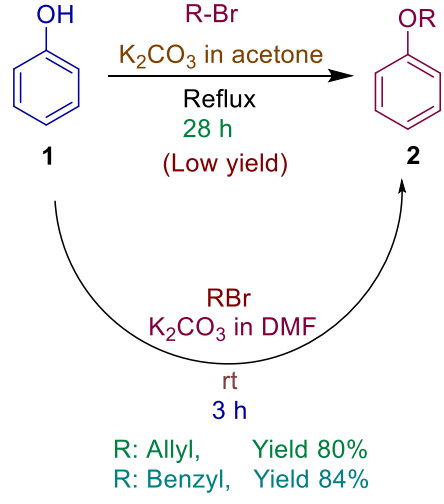


Figure 2: Failed reduction with ethyl 3-phenylpropanoate

III.3.2. Results and Discussion:

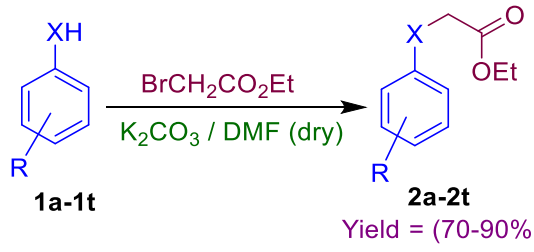
A novel reduction process of α-heteroatomic esters in presence of $NaBH_4$ and methanol was studied, where the reaction conditions were optimized for better yield. The substrate scope of the reaction was also verified with different types of α-heteroatomic esters in accordance with their property to react under the optimized reaction condition.

For the purpose of detailed and systematic investigation we prepared a number of heteroatomic esters starting from the corresponding phenols. The most conventional protocol for O-alkylation of phenolic -OH group involved the reaction of the phenol with the alkyl halide in anhydrous acetone in the presence of K_2CO_3. But this method was modified by choosing anhydrous DMF as the solvent in place of anhydrous acetone and it brought appreciable improvement in terms of reaction temperature, time and the yield of the esters (Scheme 24).



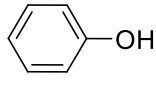
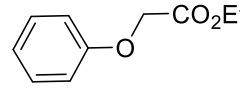
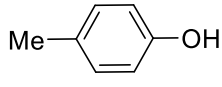
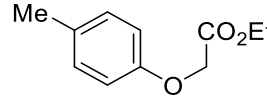
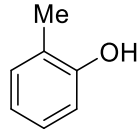
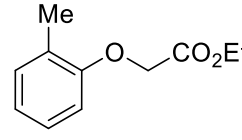
Scheme 24: Modified protocol for O-alkylation of phenol

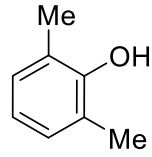
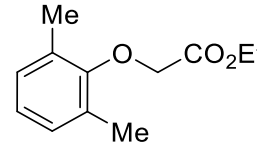
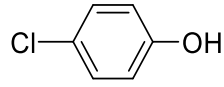
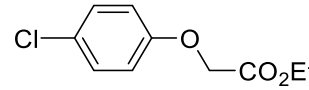
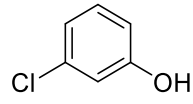
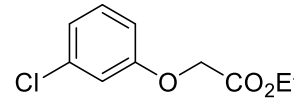
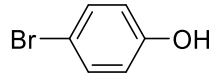
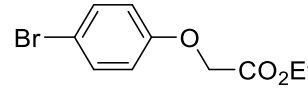
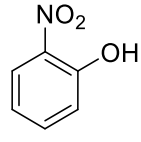
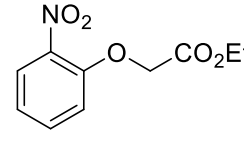
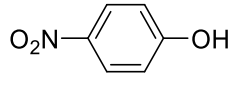
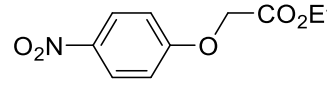
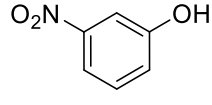
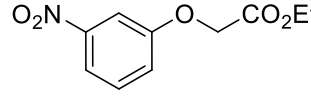
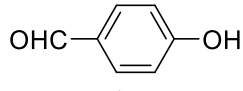
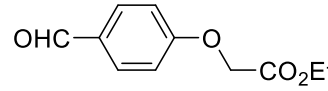
The superiority of DMF as a solvent for this reaction might be attributed to its aprotic polar nature which was responsible not only for the increased basicity of K_2CO_3 but also increased nucleophilicity of the anionic phenoxide due to its inefficient solvation with DMF. The modified procedure using K_2CO_3 in DMF was followed to prepare a number of esters with different heteroatoms at the α-position with respect to the ethoxycarbonyl functional group and various substituents in the aromatic ring (Scheme 25). The detailed results are presented in Table 1.

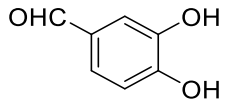
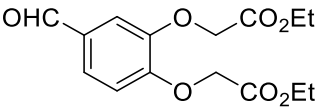
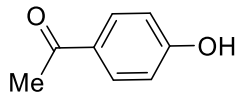
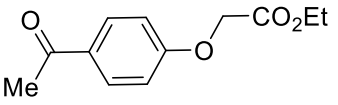
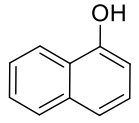
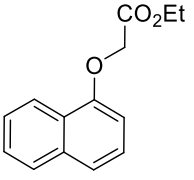
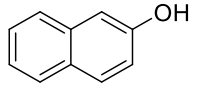
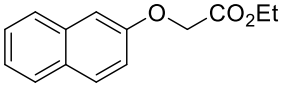
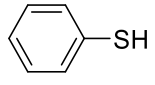
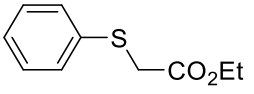
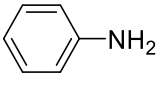
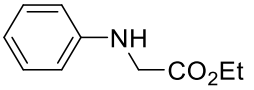
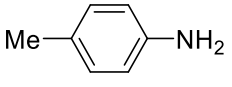
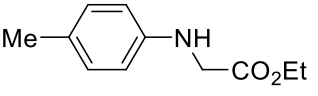
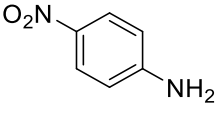
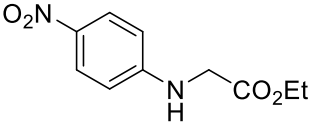
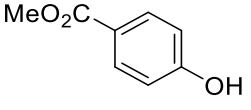
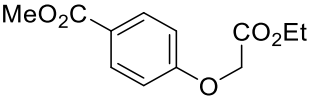


Scheme 25: Preparation of esters with the heteroatom at α-position

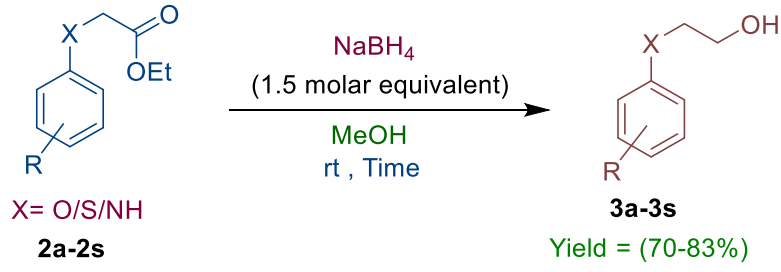
Table 1: Preparation of α-heteroatomic esters

Entry	Substrates (1)	Product (2)	Time (h)	Yield (%)
1.	 **1a**	 **2a**	4	86
2.	 **1b**	 **2b**	3	90
3.	 **1c**	 **2c**	3	87

4.	 **1d**	 **2d**	3	85
5.	 **1e**	 **2e**	4	80
6.	 **1f**	 **2f**	4	75
7.	 **1g**	 **2g**	4.5	70
8.	 **1h**	 **2h**	4	75
9.	 **1i**	 **2i**	3.5	78
10.	 **1j**	 **2j**	4	80
11.	 **1k**	 **2k**	3.5	82

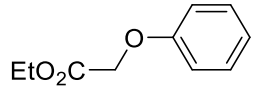
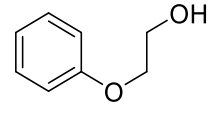
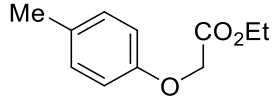
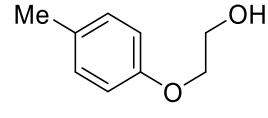
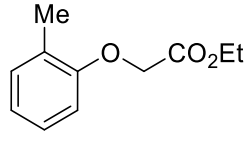
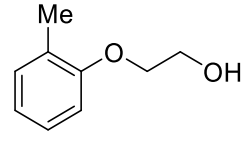
12.	 **1l**	 **2l**	3	84
13.	 **1m**	 **2m**	3	81
14.	 **1n**	 **2n**	4	78
15.	 **1o**	 **2o**	4	77
16.	 **1p**	 **2p**	3.5	84
17.	 **1q**	 **2q**	3	86
18.	 **1r**	 **2r**	2.5	88
19.	 **1s**	 **2s**	3.5	83
20.	 **1t**	 **2t**	3	87

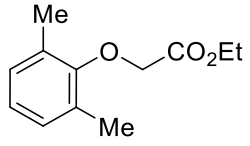
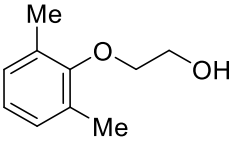
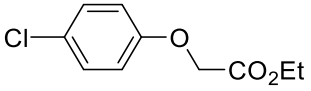
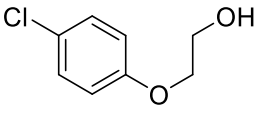
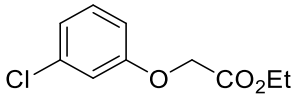
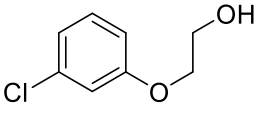
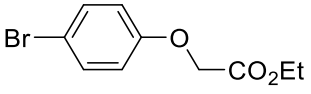
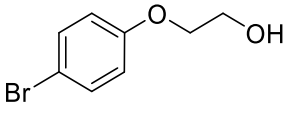
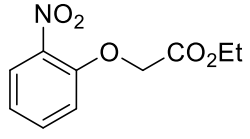
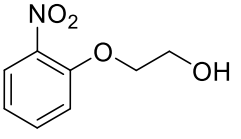
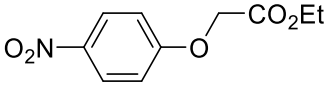
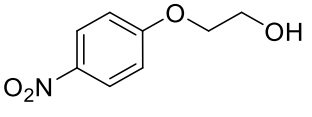
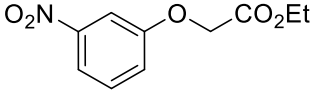
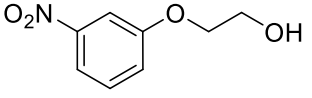
The substrates **2a-2t**, were prepared by utilizing the modified procedure of K_2CO_3 in DMF, where all the reactions were complete within 5 hours at room temperature. These substrates were then reacted with methanolic $NaBH_4$ at room temperature (Scheme 26). In every case the ethoxycarbonyl group was completely reduced to the hydroxymethyl moiety to produce the products (**3a-3s**). The detailed results are presented in Table 2.

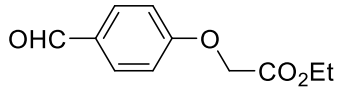
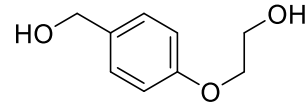
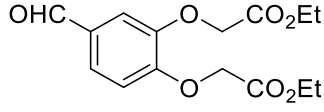
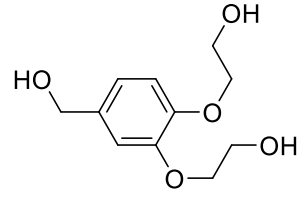
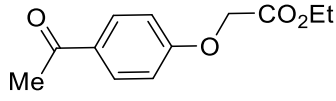
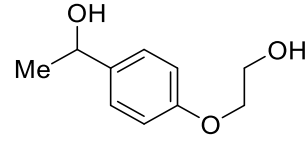
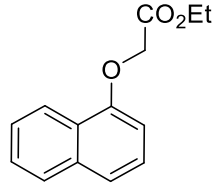
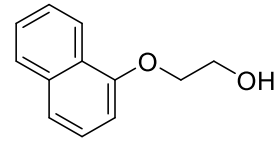
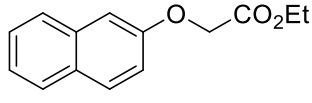
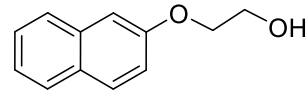
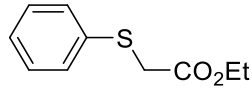
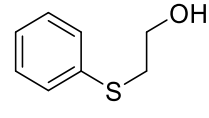
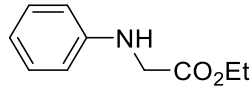
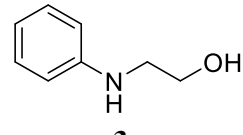


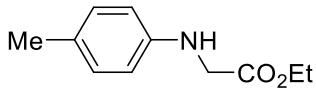
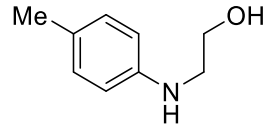
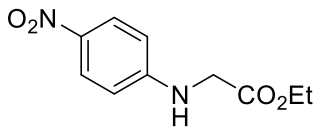
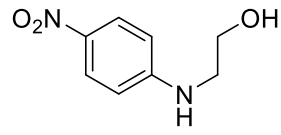
Scheme 26: Reduction of α-heteroatomic esters with $NaBH_4$

Table 2: Reduction of α-heteroatomic esters with $NaBH_4$

Entry	Substrates (2)	Product (3)	Time (h)	Yield (%)
1.	 **2a**	 **3a**	4	81
2.	 **2b**	 **3b**	3	80
3.	 **2c**	 **3c**	3	80

4.	 **2d**	 **3d**	4	83
5.	 **2e**	 **3e**	5	75
6.	 **2f**	 **3f**	4	72
7.	 **2g**	 **3g**	4	70
8.	 **2h**	 **3h**	4	82
9.	 **2i**	 **3i**	4	83
10.	 **2j**	 **3j**	4	80

11.	 **2k**	 **3k**	4	75[a]
12.	 **2l**	 **3l**	4	74[b]
13.	 **2m**	 **3m**	5	75[a]
14.	 **2n**	 **3n**	5	70
15.	 **2o**	 **3o**	5	73
16.	 **2p**	 **3p**	4	80
17.	 **2q**	 **3q**	4	76

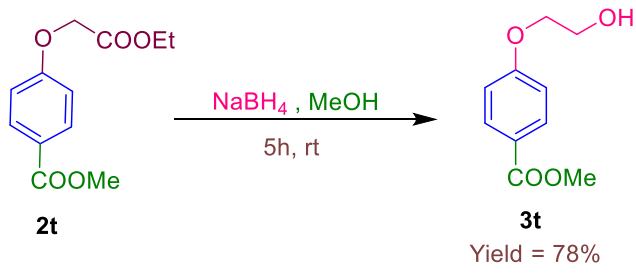
18.	 **2r**	 **3r**	4	74
19.	 **2s**	 **3s**	5	73

[a]3.0 molar equivalent of $NaBH_4$ was used. [b]5.0 molar equivalent of $NaBH_4$ was used.

As shown in Table 2, the reaction was quite efficient to furnish the products with alkyl substituents present in the benzene ring giving the products **3a**-**3d** with around 80% yield. Simultaneous reduction of the formyl and ketomethyl along with the ethoxycarbonyl moieties took place with sodium borohydride to produce **3k**, **3l** and **3m** with the respective yield of 75%, 74% and 75%. The nitro group survived under this reaction protocol making the reduction facile only at the ethoxycarbonyl moiety, and as a result products **3h**-**3j** were produced. Similarly the carbon-halogen bond also remained unchanged after the reaction providing **3e**-**3g**. The ethoxycarbonyl group attached to a naphthyl ring at α as well as β positions were reduced successfully to furnish products **3n** and **3o** with satisfactory yields around 70%.

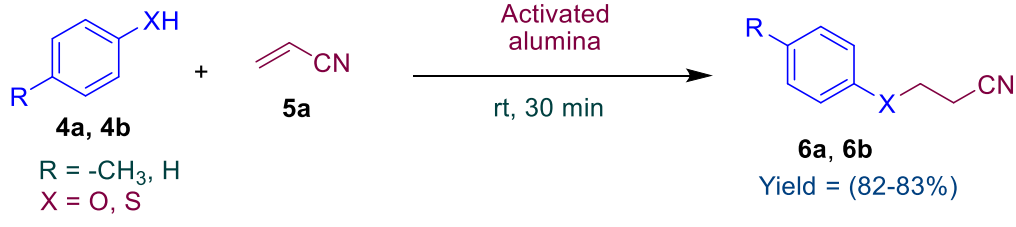
So far the compounds having oxygen as α-heteroatom were studied. Similar trend was also observed with nitrogen and sulfur as the α–heteroatoms. This reaction was tried with some other α-heteroatomic (S, N) esters and all the experiments were highly successful providing **3p**-**3s** in very good yield.

The substrate **2t,** under the present reaction condition, afforded the mono-ester **3t** (Scheme 27); here the methoxycarbonyl moiety directly attached with aromatic ring remained totally unaffected. It was therefore obvious that mere aromatic esters were not susceptible to extensive reduction, only the α-heteroatomic ester was completely reduced with methanolic $NaBH_4$. This observation also confirmed the fact that this reduction is happening only because of the α-heteroatom without any significant role of the phenyl ring and thus the chemoselectivity of the process was firmly established.



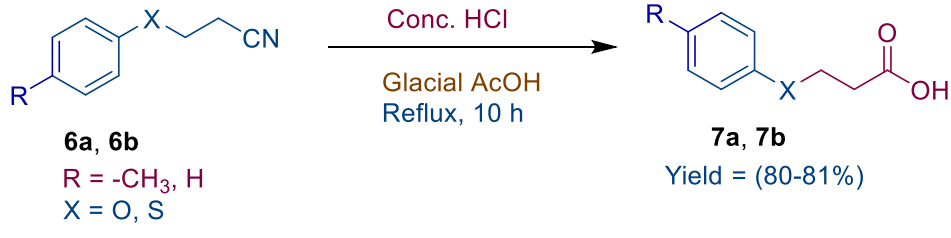
Scheme 27: Chemoselectivity of reduction of α-heteroatomic esters with $NaBH_4$

Our next idea was to extend the substrate scope for further reaction probabilities and check the effect of the heteroatoms at the β position. For this, we did the reaction on *p*-cresol (**4a**) and thiophenol (**4b**) with acrylonitrile (**5a**) under solvent-free condition using activated alumina (Scheme 28). The products **6a** and **6b** were obtained in high yields.



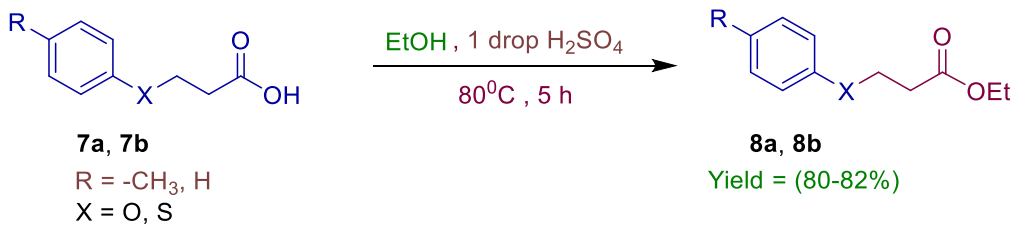
Scheme 28: Reaction of *p*-cresol and thiophenol with acrylonitrile

The product nitriles were then hydrolysed under acidic conditions using conc. HCl and glacial acetic acid under reflux for about 10 hours (Scheme 29).



Scheme 29: Hydrolysis of the prepared nitriles

The completion of the reaction was constantly monitored by Thin Layer Chromatography (TLC). **7a** and **7b** were formed in this process with around 80% yield. These acids were the converted to their corresponding β-heteroatomic ethyl esters **8a** and **8b** with high yields under acid-catalysed esterification process (Scheme 30).

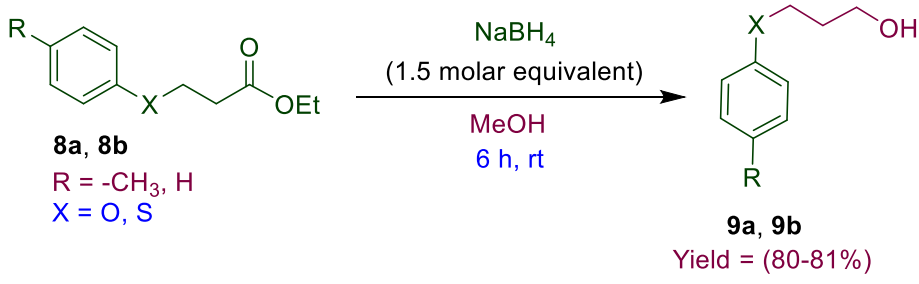


7a, **7b**
R = -CH_3, H
X = O, S

8a, **8b**
Yield = (80-82%)

Scheme 30: Esterfication of the prepared acids under acidic condition

These β-heteroatomic ethyl esters were the main substrates used for checking the probability of reduction with heteroatoms present at the β position. Final results were quite satisfactory as this protocol was completely applicable for these β-heteroatomic ethyl esters also. The corresponding primary alcohols **9a** and **9b** were prepared under this method with high yields and no unwanted by products were generated (Scheme 31).

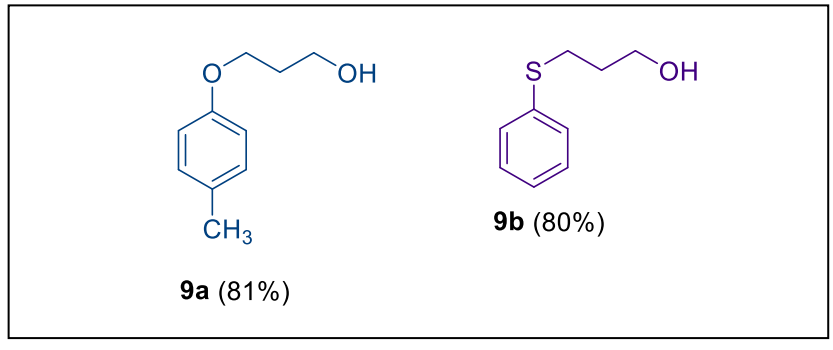


8a, **8b**
R = -CH_3, H
X = O, S

9a, **9b**
Yield = (80-81%)

Scheme 31: Reduction of the β-heteroatomic ethyl esters with $NaBH_4$

Compounds prepared according to Scheme 31

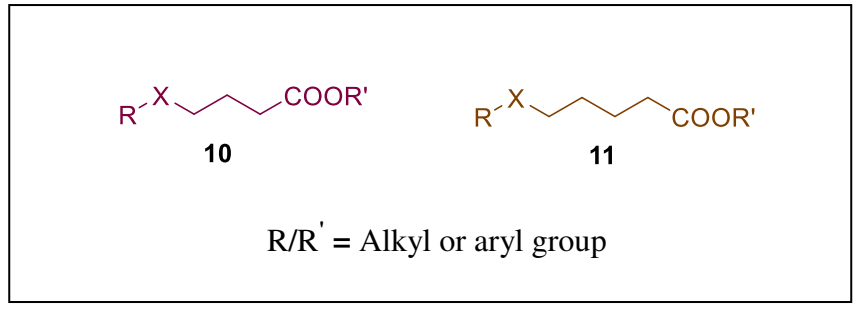


9a (81%)

9b (80%)

The chemoselectivity study along with these observations recommended the absolute necessity of heteroatomes to govern the reduction of esters with $NaBH_4$ in methanol.

The actual mechanism for this type of reduction is still unknown, so we are trying out reactions to investigate the mechanism of this process. On the other hand we are also checking the probability and substrate scope of this reaction with substrates having heteroatoms in γ and δ positions (**10**, **11**).



Moreover, the effect of aliphatic acyclic, alicyclic and vinylic, propargylic moieties in place of aromatic rings towards this reduction needs to be studied.

III.3.3. Conclusion:

To summarize, the present experimental protocol introduced a novel and modified method for the reduction of α- as well as β- heteroatomic esters with mild reducing reagent, namely, sodium borohydride ($NaBH_4$). This promising catalytic method was carried out without the addition of any additive and thus contributed to sustainable chemistry. Compared to other existing methodologies, this was rapid, cost effective, easy work up process and worked at room temperature giving excellent product yield with no undesired side products.

III.3.4. Experimental

General:

All organic solvents used for the reaction were purchased from Merck and SRL, and were distilled before use. Melting points were recorded in open capillary on electrical bath which are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker–300 (300 MHz) and Bruker–400 (400 MHz) spectrometer in $CDCl_3$ solvent with TMS as internal reference. Column chromatography were performed on silica gel (60–120 mesh) supplied by SRL, India. Thin layer chromatographic separations were performed on pre-coated glass plates using silica gel G for TLC (E. Merck).

(v) Representative procedure for the reaction:

To a mixture of ethyl 2-phenoxyacetate (**2a**, 180 mg, 1.0 mmol) and MeOH (2 ml) the $NaBH_4$ (57 mg) was added. The reaction mixture was stirred for the required period of time at room temperature till the reaction was completed (monitored with TLC). Then the reaction mixture was taken out, excess MeOH was removed under reduced pressure and ethyl acetate (10 ml) was added to dissolve the product. The organic extract was thoroughly washed with water (3×10 ml) to remove any trace of MeOH and dried over anhydrous Na_2SO_4. The crude product was obtained by removal of the solvent under reduced pressure to afford 2-phenoxyethan-1-ol (**3a**, 112 mg, Yield 81%).

(vi) Spectral and analytical data of the compounds:

1. **2-phenoxyethan-1-ol** (**3a**)[23] Colourless semisolid (Yield 81%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.95 (2H, t, *J* = 3.9 Hz), 4.06 (2H, t, *J* = 3.9 Hz), 4.80 (1H, bs), 6.91-7.00 (3H, m), 7.27-7.32 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.1, 69.2, 114.7, 121.1, 129.6, 158.8

2. **2-(p-tolyloxy)ethan-1-ol** (**3b**)[24] Colourless semisolid (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.31 (3H, s), 3.95 (2H, t, *J* = 3.9 Hz), 4.04 (2H, t, *J* = 3.9 Hz), 5.28 (1H, bs), 6.83 (2H, d, *J* = 8.2 Hz), 7.10 (2H, d, *J* = 7.9 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 20.5, 61.2,69.4, 114.6, 130.0, 130.2, 156.7

3. **2-(o-tolyloxy)ethan-1-ol** (**3c**)[24] Yellowish semisolid (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.27 (3H, s), 3.99 (2H, t, *J* = 3.9 Hz), 4.08 (2H, t, *J* = 3.9 Hz), 6.82-6.93 (3H,

m), 7.16-7.26 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.5, 61.2,69.9, 112.6, 120.4, 126.2, 131.7, 155.7

4. **2-(2, 6-dimethylphenoxy)ethan-1-ol** (**3d**)[25] Yellowish semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.17 (6H, s), 3.71 (2H, t, *J* = 3.9 Hz), 4.35 (2H, t, *J* = 3.9 Hz), 7.06-7.12 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.2, 62.4,73.0, 112.6, 124.1, 128.9, 130.8, 155.3

5. **2-(4-chlorophenoxy)ethan-1-ol** (**3e**)[26] Yellowish semisolid (Yield 75%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.88 (2H, t, *J* = 3.6 Hz), 3.95 (2H, t, *J* = 3.6 Hz),6.78 (2H, d, *J* = 8.8 Hz), 7.18 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.4, 69.7, 117.7, 126.2, 130.5, 157.7

6. **2-(3-chlorophenoxy)ethan-1-ol** (**3f**)[25] Yellow semisolid (Yield 72%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.94 (2H, t, *J* = 3.9 Hz), 4.04 (2H, t, *J* = 3.8 Hz),6.77-6.83 (1H, m), 6.90-6.95 (1H, m), 7.15-7.26 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 60.9,69.5, 112.9, 114.8, 120.1, 130.3, 134.8, 159.4

7. **2-(4-bromophenoxy)ethan-1-ol** (**3g**)[27] Yellow semisolid (Yield 70%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.62 (2H, t, *J* = 4.0 Hz), 3.91 (2H, t, *J* = 4.0 Hz), 5.23 (1H, s),6.71 (2H, d, *J* = 8.7 Hz), 7.30 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.1, 69.5, 113.2, 116.4, 132.3, 157.7

8. **2-(2-nitrophenoxy)ethan-1-ol** (**3h**)[28] Yellowish semisolid (Yield 82%); ^{1}H NMR (300 MHz; $CDCl_3$): 3.88 (2H, t, *J* = 4.2 Hz), 4.13 (2H, t, *J* = 4.2 Hz), 6.91-7.04 (1H, m), 7.44 (2H, t, *J* = 6.8 Hz), 7.72 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 15.5, 61.2,69.9, 112.6, 120.4, 126.2, 131.7, 155.7

9. **2-(4-nitrophenoxy)ethan-1-ol** (**3i**)[24] Yellow semisolid (Yield 83%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.02 (2H, t, *J* = 4.1 Hz), 4.18 (2H, t, *J* = 4.1 Hz), 5.29 (1H, s) 6.97 (2H, d, *J* = 9.1 Hz), 8.19 (2H, d, *J* = 9.1 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.0, 70.0, 113.2, 114.5, 125.9, 141.6, 163.8

10. **2-(3-nitrophenoxy)ethan-1-ol** (**3j**)[24] Yellow semisolid (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): 4.01 (2H, t, *J* = 3.8 Hz), 4.15 (2H, t, *J* = 3.8 Hz), 7.26 (1H, t, *J* = 7.7 Hz), 7.42 (1H, t, *J* = 8.1 Hz), 7.73-7.83 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.2,69.7, 111.6, 115.4, 130.2, 151.4, 158.4

11. **2-(4-hydroxymethyl-phenoxy)-ethanol** (**3k**)[29] Colourless semisolid (Yield 75%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.12 (1H, bs), 3.96 (2H, t, *J* = 4.0 Hz), 4.09 (2H, t, *J* = 4.0 Hz), 5.34 (2H, s), 6.88-6.90 (2H, m), 7.33-7.39 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.4, 64.9, 69.3, 114.6, 128.7, 133.6, 158.2

12. **2-[2-(2-hydroxy-ethoxy)-4-hydroxymethyl-phenoxy]-ethanol** (**3l**) Yellowish semisolid (Yield 74%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.88 (2H, t, *J* = 3.9 Hz), 4.04 (2H, t, *J* = 3.9 Hz), 4.79 (2H, s), 6.82-6.85 (2H, m), 6.94-6.97 (1H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 63.4, 68.7, 76.2, 113.6, 115.1, 119.7, 133.2, 143.2, 144.8

13. **1-(4-(2-hydroxyethoxy)phenyl)ethan-1-ol** (**3m**)[29] Colourless semisolid (Yield 75%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.48 (2H, d, *J* = 6.3 Hz), 3.96 (2H, t, *J* = 3.9 Hz), 4.07 (2H, t, *J* = 3.9 Hz), 4.84-4.87 (1H, m), 6.89 (2H, d, *J* = 8.3 Hz), 7.28 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 25.1, 61.4, 69.3, 69.9, 114.5, 126.7, 138.5, 158.0

14. **2-(naphthalen-1-yloxy)ethan-1-ol** (**3n**)[30] Yellowish semisolid (Yield 70%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.86 (2H, s), 4.36 (2H, t, *J* = 6.9 Hz), 4.85 (1H, s), 6.29-6.33 (1H, m), 6.74-6.84 (1H, m), 7.28-7.53 (2H, m) 7.53-7.86 (1H, m), 8.25-8.27(1H, m), 8.46 (1H, s); ^{13}C NMR (75 MHz; $CDCl_3$): δ 60.9, 69.9, 107.3, 120.4, 123.5, 125.4, 126.1, 126.6, 127.5, 134.5, 154.3

15. **2-(naphthalen-2-yloxy)ethan-1-ol** (**3o**)[27] Yellow semisolid (Yield 73%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.86 (2H, s), 4.76 (2H, d, *J* = 4.0 Hz), 5.51 (1H, s), 7.11-7.15 (1H, m), 7.32-7.47 (3H, m), 7.66-7.80 (3H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 61.9, 65.5, 107.2, 118.6, 124.2, 126.5, 127.8, 128.9, 153.5

16. **2-(phenylthio)ethan-1-ol** (**3p**)[31]Yellowish semisolid (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.10 (2H, t, *J* = 5.9 Hz), 3.72 (2H, t, *J* = 5.9 Hz), 5.28 (1H, s), 7.21-7.39 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 36.8, 60.5,126.5, 129.1, 129.9, 132.9, 135.2

17. **2-(phenylamino)ethan-1-ol** (**3q**)[32] Yellow semisolid (Yield 76%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.54 (2H, t, *J* = 5.9 Hz), 3.78 (2H, t, *J* = 5.9 Hz), 4.83 (1H, bs), 6.64-6.77 (3H, m), 7.17-7.26 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 46.1, 61.0,113.4, 120.7, 129.3, 147.5

18. **2-(p-tolylamino)ethan-1-ol** (**3r**)[33] Yellow semisolid (Yield 74%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.25 (3H, s), 3.49 (2H, t, *J* = 4.5 Hz), 3.77 (2H, t, *J* = 4.7 Hz), 6.56-6.63 (2H, m), 6.98-7.06 (2H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 21.1, 45.8, 61.5, 113.2, 129.4, 129.8, 144.7

19. **2-((4-nitrophenyl)amino)ethan-1-ol** (**3s**)[34] Yellowish semisolid (Yield 73%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 3.41 (2H, t, *J* = 4.5 Hz), 3.91 (2H, t, *J* = 4.7 Hz), 4.91 (1H, bs), 6.58 (2H, t, *J* = 8.9 Hz), 8.09 (2H, d, *J* = 8.9 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 46.1, 61.3, 61.5, 110.3, 127.4, 136.1, 153.7

20. **methyl 4-(2-hydroxyethoxy)benzoate** (**3t**)[29] White solid (Yield 78%, m.p. 65^{o}C); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.39 (1H, s), 3.87 (3H, s), 3.96-3.97 (2H, m), 4.10-4.13

(2H, m), 6.91 (2H, d, *J*= 8.7 Hz), 7.97 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 51.9, 61.1, 69.4, 114.1, 122.7, 131.6, 162.5, 166.9

21. **3-(p-tolyloxy)propan-1-ol** (**9a**)[35] Colourless semisolid (Yield 81%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 2.02 (2H, t, *J* = 5.7 Hz), 2.30 (3H, s), 3.84 (2H, t, *J* = 4.0 Hz), 4.08 (2H, t, *J* = 5.7 Hz), 6.82 (2H, d, *J* = 8.0 Hz), 7.09 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 20.5, 32.1, 60.3, 65.7, 114.4, 129.9, 130.1, 156.7

22. **3-(phenylthio)propan-1-ol** (**9b**)[36] Colourless semisolid (Yield 80%); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.87 (2H, t, *J* = 6.2 Hz), 3.02 (2H, t, *J* = 6.8 Hz), 3.71 (2H, t, *J* = 5.2 Hz), 7.18-7.33 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 30.0, 31.7, 61.5, 65.7, 126.0, 128.8, 136.3.

^{1}H and ^{13}C spectra of some representative compounds:

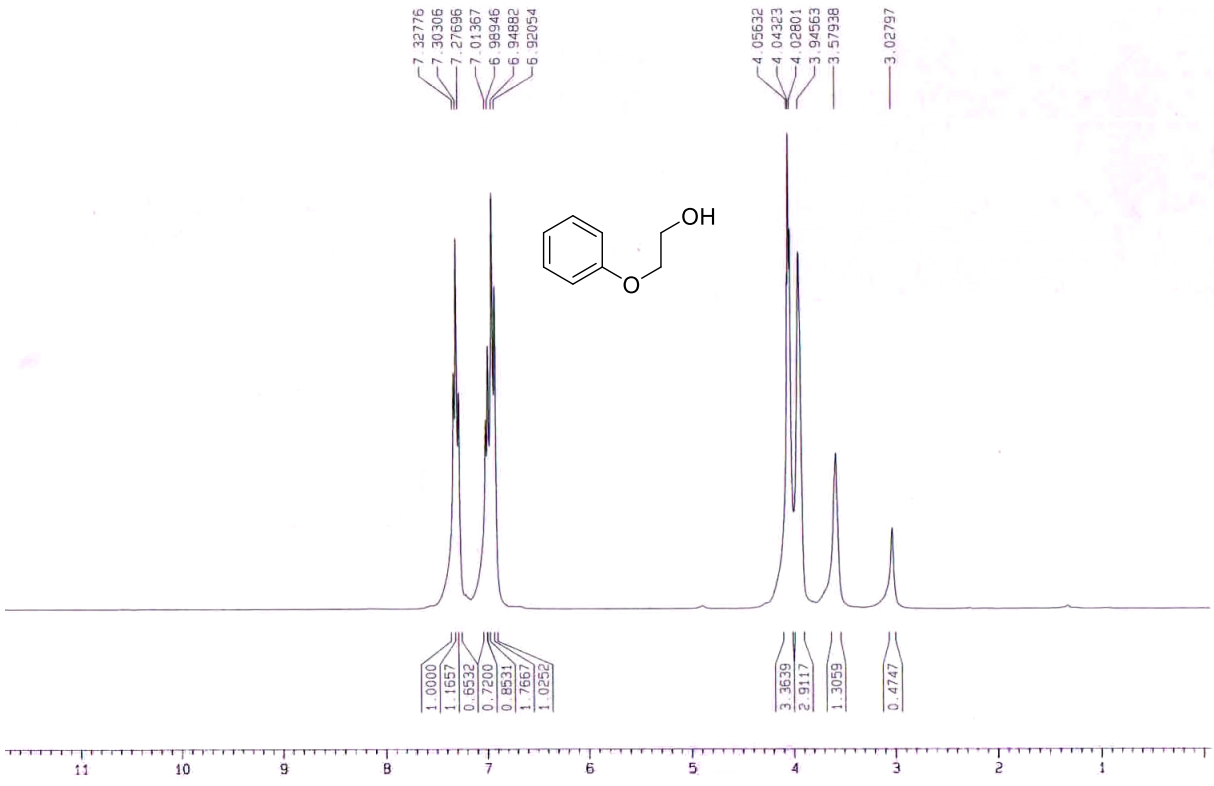


Figure 1: ^{1}H NMR of 2-phenoxyethan-1-ol (**3a**)

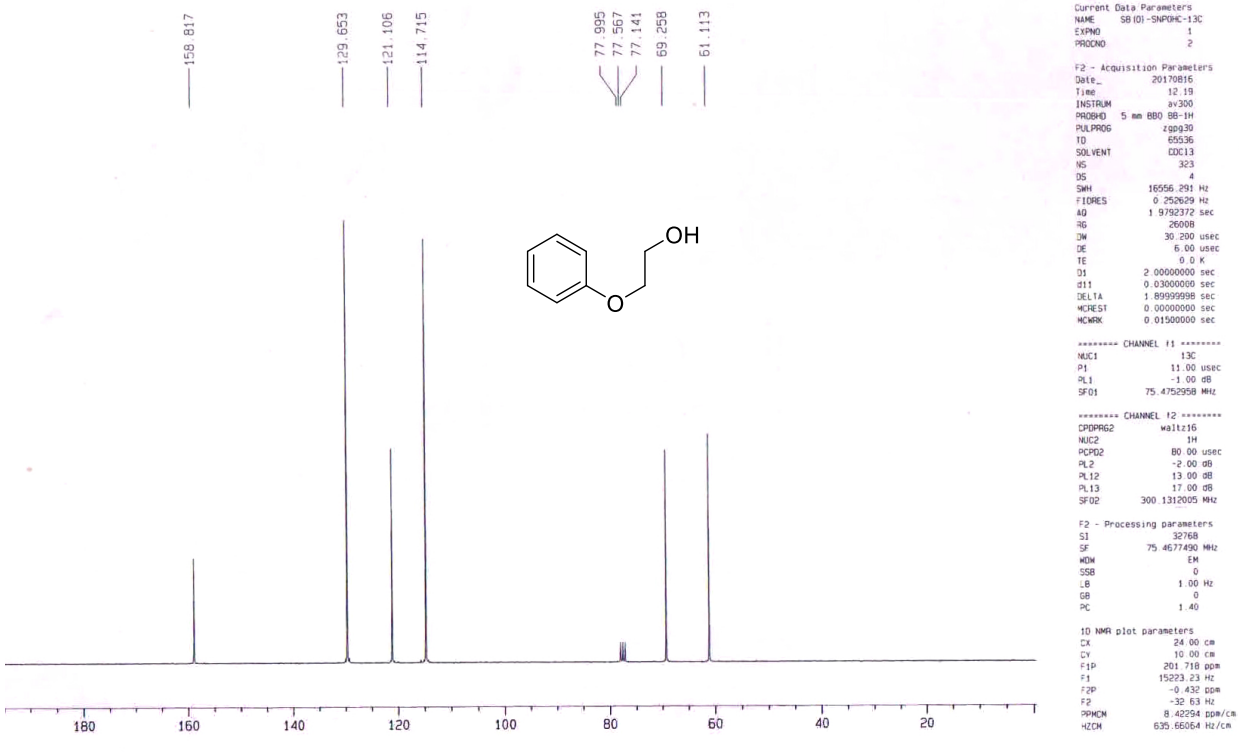


Figure 2: ^{13}C NMR of 2-phenoxyethan-1-ol (**3a**)

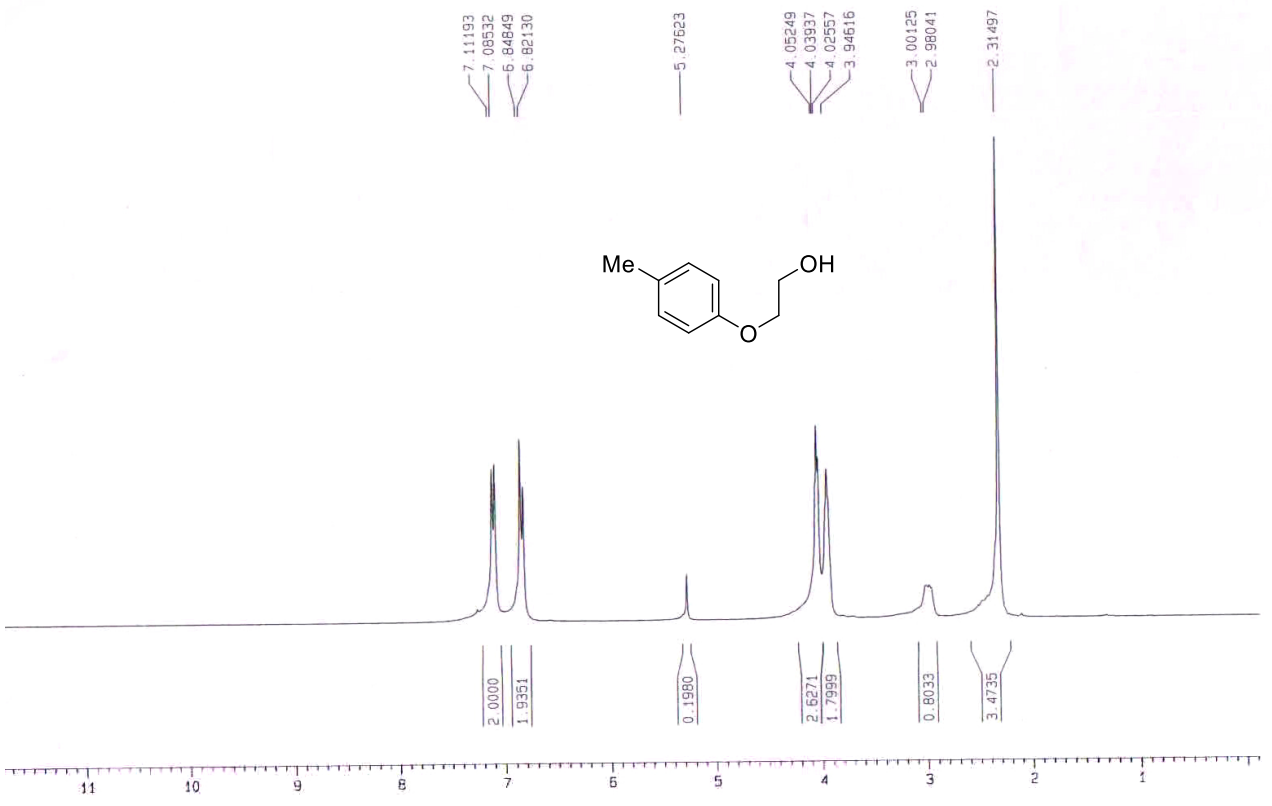


Figure 3: ^{1}H NMR of 2-(p-tolyloxy)ethan-1-ol (**3b**)

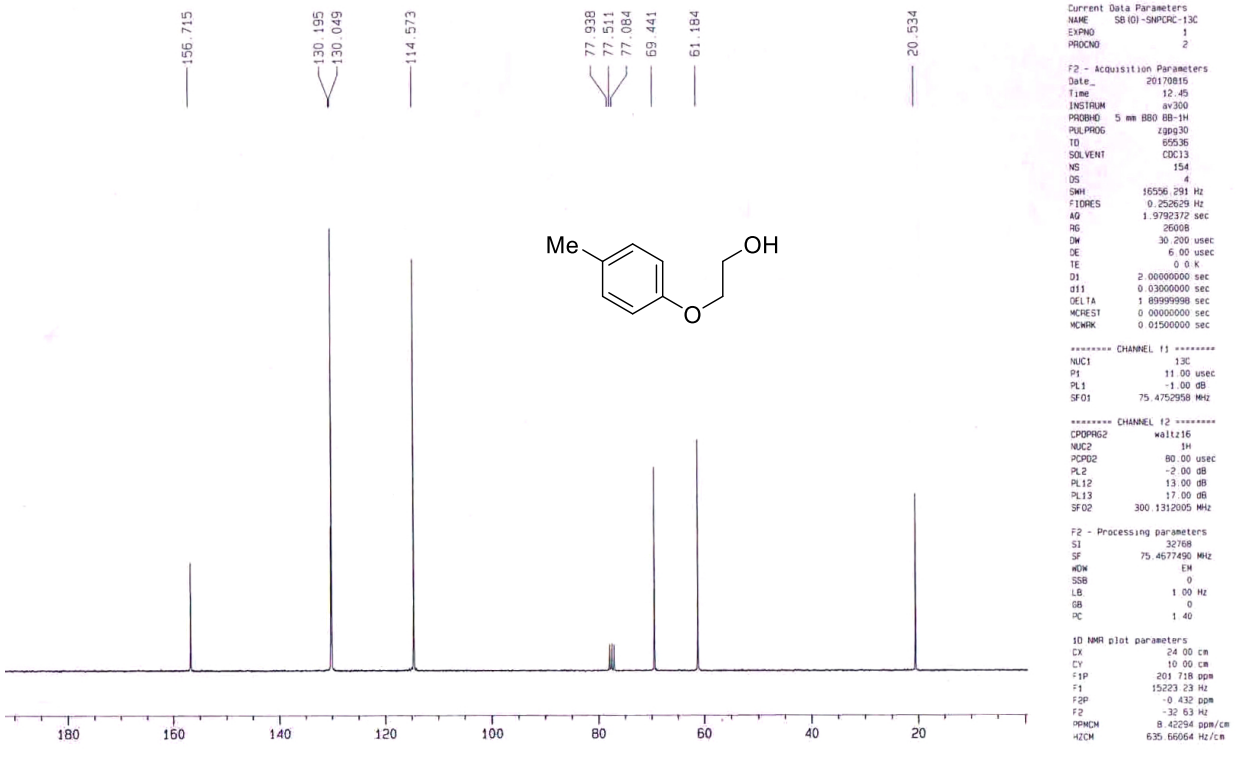


Figure 4: ^{13}C NMR of 2-(p-tolyloxy)ethan-1-ol (**3b**)

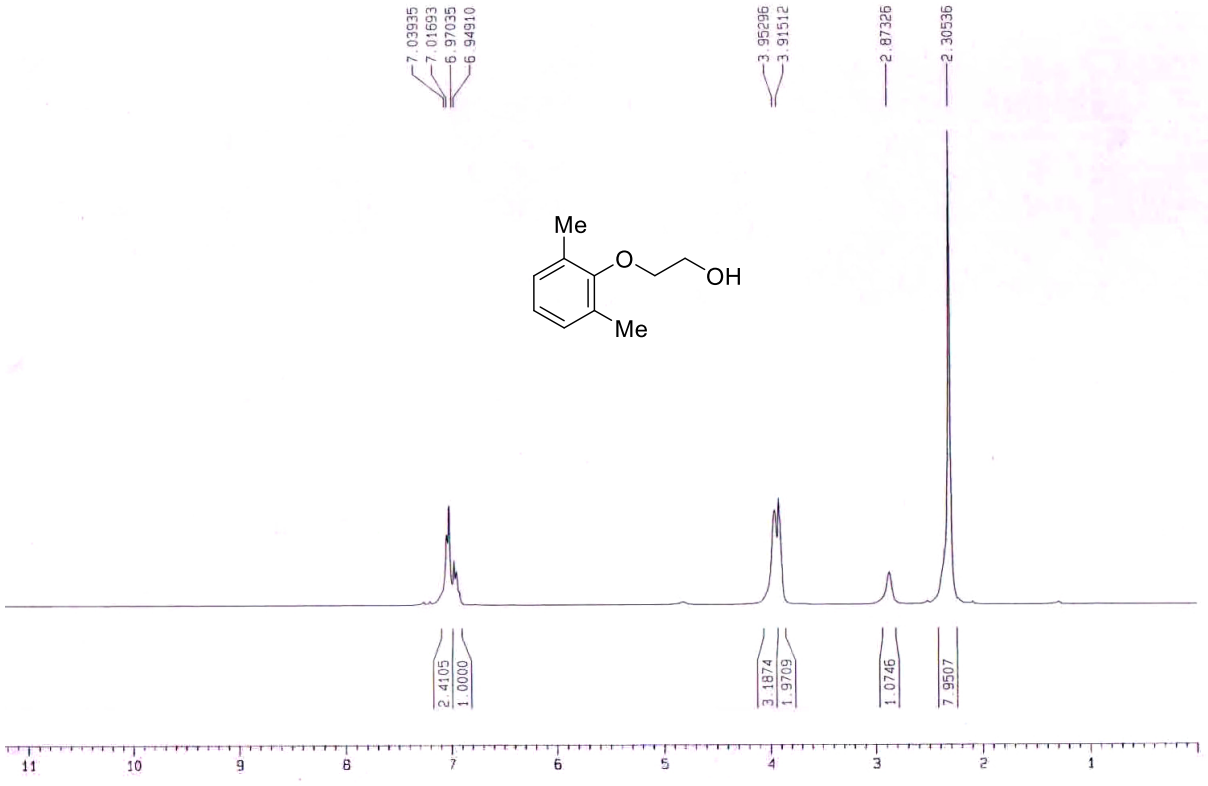


Figure 5: ^{1}H NMR of 2-(2, 6-dimethylphenoxy)ethan-1-ol (**3d**)

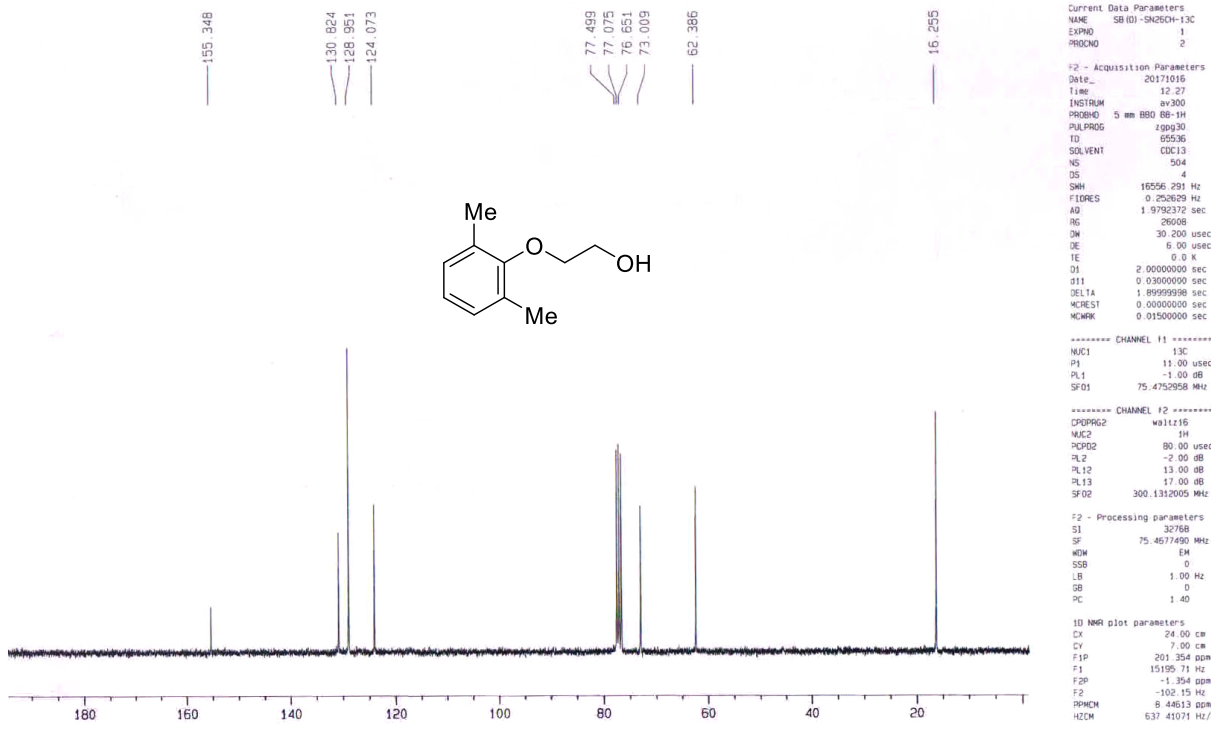


Figure 6: ^{13}C NMR of 2-(2, 6-dimethylphenoxy)ethan-1-ol (**3d**)

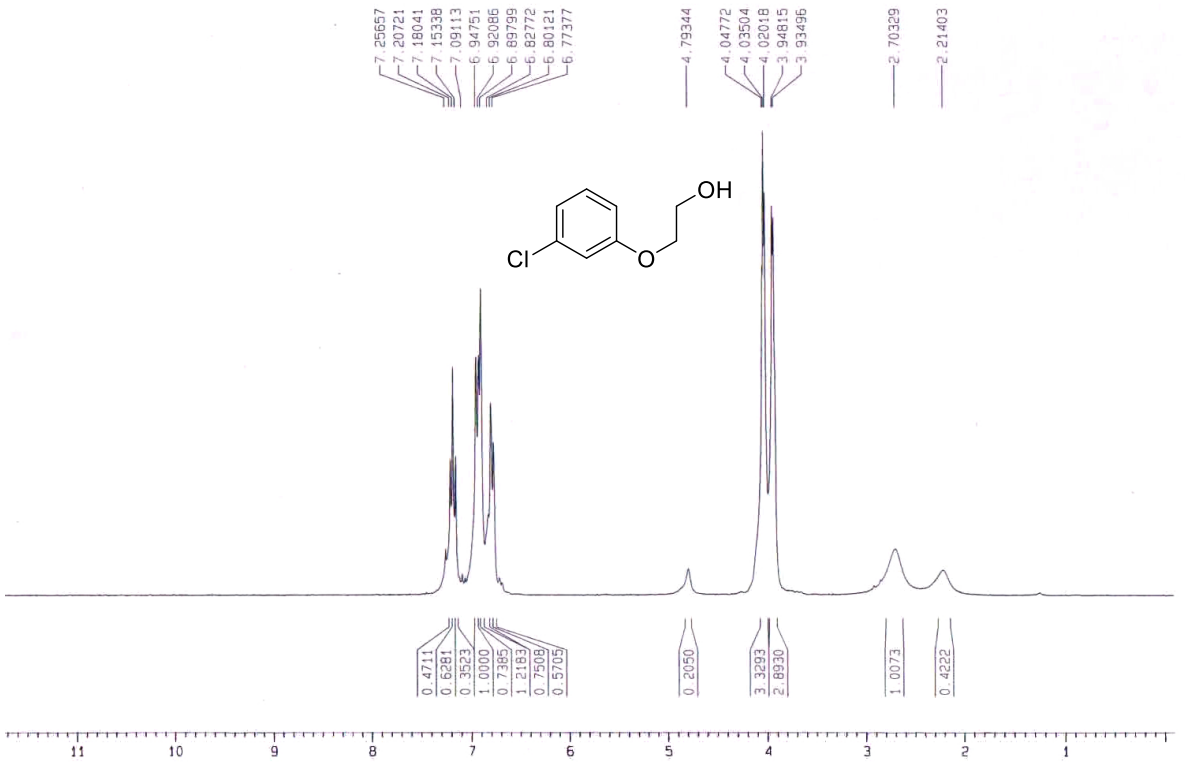


Figure 7: ^{1}H NMR of 2-(3-chlorophenoxy)ethan-1-ol (**3f**)

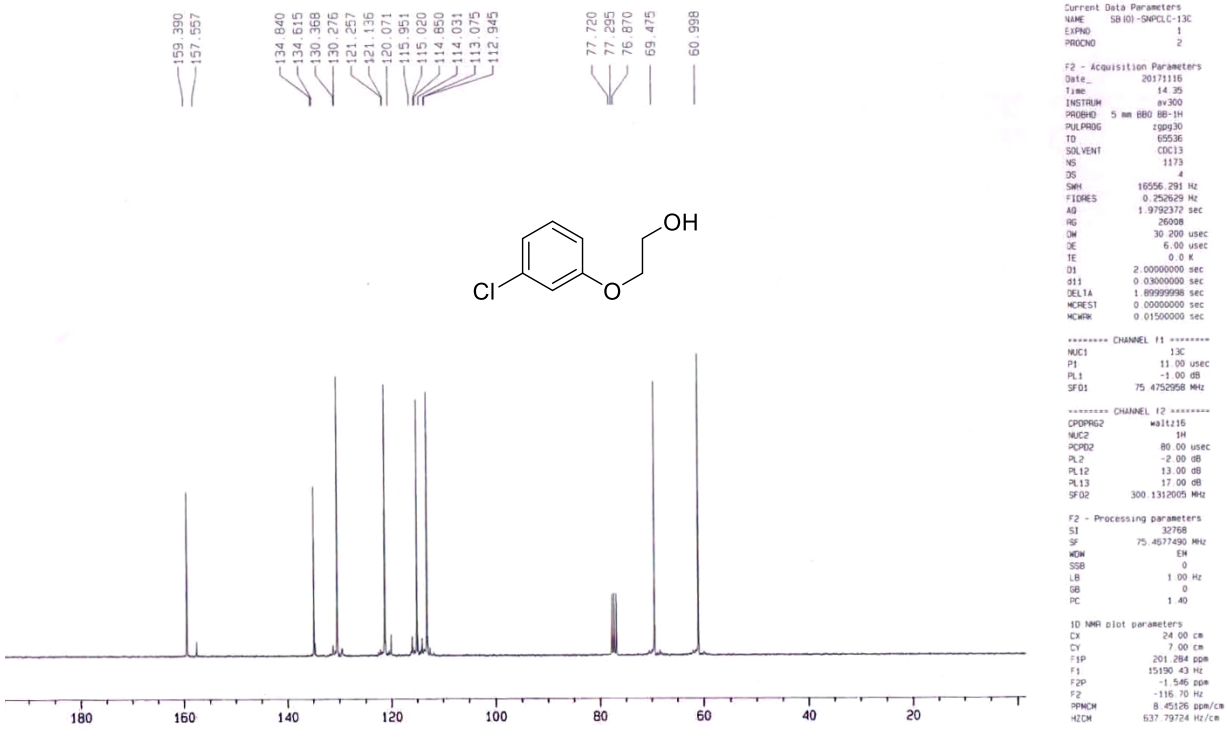


Figure 8: ^{13}C NMR of 2-(3-chlorophenoxy)ethan-1-ol (**3f**)

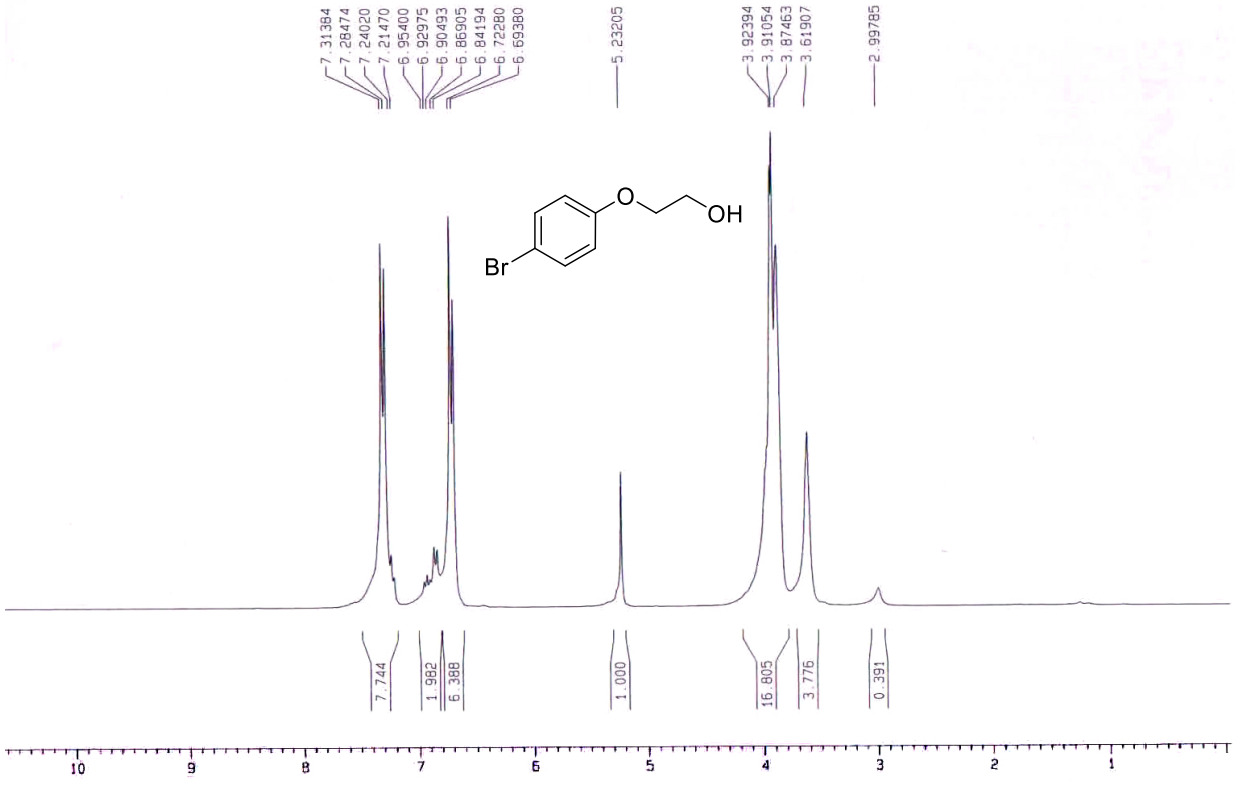


Figure 9: ^{1}H NMR of 2-(4-bromophenoxy)ethan-1-ol (**3g**)

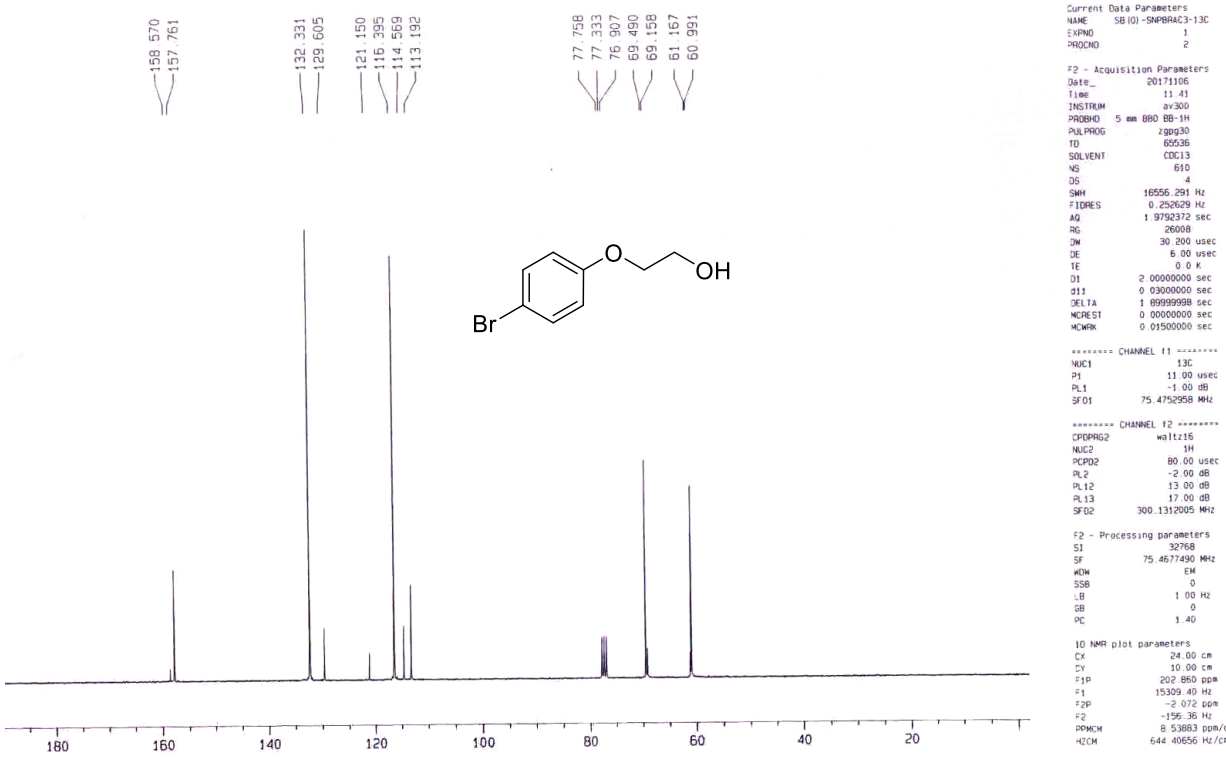


Figure 10: ^{13}C NMR of 2-(4-bromophenoxy)ethan-1-ol (**3g**)

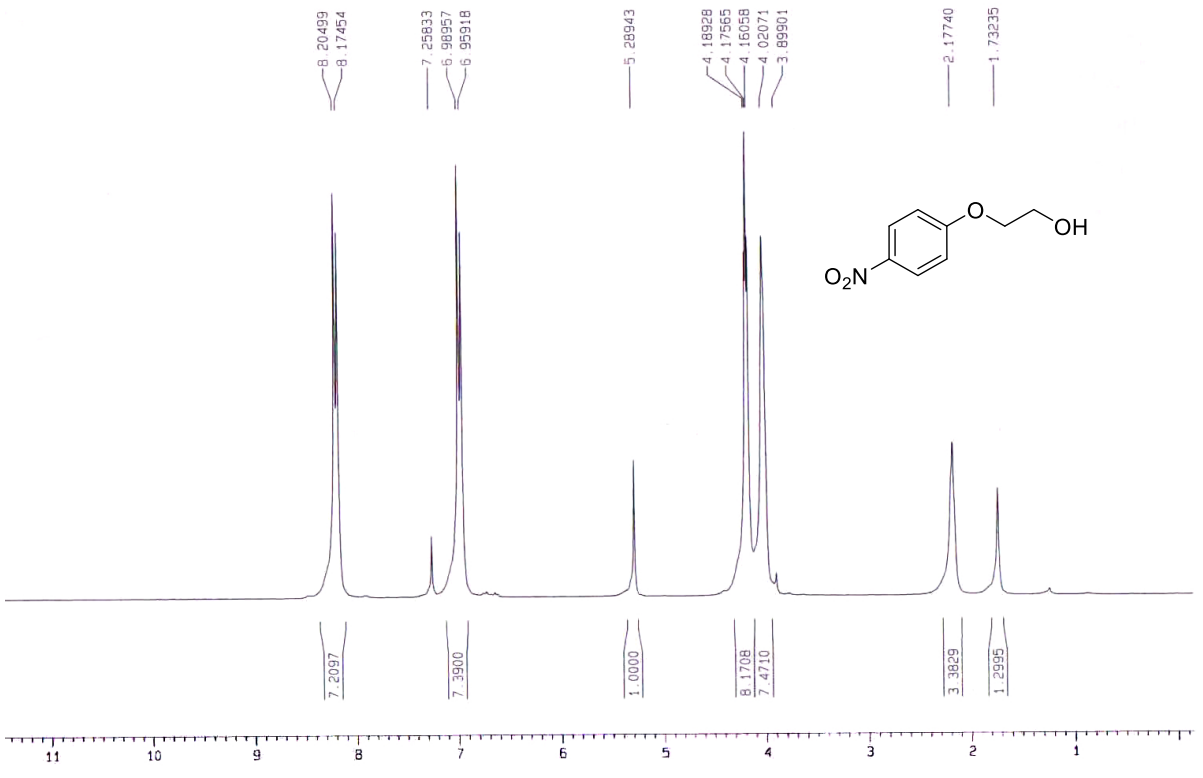


Figure 11: ^{1}H NMR of 2-(4-nitrophenoxy)ethan-1-ol (**3i**)

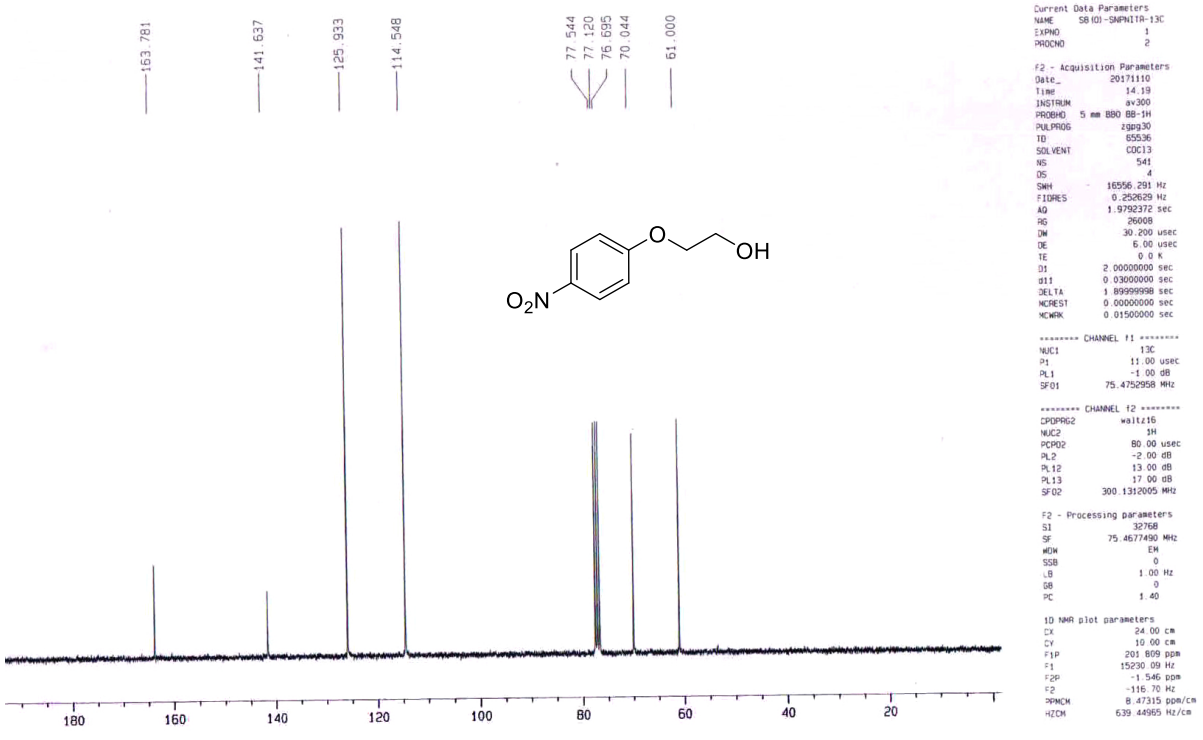


Figure 12: ^{13}C NMR of 2-(4-nitrophenoxy)ethan-1-ol (**3i**)

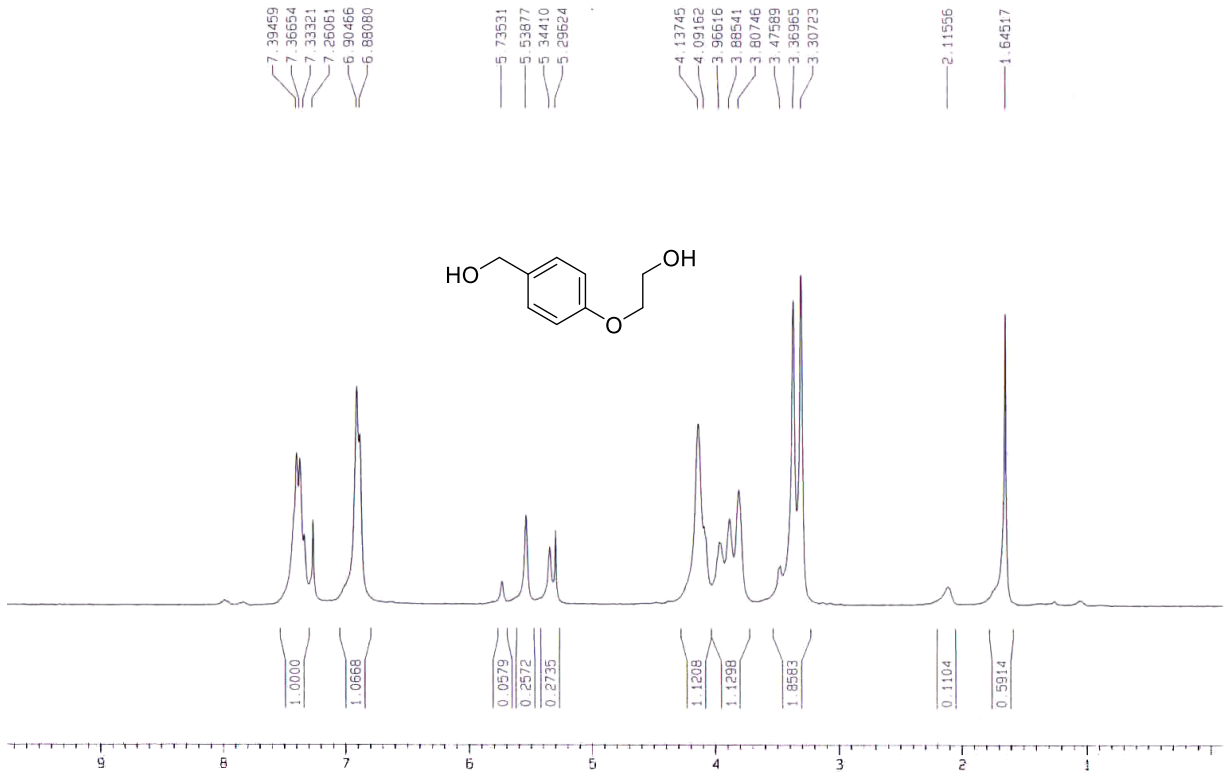


Figure 13: [1]H NMR of 2-(4-hydroxymethyl-phenoxy)-ethanol (**3k**)

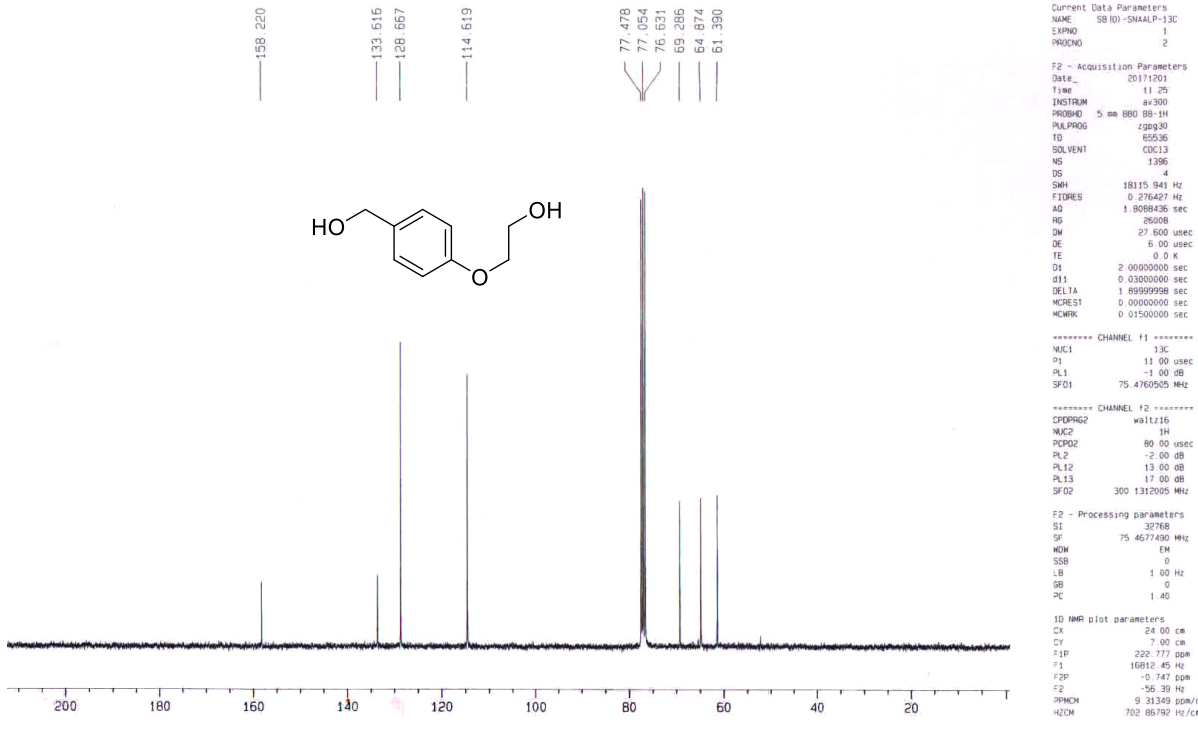


Figure 14: [13]C NMR of 2-(4-hydroxymethyl-phenoxy)-ethanol (**3k**)

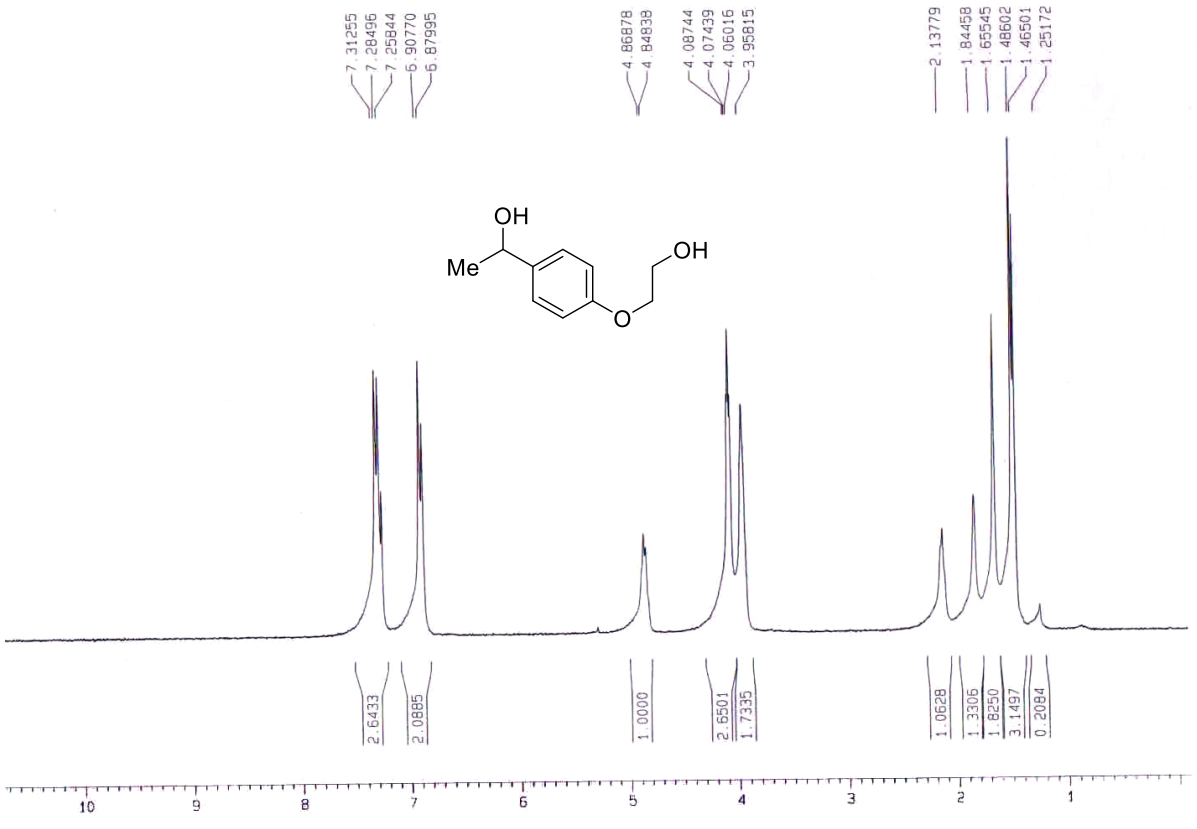


Figure 15: [1]H NMR of 1-(4-(2-hydroxyethoxy)phenyl)ethan-1-ol (**3m**)

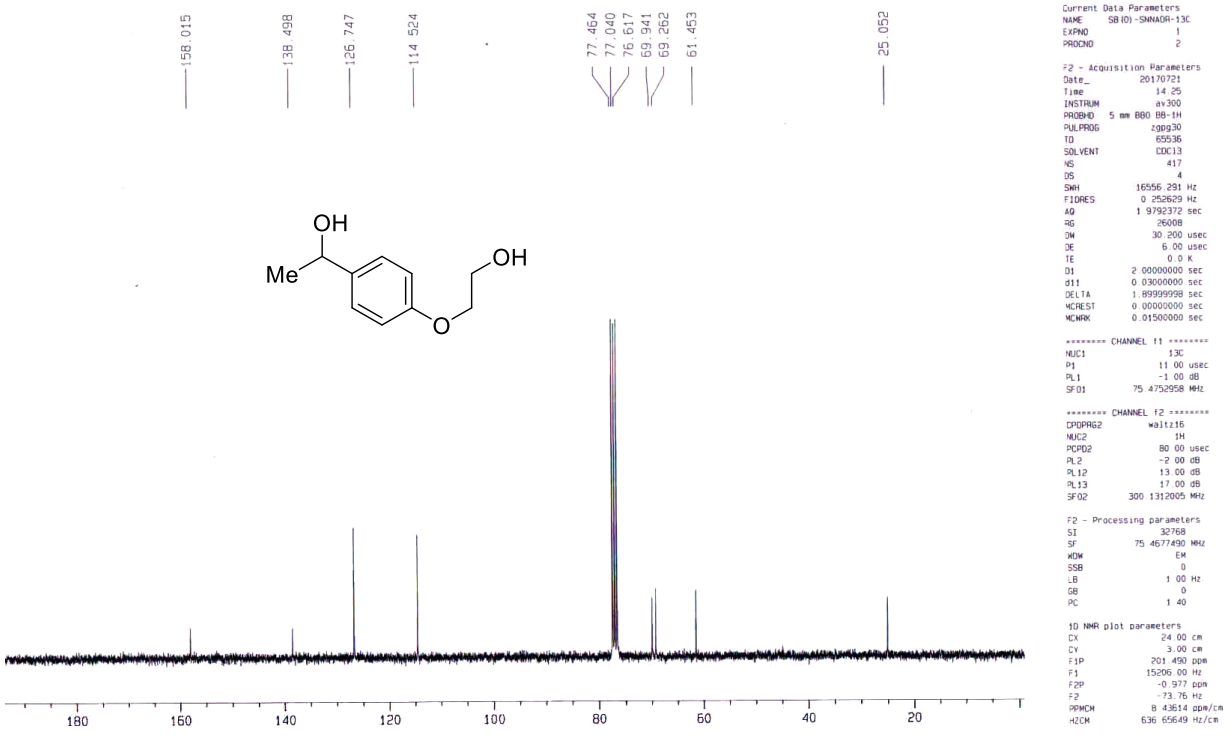


Figure 16: [13]C NMR of 1-(4-(2-hydroxyethoxy)phenyl)ethan-1-ol (**3m**)

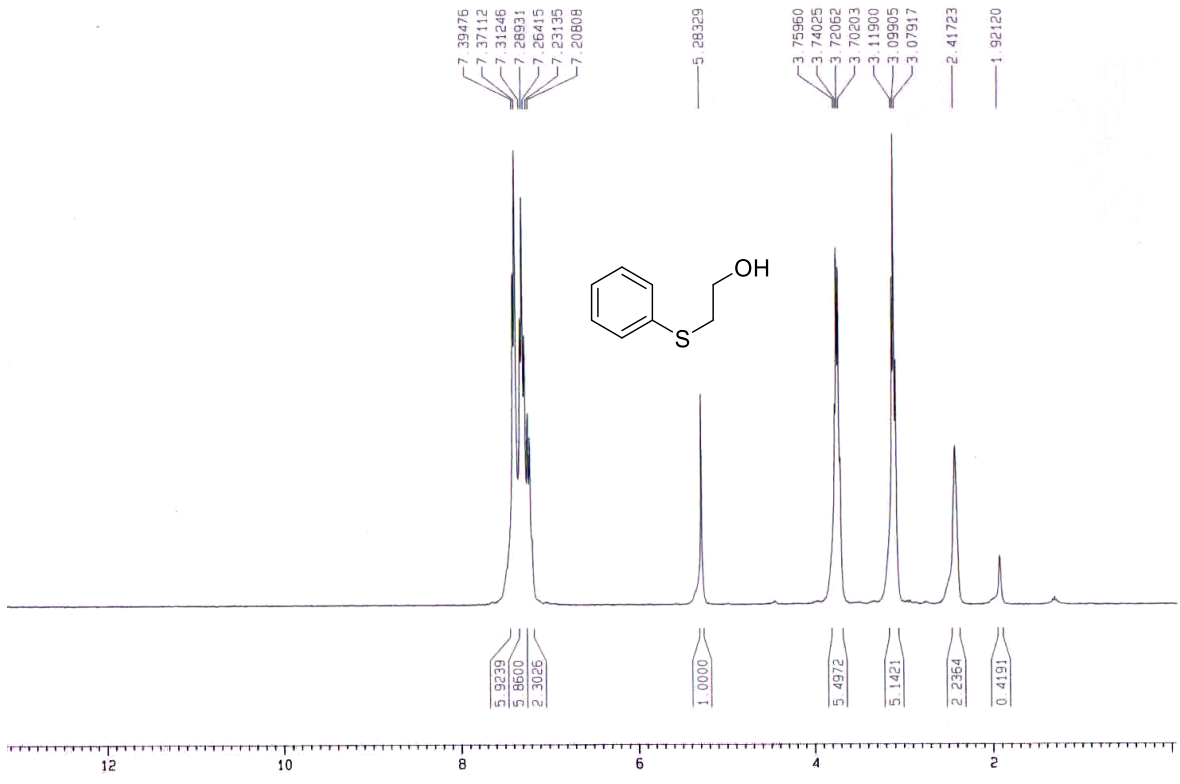


Figure 17: ^{1}H NMR of 2-(phenylthio)ethan-1-ol (**3p**)

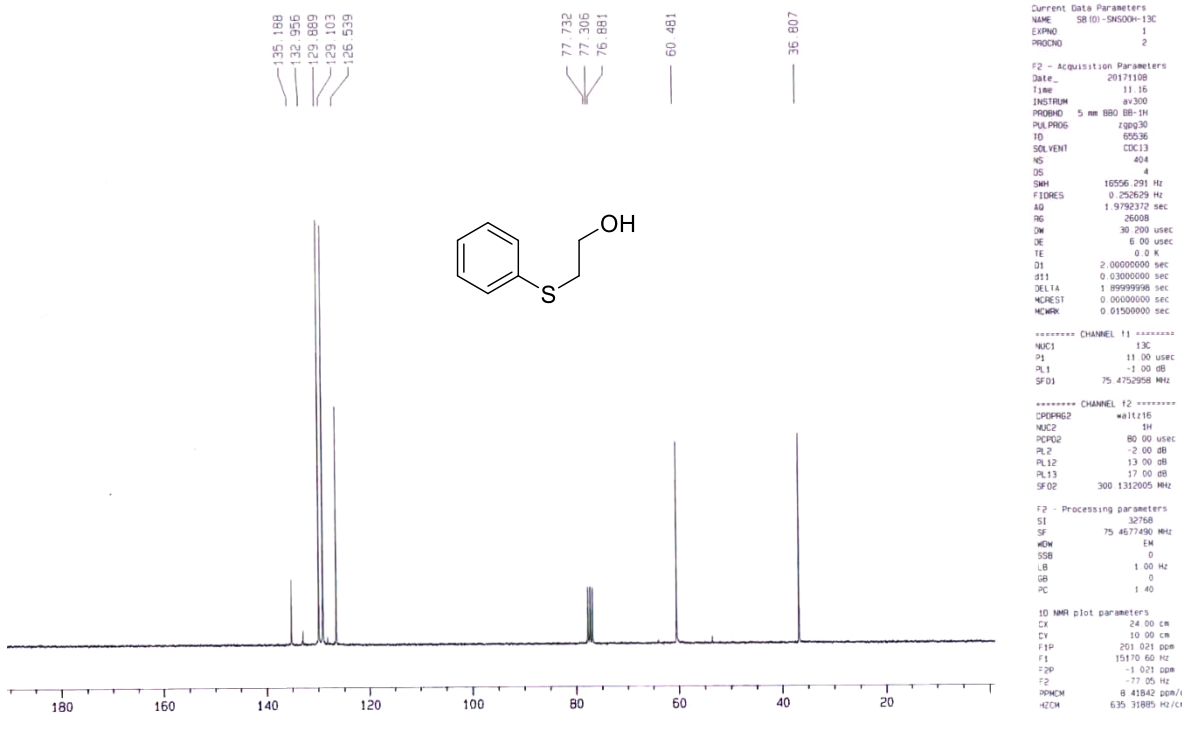


Figure 18: ^{13}C NMR of 2-(phenylthio)ethan-1-ol (**3p**)

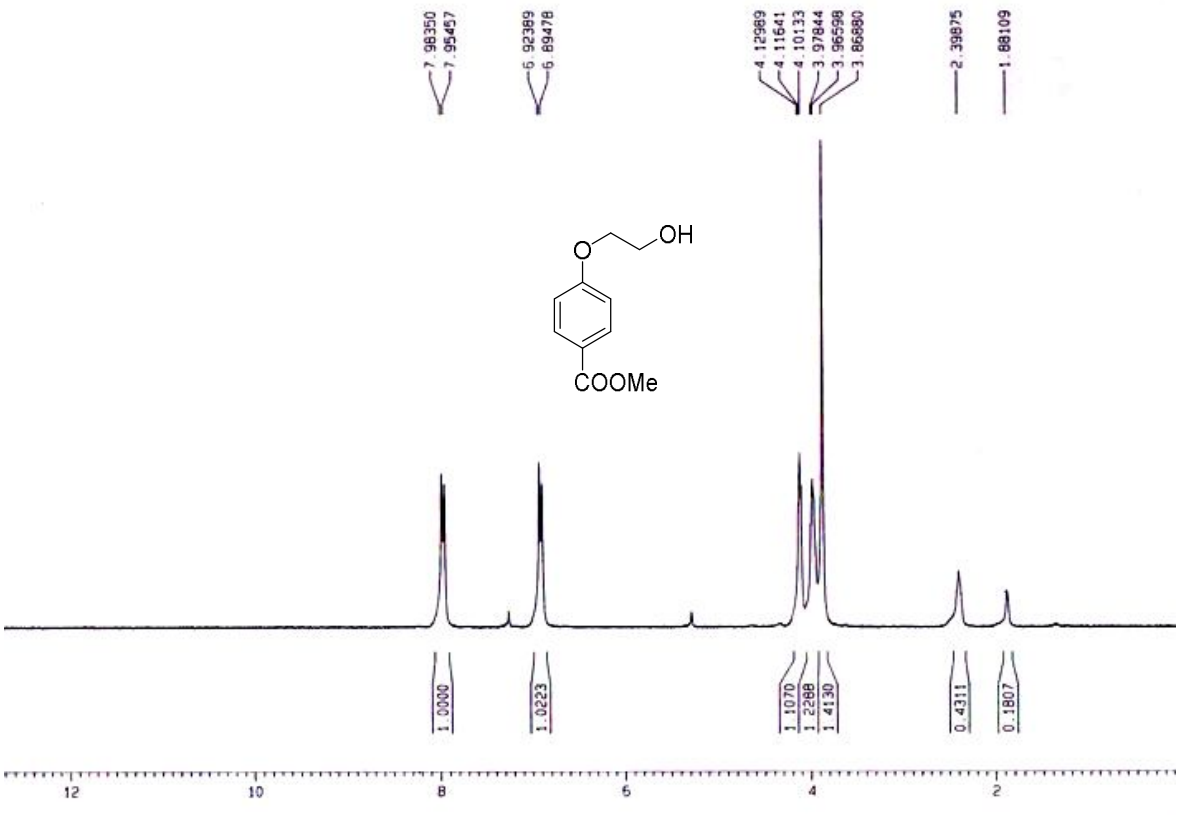


Figure 19: [1]H NMR of methyl 4-(2-hydroxyethoxy)benzoate **(3t)**

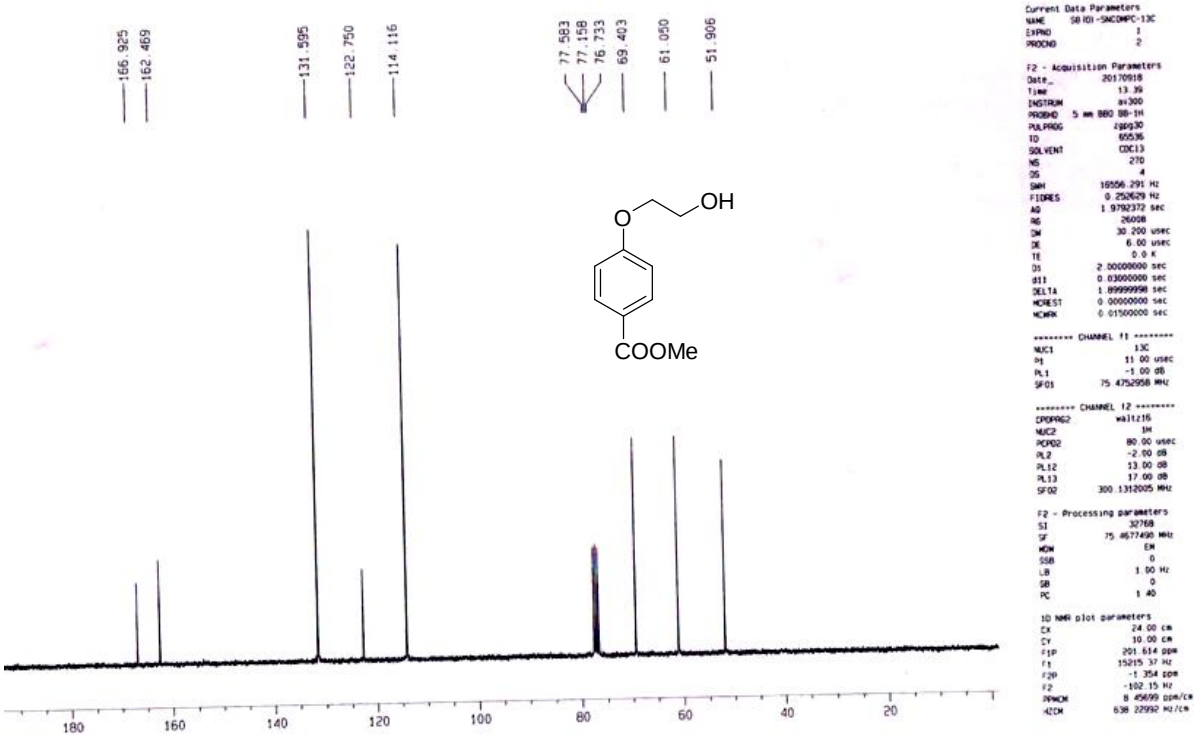


Figure 20: [13] C NMR of methyl 4-(2-hydroxyethoxy)benzoate **(3t)**

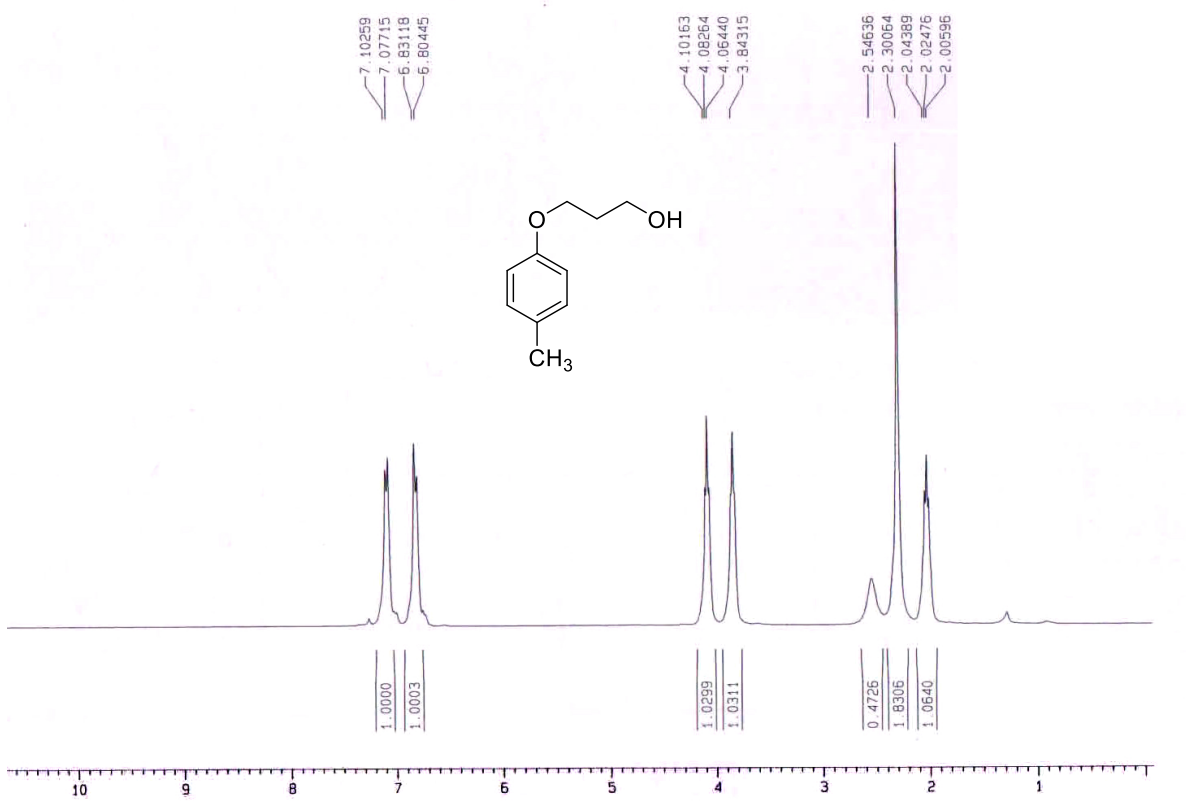


Figure 21: ^{1}H NMR of 3-(p-tolyloxy)propan-1-ol (**9a**)

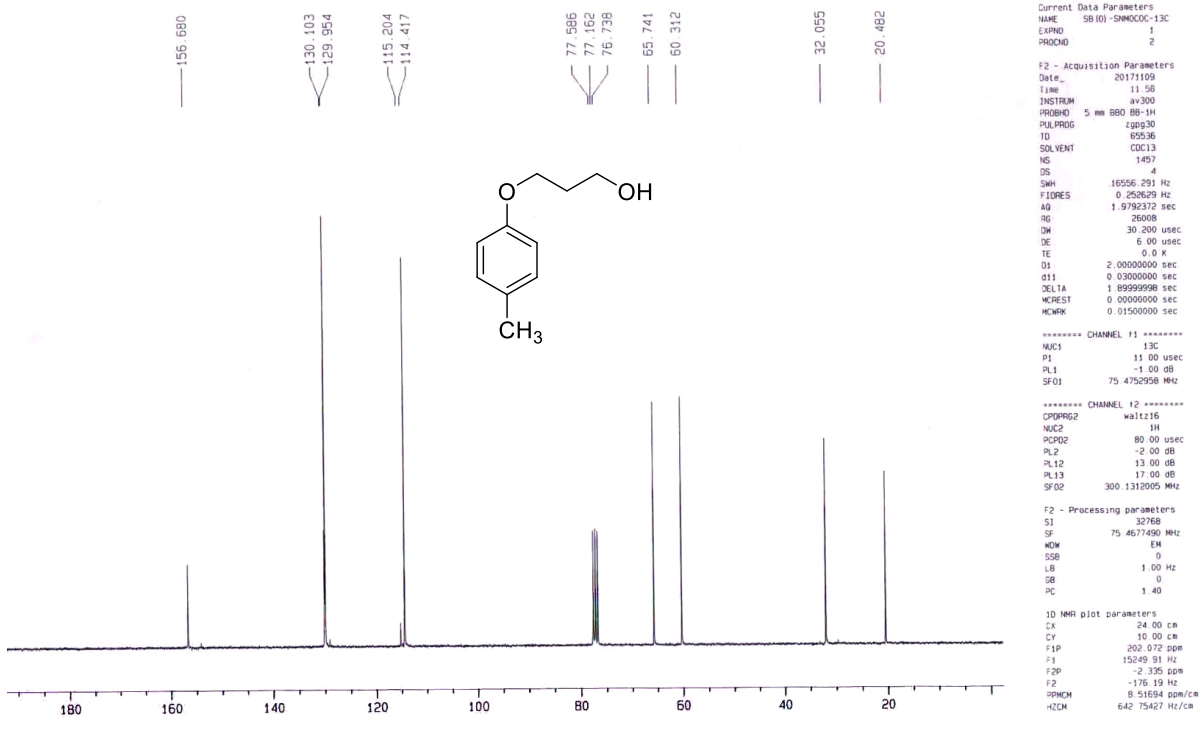


Figure 22: ^{13}C NMR of 3-(p-tolyloxy)propan-1-ol (**9a**)

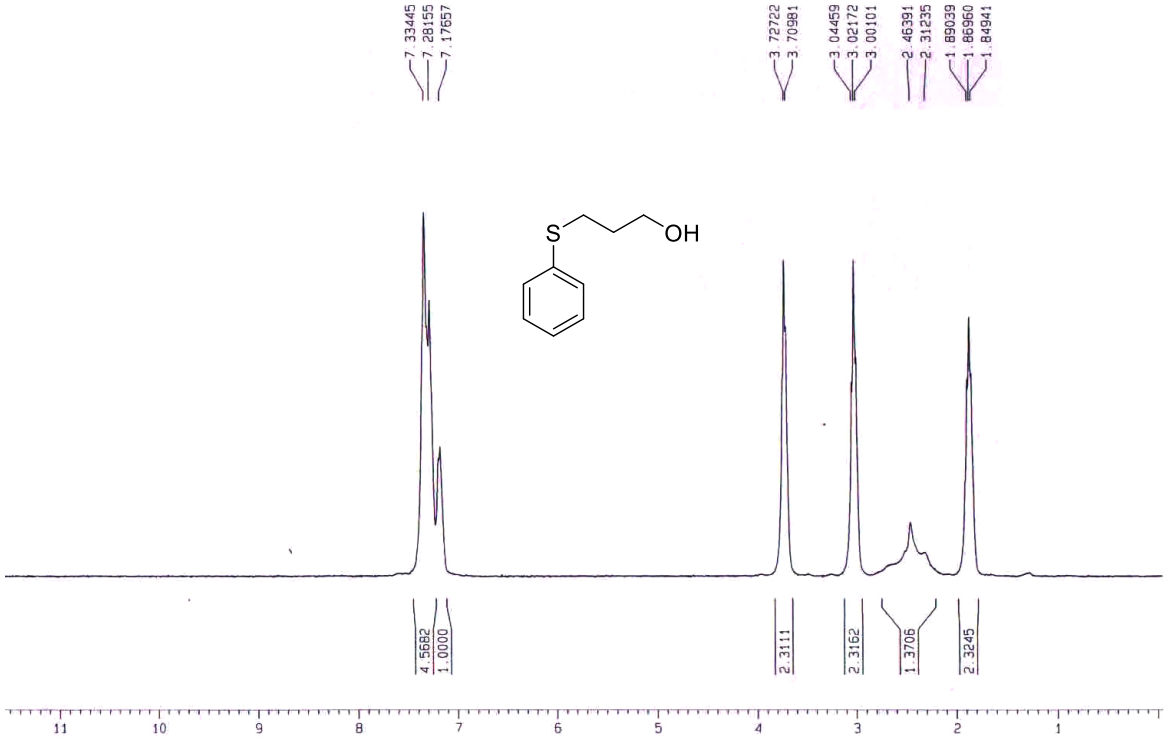


Figure 23: ^{1}H NMR of 3-(phenylthio)propan-1-ol (**9b**)

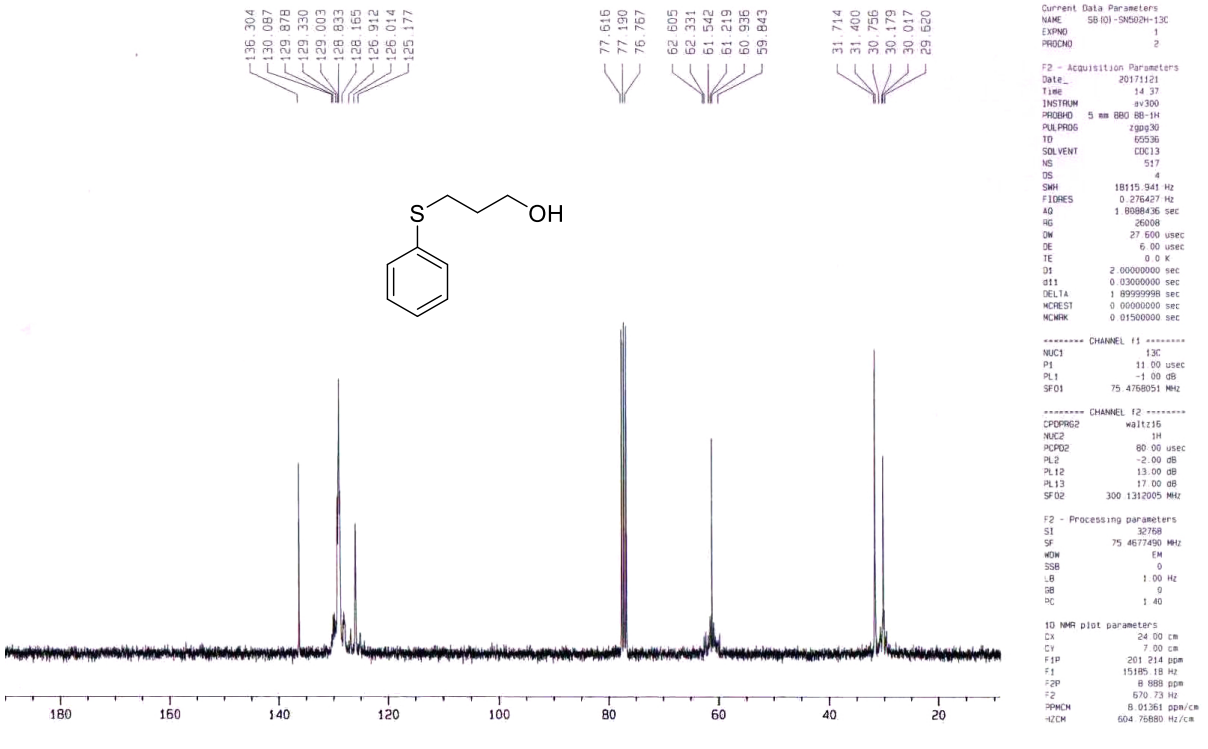


Figure 24: ^{13}C NMR of 3-(phenylthio)propan-1-ol (**9b**)

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LIST OF PUBLICATIONS

(A) PUBLISHED PAPERS INCLUDED IN THESIS (Reprints enclosed):

1. "Chemoselective and metal-free synthesis of aryl esters from the corresponding benzylic alcohols in aqueous medium using TBHP/TBAI as an efficient catalytic system"- Nandy, S.; Ghatak, A.; Das, A. K.; Bhar, S. *Synlett* **2018**, *29*, 2208-2212.

2. "Chemoselective formation of C-N bond in wet acetonitrile using Amberlyst®-15(H) as a recyclable catalyst"- Nandy, S.; Das, A. K.; Bhar, S. *Synth .Commun.* **2020**, *50*, 3326-3336.

(B) PUBLISHED PAPERS NOT INCLUDED IN THESIS:

1. "Catalytic efficiency of β-cyclodextrin hydrate-chemoselective reaction of indoles with aldehydes in aqueous medium"- Das, A. K.; Sepay, N.; Nandy, S.; Ghatak, A.; Bhar, S. *Tetrahedron Lett*. **2020**, *61*, 152231-152237.

2. "Chemoselective and ligand-free aerobic oxidation of benzylic alcohols to carbonyl compounds using alumina-supported mesoporous nickel nanoparticle as an efficient recyclable heterogeneous catalyst"- Das, A. K.; Nandy, S.; Bhar, S. *Appl. Organomet. Chem*. **2021**, *35*, e6282.

(C) MANUSCRIPTS UNDER PREPARATION:

1. "Chemoselective C-O bond formation in aliphatic skeleton using Amberlyst®-15(H) as a recyclable catalyst" - Nandy, S.; Bhar, S.

2. "C-C bond cleavage in cyclopropane ring system using Amberlyst®-15(H) as a recyclable catalyst" - Nandy, S.; Bhar, S.

3. "Reduction of α-heteroatomic esters with $NaBH_4$ in MeOH" - Nandy, S.; Bhar, S.

LIST OF PAPERS PRESENTED

IN NATIONAL AND INTERNATIONAL SYMPOSIA

(IN THE FORM OF POSTERS)

1. "Synthesis of alkyl and aryl esters from the corresponding alcohols in aqueous medium using TBHP/TBAI as an efficient catalyst", Nandy, S.; Ghatak, A.; Das, A. K.; Chakraborty, D.; Bhar, S. in the National Symposium on Indian Chemical Industries: Retrospect and Prospect by Department of Chemistry, Jogesh Chandra Chaudhuri College, Kolkata on 27th February, 2017. (Book of Abstract was not published)

2. "C–N bond formation in wet acetonitrile using Amberlyst®-15(H) as a catalyst", Nandy, S.; Das, A. K.; Bhar, S. in the National Symposium on Current Developments in Chemical Sciences by Department of Chemistry, Jadavpur University, Kolkata on 7th March, 2018. (Poster No. P27)

3. "C–O bond formation using Amberlyst®-15(H) as a recyclable catalyst", Nandy, S.; Dinda, T. K.; Bhar, S. in the National Symposium on Chemical Sciences: Today and Tomorrow by Department of Chemistry, Jadavpur University, Kolkata on 14th March, 2019. (Book of Abstract page no. 22)

4. "Amberlyst®-15(H) – a versatile and recyclable catalyst for organic transformations", Nandy, S.; Das, A. K.; Bhar, S. in the International Symposium on Chemistry for Human Development (ICCHD-2020) by Professor Asima Chatterjee Foundation, Heritage Institute of Technology, Kolkata on 9th-11th January, 2020. (Poster No. P-017, Book of Abstract page no. 162)

Synlett S. Nandy et al. Letter

Chemoselective and Metal-Free Synthesis of Aryl Esters from the Corresponding Benzylic Alcohols in Aqueous Medium Using TBHP/TBAI as an Efficient Catalytic System

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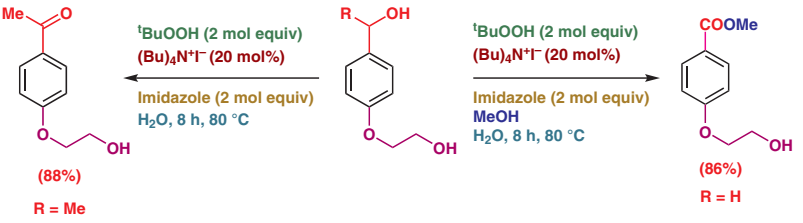


Received: 09.07.2018
Accepted after revision: 23.07.2018
Published online: 12.09.2018
DOI: 10.1055/s-0037-1610247; Art ID: st-2018-v0237-l

Abstract A novel and transition-metal-free strategy has been developed for the synthesis of aryl esters starting from corresponding benzylic primary alcohols as the exclusive substrates using *tert*-butyl hydroperoxide (TBHP) as a terminal oxidant in the presence of catalytic amount of tetrabutylammonium iodide (TBAI) and imidazole, where the aliphatic alcohols remained unaffected. These reactions are highly chemoselective and associated with high yield and wide applicability accommodating a wide range of substituents. Excellent chemoselectivity has also been demonstrated through intramolecular competition experiments. This protocol can be considered as an important analogue of Tishchenko reaction using benzylic alcohols as the substrates instead of benzaldehydes.

Key words aqueous reaction, chemoselectivity, green chemistry, esters, oxidation

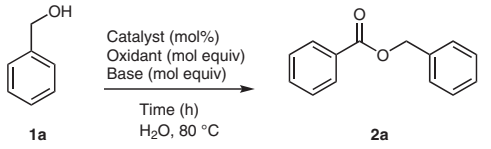
Esters constitute an important and useful class of functional groups at all times with immense applications in medicinal chemistry as well as pharmaceutical and cosmetic industry. Usually, conventional esterification between a carboxylic acid and alcohol needs dehydrating agents. To get rid of a dehydrating agent, different protocols for oxidative esterification of primary alcohols have been reported to produce symmetrical as well as unsymmetrical esters.[1–7] Some other methods have been developed to generate the ester moiety by the reaction of aryl methyl ketone with I_2-TBHP,[8] from aryl aldehydes using *tert*-butyl hydroperoxide (TBHP) in DMSO in the presence of Cu salt to obtain the methyl ester using TBHP as the methyl source[9] and benzyl esters from benzylic alcohols using TBHP in toluene (where toluene delivered the benzyloxy moiety).[10] Recently, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) catalyzed oxidation using Oxone and calcium chloride have been reported to produce esters.[11] Of late, TBHP has come out as an efficient reagent for oxidative transformations where α-acyloxycarbonyl compounds were prepared by the reaction of benzyl alcohols with ketones taking Bu_4NI in catalytic amount.[12] Very recently, the mechanistic pathway of vicinal difunctionalization of alkenes with iodine and TBHP was established[13] where 1-(*tert*-butylperoxy)-2-iodoethanes were obtained as the products. However, many of the reported methods suffer from the drawbacks like moisture sensitivity of the sophisticated reagent systems,[3–8] relatively long reaction time,[2–6,8–13] involvement of exotic reagents containing expensive metals,[1–4,9,11] lack of chemoselectivity,[1–4,6,11] formation of byproducts, and limited applicability to selected domain of substrates.[2,3,6,9–11] Therefore, development of a highly chemoselective metal-free oxidative protocol for esterification from the primary alcohol is in great demand in the present scenario.

The choice of a specific solvent for a desired synthetic pathway can have profound economical and environmental implications from the standpoint of 'green chemistry'. In order to proceed for a 'sustainable future' an aqueous medium has drawn considerable attention[14] not only due to its innocuous, inexpensive, and nonflammable nature but also its widespread applicability, unique reactivity, and excellent selectivity imposed to the reaction outcome. Therefore, the development of an efficient and eco-compatible method for an organic reaction in aqueous medium constitutes an essential target to the modern synthetic organic chemists. As a part of our recent explorations[15] in the field of organic transformations in aqueous medium we report a novel highly chemoselective metal-free oxidative transforma-

tion of primary benzylic alcohols employed by combination of TBHP, tetrabutylammonium iodide (TBAI), and imidazole to obtain a variety of aryl esters in aqueous medium.

To check the applicability of the TBHP-TBAI couple, the reaction was carried out with benzyl alcohol **1a** (1 mmol) using H_2O_2 and TBHP (2 mmol) as the oxidant in the presence of various catalysts along with different bases in water at 80 °C to obtain the product benzyl benzoate (**2a)** as presented in Table 1.

Table 1 Optimization of Esterification of Benzyl Alcohol



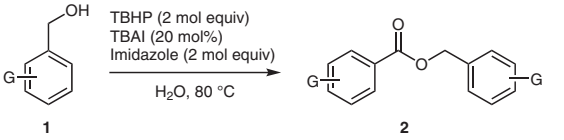
Entry	Catalyst	mol (%)	Oxidant	mol equiv	Base	mol equiv	Time (h)	Yield of **2a** (%)
1	KI	10	H_2O_2	1	KOH	2	8	–
2	KI	10	H_2O_2	2	KOH	4	10	–
3	I_2	10	H_2O_2	1	K_2CO_3	2	10	–
4	I_2	10	H_2O_2	2	K_2CO_3	4	10	trace
5	TBAI	10	TBHP	1	imidazole	1	6	65
6	TBAI	15	TBHP	2	imidazole	2	8	73
7	TBAI	20	TBHP	2	imidazole	2	8	86
8	TBAI	15	TBHP	3	imidazole	3	8	74
9	TBAB	20	TBHP	2	imidazole	2	8	24[a]
10	KBr	20	TBHP	2	imidazole	2	8	–
11	SDS	20	TBHP	2	imidazole	2	8	–
12	TBAI	20	–	–	imidazole	2	8	9[b]
13	TBAI	20	TBHP	2	imidazole	2	8	12[c]
14	TBAI	20	H_2O_2	2	imidazole	2	8	–

[a] Extent of unreacted alcohol, aldehyde, and ester is 34%, 42%, and 24%, respectively, by 300 MHz ^{1}H NMR analysis.
[b] Extent of unreacted alcohol and ester is 91% and 9%, respectively, no aldehyde was detected by 300 MHz ^{1}H NMR analysis.
[c] The reaction was carried out under inert (argon) atmosphere and the extent of unreacted alcohol, aldehyde, and ester is 47%, 41%, and 12%, respectively, by 300 MHz ^{1}H NMR analysis.

The reaction did not occur in the absence of either any iodide salt or a base. Initially H_2O_2 was used as oxidant using KI as catalyst and KOH as the base in different molar proportions, but no reaction took place (Table 1, entries 1 and 2). When I_2 and K_2CO_3 were used for their respective purpose the results were not satisfactory (Table 1, entries 3 and 4). In the contrary, TBHP in the presence of TBAI (as iodide source) and imidazole (as the base) at different relative concentrations promoted the oxidative transformation of **1a** more efficiently and produced **2a** with better yield (Table 1, entries 5–8). The most satisfactory result was obtained following the stoichiometry corresponding to entry 7 in Table 1, which was subsequently used as the optimized conditions for further reactions in order to extend the substrate scope and establish the general applicability as well as the selectivity of the aforesaid protocol. This reaction was less effective with TBAB, and extent of alcohol, aldehyde, and ester was detected in the reaction mixture as 34%, 42%, and 24%, respectively (Table 1, entry 9). The reaction did not take place at all using KBr instead of TBAB (Table 1, entry 10). Similarly, using SDS as a surfactant in place of quaternary ammonium halides ended up with no transformation of the substrate (Table 1, entry 11).

It is very important to note that the reaction was much slower in the presence of aerial oxygen as the sole oxidant in the absence of TBHP, but no aldehyde was detected in the reaction mixture although the extent of conversion of the substrate was very low (Table 1, entry 12). Similarly, this reaction with TBHP under inert (Ar) atmosphere in the absence of aerial oxygen was quite sluggish, and the extent of unreacted alcohol, aldehyde, and ester was detected as 47%, 41%, and 12%, respectively (Table 1, entry 13). Benzyl alcohol was also treated with TBAI and H_2O_2in the presence of imidazole. No conversion was noted in the aforesaid reaction, and benzyl alcohol was recovered totally unaffected (Table 1, entry 14). Therefore, the dual necessity of TBHP and aerial oxygen towards this oxidative transformation has been firmly established along with a quaternary ammonium iodide. This reaction bodes for eco-compatibility in terms of the reaction medium (water), limited toxicity of the reagents, acceptable organic solvent (ethyl acetate) during workup, and recyclability of TBAI.

As a continuity of this theme, benzyl carbinols **1** with different substituents at the aromatic ring were subjected to the oxidative reaction under the optimized conditions (Scheme 1) where the corresponding benzyl benzoates **2** were obtained with good yield.



Scheme 1 Reaction of substituted benzyl alcohols under optimized conditions

Under the optimized conditions unsubstituted benzyl alcohol (**1a**) produced benzyl benzoate (**2a**) in satisfactory yield (yield of the isolated pure product was fully characterized spectroscopically). This oxidative self-esterification also took place very efficiently with reactants having high susceptibility to oxidative decomposition to afford **2c** with good yield (Figure 1). Benzylic carbinols bearing halogen, alkyl, and alkoxy substituents also responded smoothly to yield the corresponding benzyl benzoates **2b**, **2d**, and **2e**, respectively. No such reaction took place with aliphatic primary alcohols where the substrates were recovered unchanged. Therefore, this protocol can serve as an alternative

to Tischenko reaction for the synthesis of differently substituted benzyl benzoates using the corresponding benzylic primary alcohols as the substrates instead of aryl aldehydes. Quite interestingly, **1a** was converted into **2a** with I_2 in KOH, but other alcohols failed to react. Diarylcarbinol **3** produced the corresponding ketone **4** under the present oxidative reaction without any cleavage of aryl-carbonyl C–C bond (Scheme 2).

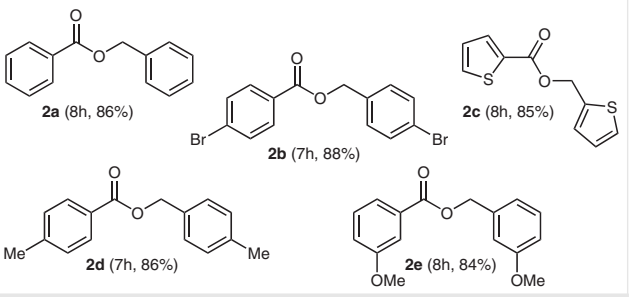
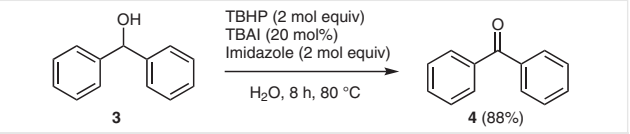
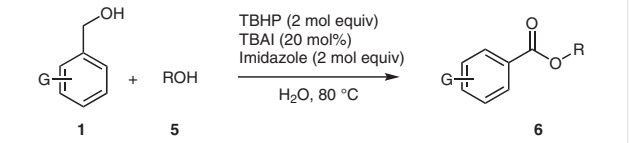


Figure 1 List of products formed by oxidation of substituted benzyl alcohols using TBHP-TBAI-imidazole combination



Scheme 2 Oxidation of diarylcarbinol

Inspired by the aforesaid results with a promise of showing chemoselectivity, we attempted for the synthesis of alkyl benzoates from a mixture of alkyl and aryl alcohols using this oxidative protocol (Scheme 3).



Scheme 3 Reaction of substituted benzyl alcohols with aliphatic alcohols under optimized conditions

As evident from the following chart, a number of substituted benzyl alcohols **1** reacted with various structurally different aliphatic alcohols **5** to produce the corresponding alkyl benzoates **6** in good yield (yield of the isolated pure product was fully characterized spectroscopically). Sterically crowded benzylic alcohols having substituents at *ortho* positions reacted smoothly to furnish the products **6f** and **6g**, respectively (Figure 2). Even the bulky and less reactive tertiary alcohol responded efficiently to produce the corresponding *tert*-butyl esters (e.g., **6c**,**e**,**j**,**l**) which are otherwise difficult to prepare. Hydrolysable functional groups, like –CN and methylenedioxy, also survived in the present protocol of cross-dehydrogenative coupling[16] reaction in aqueous medium to produce the esters **6m** and **6n**, respectively. Benzyl benzoate (**2a**) acts as a potential savior for the patients affected with human scabies, lice infestation, asthma, and whooping cough; while methyl benzoate (**6a**) is used as pesticide. Excess TBHP (6 molar equiv in three equal instalments) was needed to get **6m**, and the reaction was quite sluggish.

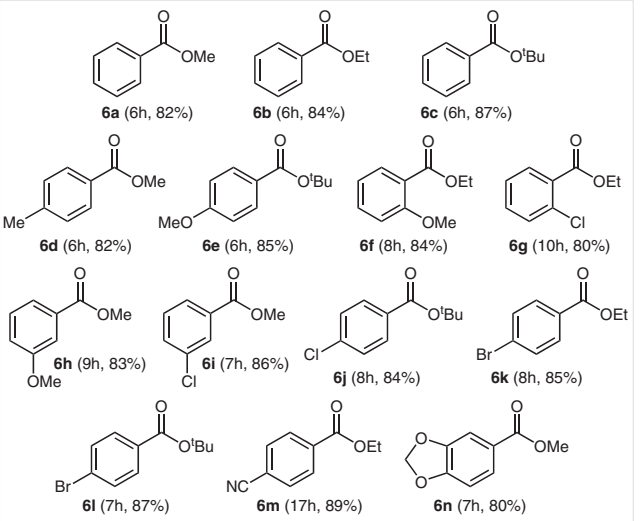
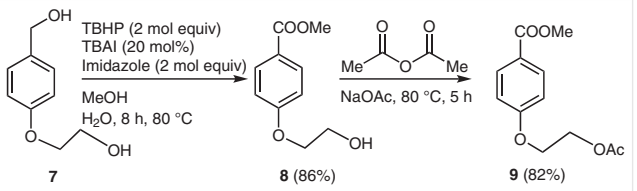


Figure 2 TBHP-TBAI-catalyzed synthesis of esters by the cross-coupling of benzylic primary alcohols with other aliphatic alcohols

Among heteroarylcarbinols, highly vulnerable furan-2-yl-methanol (furfuryl alcohol) responded under the present oxidative protocol in the presence of methanol to furnish a mixture of methyl furoate, furfural, and unreacted furfuryl alcohol in 58:11:31 ratio (determined by 400 MHz ^{1}H NMR spectroscopy). Under the optimized conditions thiophen-2-yl-methanol was found quite sluggish and was converted into thiophene-2-carbaldehyde only to the extent of 20% (determined by 400 MHz ^{1}H NMR spectroscopy). After prolonged reaction (16 h), a mixture of the methyl thiophene-2-carboxylate, thiophene-2-carbaldehyde, and unreacted thiophen-2-yl-methanol was obtained in a 7:30:63 ratio (determined by 400 MHz ^{1}H NMR spectroscopy). Pyridin-2-yl-methanol did not respond to the present protocol.

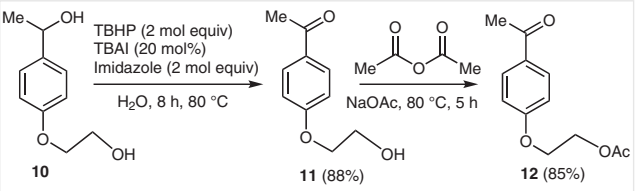
To establish further the chemoselectivity of the said protocol, intramolecular competition experiment was carried out. When the substrate **7**, with both the benzylic and aliphatic primary alcohols present in the same molecule, reacted under this oxidative method in MeOH, primary benzylic alcohol was oxidatively esterified selectively to the corresponding methyl ester **8**, and the primary aliphatic alcohol moiety remained unaffected (Scheme 4). The selective formation of aromatic methoxycarbonyl group was confirmed by the presence of only one singlet (at δ = 3.87 ppm) at a relatively downfield region in its ^{1}H NMR spectrum as well as from the signal (at δ = 166.9 ppm) in the ^{13}C NMR spectrum. The presence of unreacted aliphatic prima-

ry alcohol was further established through acetylation of **8** (Scheme 4) which was confirmed by a singlet at δ = 2.10 ppm (in the ^{1}H NMR spectrum) as well as a signal at δ = 170.9 ppm (in the ^{13}C NMR spectrum) in compound **9**.



Scheme 4 Chemoselective oxidation of 1°-benzylic alcohol

Similar chemoselectivity was also observed with the compound **10** where the secondary benzylic alcohol was selectively oxidized to the ketomethyl moiety under the present oxidative protocol to yield the compound **11** leaving the aliphatic primary alcohol group intact (Scheme 5). The occurrence of aromatic ketomethyl moiety in **11** was confirmed by the singlet at δ = 2.54 ppm (in the ^{1}H NMR spectrum) as well as a signal at δ = 200.4 ppm (in the ^{13}C NMR spectrum). Survival of the 1°-aliphatic alcohol moiety was further substantiated through the acetylation of **11** to **12**.



Scheme 5 Chemoselective oxidation of 2°-benzylic alcohol

A cost-effective, operationally simple, transition-metal free, chemoselective, eco-compatible protocol in aqueous medium has been developed for the synthesis of a variety of aryl esters directly from primary benzylic alcohols where aliphatic alcoholic moiety remained unaffected.[17,18] Such chemoselectivity was also observed during the reaction of secondary benzylic alcohols where the corresponding ketones were obtained. Investigations towards the extension of this protocol towards other oxidative transformations are recently in progress.

Funding Information

S. N. thanks DST-INSPIRE, India for junior research fellowship. Financial support from UGC-CAS-II program in Chemistry and DST-PURSE-II program at Jadavpur University as well as Infrastructural support from DST-FIST program are gratefully acknowledged.

Acknowledgment

The authors thank Mr. N. Dutta of IACS for necessary assistance.

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(17) **Representative Procedure for the Reaction**
To a mixture of benzyl alcohol (108 mg, 1.0 mmol) and TBHP (180 mg, 2.0 mmol) in water (5 ml), the catalyst TBAI (73.8 mg, 0.2 mmol) and imidazole (136 mg, 2.0 mmol) were added, and the mixture was stirred at 80 °C for 8 h. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the reaction mixture was cooled to room temperature. Then the organic product was extracted with ethyl acetate (3 × 10 ml), repeatedly washed with distilled water (4 × 5 ml) to remove the unreacted TBHP, dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to afford benzyl benzoate (182 mg, yield 86%).
To a mixture of benzyl alcohol (108 mg, 1.0 mmol) and TBHP (180 mg, 2.0 mmol) in water (3 ml), the catalyst TBAI (73.8 mg, 0.2 mmol), imidazole (136 mg, 2.0 mmol), and MeOH (2 ml) were added, and the mixture was stirred at 80 °C for 8 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. Then MeOH was distilled out, and the organic product was extracted with ethyl acetate (3 × 10 ml), repeatedly washed with distilled water (4 × 5 ml) to remove the unreacted TBHP, dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to afford methyl benzoate (112 mg, yield 82%).
(18) **Spectral and Analytical Data of some Representative Compounds**
(Thiophen-2-yl) Methyl Thiophene-2-carboxylate (2c)
Yellow oil (yield 85%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.47 (2 H, s), 7.00–7.02 (1 H, m), 7.07–7.10 (1 H, m), 7.17–7.18 (1 H, m),

7.33–7.35 (1 H, m) 7.55–7.57 (1 H, m), 7.82–7.83 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.1, 126.8, 126.9, 127.7, 128.3, 132.7, 133.4, 133.7, 137.7, 161.9. HRMS (ESI-TOF): *m/z* calcd for $C_{10}H_8O_2S_2$ [M + Na^+]: 246.9866; found: 246.9868.

Methyl Benzo[1,3]dioxole-5-carboxylate (6n)

Colorless viscous oil (yield 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (3 H, s), 6.05 (2 H, s), 6.82 (1 H, d, *J* = 8.8 Hz), 7.45 (1 H, d, *J* = 1.4 Hz), 7.64 (1 H, dd, J_1 = 9.0 Hz, J_2 = 1.5Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 101.7, 107.9, 109.5, 124.2, 125.3, 147.7, 151.6, 166.4.

Methyl 4-(2-Acetoxyethoxy)benzoate (9)

White solid (mp 76 °C; yield 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (3 H, s), 3.87 (3 H, s), 4.22–4.23 (2 H, m), 4.44 (2 H, t, *J* = 4.3 Hz), 6.92 (2 H, d, *J* = 8.7 Hz), 7.99 (2 H, d, *J* = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 51.9, 62.5, 65.9, 114.1, 123.1, 131.6, 162.2, 166.7, 170.9. HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{14}O_5$ [M + Na^+]: 261.0741; found: 261.0736

1-[4-(2-Hydroxyethoxy)phenyl]ethanone (11)

Yellowish oil (yield 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (3 H, s), 3.98 (2 H, t, *J* = 4.3 Hz), 4.13 (2 H, t, *J* = 4.4 Hz), 6.93 (2 H, d, *J* = 8.7 Hz), 7.91 (2 H, d, *J* = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 61.7, 72.2, 114.7, 129.1, 130.1, 162.3, 200.4. HRMS (ESI-TOF): *m/z* calcd for $C_{10}H_{12}O_3$ [M + Na^+]: 203.0687; found: 203.0684

2-(4-Acetyl-phenoxy) Ethyl Acetate (12)

Colorless semisolid (yield 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (3 H, s), 2.54 (3 H, s), 4.13–4.23 (2 H, m), 4.43 (2 H, t, *J* = 4.4 Hz), 6.93 (2 H, d, *J* = 8.6 Hz), 7.92 (2 H, d, *J* = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 26.3, 62.5, 66.0, 114.2, 130.6, 130.7, 162.3, 170.9, 196.7. HRMS (ESI-TOF): *m/z* calcd for $C_{12}H_{14}O_4$ [M + K^+]: 261.1872; found: 261.1876.

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An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Sneha Nandy , Asit Kumar Das & Sanjay Bhar (2020): Chemoselective formation of C–N bond in wet acetonitrile using amberlyst®-15(H) as a recyclable catalyst, Synthetic Communications, DOI: 10.1080/00397911.2020.1801745

To link to this article: https://doi.org/10.1080/00397911.2020.1801745

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Chemoselective formation of C–N bond in wet acetonitrile using amberlyst®-15(H) as a recyclable catalyst

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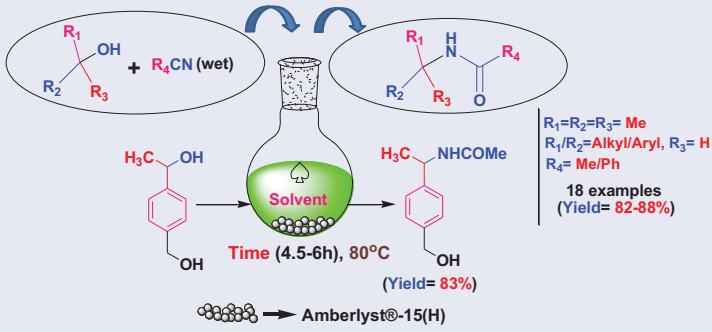
ABSTRACT

An economically efficient and environmentally benign protocol for the chemoselective one-pot synthesis of diversely N-substituted amides has been developed in good yield through the reaction of benzylic secondary alcohols as well as aliphatic tertiary alcohols and alkyl/aryl nitriles. Commercially available Amberlyst®-15(H) has been utilized at 80 °C as an air-stable and reusable heterogeneous inexpensive solid acid catalyst without any anhydrous and inert environment. The attractive features of the present synthetic protocol are mild reaction conditions, short reaction time, excellent chemoselectivity, high atom economy and tolerance of various sensitive moieties.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 26 May 2020

KEYWORDS
Alcohols; amides; chemoselectivity; heterogeneous catalysis; nitriles

Formation of C–N bond in aliphatic skeletons, especially from alkanols, is a formidable synthetic operation. Reaction of nitriles with substituted alkenes or alcohols using concentrated sulfuric acid in glacial acetic acid was classically used for this purpose through the formation of substituted amides. In order to avoid the involvement of such a strong mineral acid, several modifications have been proposed including other acidic substances like Tf_2O,[1] $BF_3.OEt_2$,[2] P_2O_5-SiO_2,[3] Bronsted acid,[4] Fe-montmorillonite K10,[5] Nafion-H,[6,7] Nafion-H along with microwave irradiation,[8] formic acid under reflux,[9]

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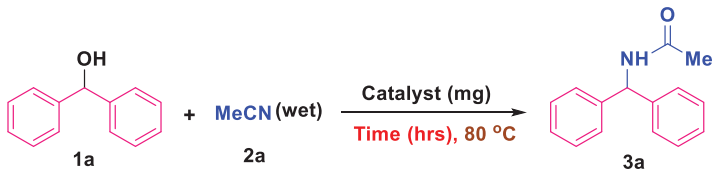


Scheme 1. Reaction of benzhydrol (**1a**) using different catalysts and reaction medium.

$HBF_4.Et_2O$,[10] 2,4-dinitrobenzenesulfonic acid,[11] TfOH,[12] $HClO_4$-functionalized silica-coated nanoparticles,[13] KI-TBHP[14] and liquid HF.[15] Ritter reaction using *tert*-butyl acetate instead of *tert*-butyl alcohol[16] was also reported to be catalyzed by metal-triflate[17] and pentafluorophenyl ammonium triflate (PFPAT),[18] Ca(II)-catalyzed reaction under microwave irradiation,[19] Molecular I_2,[20] Bi-salts,[21] $FeCl_3.6H_2O$[22] and ionic liquids[23] have also been employed for this kind of transformation. Recently a photochemical modification[24] has evolved as one of the successful alternative methods. However, most of these methods suffer from several disadvantages such as use of corrosive acid catalysts, toxic and moisture-sensitive reagents, use of expensive compounds and materials, elevated reaction temperatures, prolonged reaction time, susceptibility with acid-labile and bulky functional groups and concomitant formation of several by-products arising out of different side reactions including rearrangement. But the main drawback of most of the existing methods is the decomposition of the catalysts during aqueous work-up leading to tedious protocols for isolation, separation and recovery of the products.

Recyclable resins[25–28] bearing acidic sites offer the advantages not only due to their subtle catalytic attributes but also from the standpoint of reusability along with physical and chemical stability. Further advantages are associated with their heterogeneous nature in terms of their facile separation from the reaction mixture and easier isolation of the products. Keeping in mind the aforesaid attributes, we report herein an admirable catalytic application of Amberlyst®-15(H) for the formation of C–N bond in wet acetonitrile.

Results and discussion

To check the applicability of Amberlyst®-15(H) the reaction was carried out with benzhydrol (**1a**, 1 mmol), wet MeCN (**2a**, 1 mmol) in presence of various catalysts along with different solvent systems at 80 °C to produce N-benzhydrylacetamide (**3a**) (Scheme 1). Results are presented in Table 1.

From the results shown in Table 1, we standardized the reaction following the condition as specified in entry 8 which afforded 88% of the corresponding amide **3a**. The reactions did neither occur in anhydrous acetonitrile (entry 9) nor in water alone; wet acetonitrile came out as the suitable reaction medium where the amount of water is very crucial for optimum performance (0.1–0.3%). Best result was obtained with commercially available acetonitrile containing 0.1% of water. Use of toluene as a solvent in place of acetonitrile led to inferior results (entries 6 and 7). DMF was found not at all suitable as the solvent in this present protocol (entry 10).

Table 1. Optimization of the reaction conditions[a] using different catalysts and solvents at 80 °C.

Entry	Catalyst	Amount (mg)	Solvent	Time (h)	Yield of 3a (%)[b]
1	Dowex-50	40	Toluene	6	–
2	Dowex-50	50	DMF	8	–
3	Dowex-50	50	Acetonitrile	8	32
4	Amberlite (IR-45)	40	Toluene	6	24
5	Amberlite (IR-45)	50	DMF	8	–
6	Amberlyst®-15(H)	40	Toluene	6	40
7	Amberlyst®-15(H)	50	Toluene	6	46
8	*Amberlyst®-15(H)*	*50*	*Wet Acetonitrile (0.1% of water)*	*6*	*88*
9	Amberlyst®-15(H)	50	Acetonitrile (Anhydrous)	8	–
10	Amberlyst®-15(H)	50	DMF	8	–
11	Urea nitrate	80	Toluene	8	20
12	Alumina (acidic)	60	Acetonitrile	6	–
13	Ni- Alumina	60	Acetonitrile	6	–

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst and time (as indicated), solvent (3 mL). [b]yield of isolated product.

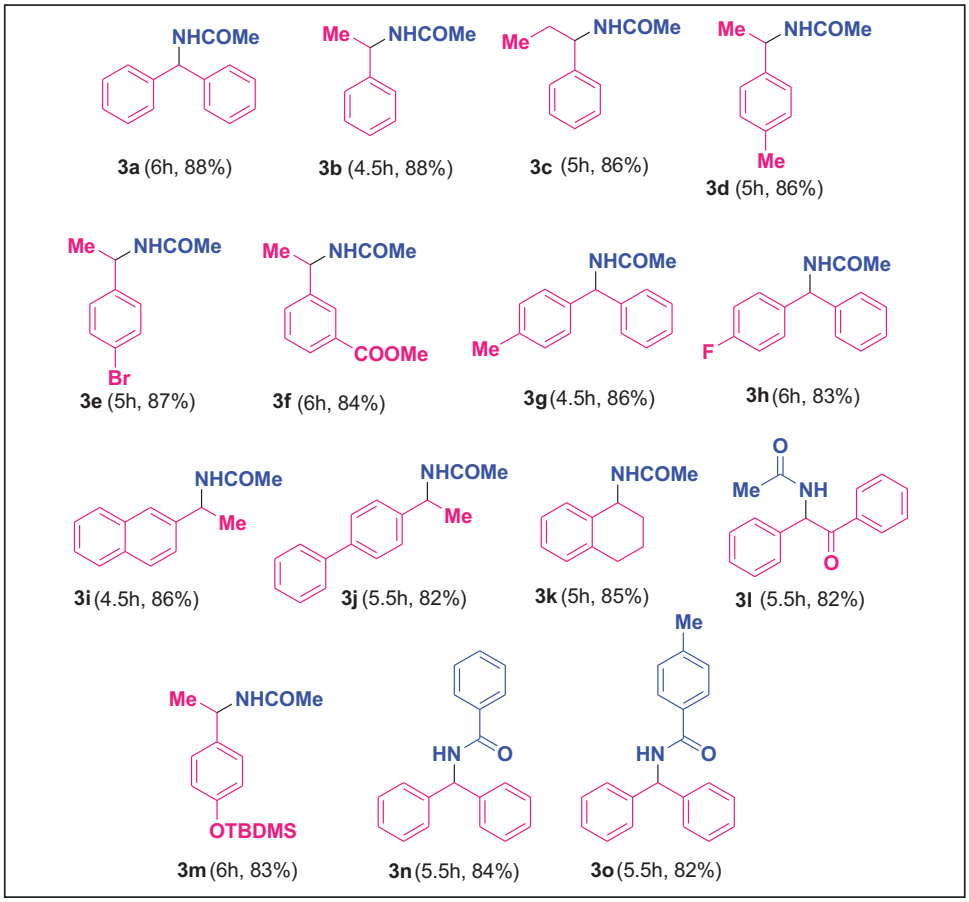
Before going to Amberlyst®-15(H), the same reaction was attempted with another well-known resin Dowex-50 where no conversion took place in toluene and DMF (entries 1 and 2) and only 32% of the product was obtained in acetonitrile solvent (entry 3). Similarly Amberlite (IR-45) produced only 24% of the required product in toluene (entry 4) and no reaction occurred in DMF (entry 5) leading to exclusive recovery of the substrate. Looking for another potential alternative of Amberlyst®-15(H), the reaction was carried out with urea nitrate where the product was obtained only in trace amount (entry 11). Even other acidic supports such as acidic alumina and Ni-alumina also failed in this case to provide the desired product (entries 12 and 13). The reaction was also carried out with 1-phenylethanol (**1b**) under optimized reaction condition at 80 °C using 1 drop of conc. H_2SO_4 as the catalyst instead of Amberlyst®-15(H) where a mixture of **3b** and styrene (**4a**) was obtained in 1:1.9 ratio (Scheme 2), but **3b** was obtained exclusively (88%) from **1b** using Amberlyst®-15(H).

In this way the essentiality, efficacy and applicability of Amberlyst®-15(H) as the solid acid resin was firmly established for the conversion of secondary alcohols to their corresponding N-acyl derivatives. Thus the present study led to the advent of a utilitarian and eco-compatible protocol for C–N bond formation using easily accessible substrates and catalyst. Moreover the same product **3a** was obtained when methyl and ethyl ethers of **1a** were used as the substrates in place of **1a**.

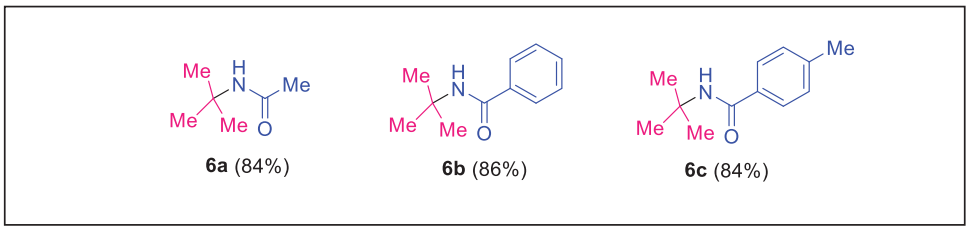
The catalyst i.e., Amberlyst®-15(H) was recovered by filtration, repeatedly washed with ethyl acetate, dried and further reused consecutively with marginal loss of its catalytic activity (Figure 1).

This protocol was further extended to substituted secondary and tertiary alcohols (Scheme 3 and Scheme 4) where a good number of substituted amides were obtained with satisfactory yield.

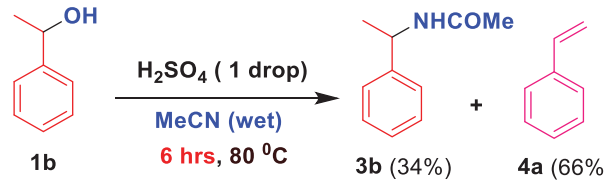
List of the products obtained in Scheme 3 using Amberlyst®-15(H)



List of the products formed in Scheme 4 using Amberlyst®-15(H)



Under the optimized condition unsubstituted benzhydrol (**1a)** produced N-benzhydrylacetamide (**3a**) in satisfactory yield (yield refers to that of the isolated pure product fully characterized spectroscopically). This condensation reaction also took place very efficiently with both ring-unsubstituted and alkyl/aryl-substituted secondary benzylic alcohols to afford **3b**, **3c**, **3d**, **3g**, **3i** and **3j** with good yield. Secondary benzylic carbinols bearing halogen substituents in the aromatic ring responded smoothly to produce **3e**



Scheme 2. Reaction of 1-phenylethanol with 1 drop H_2SO_4 under optimized condition.

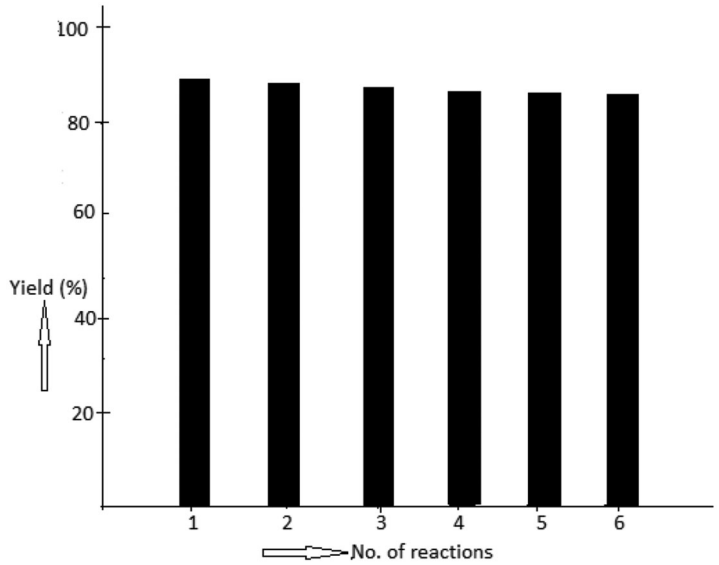
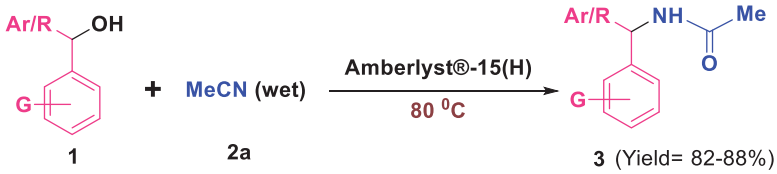
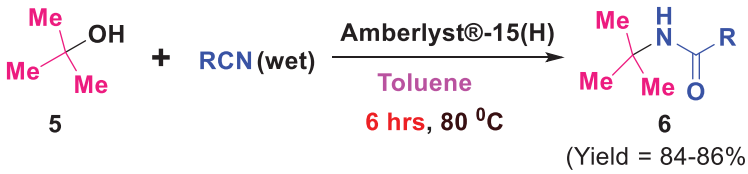


Figure 1. Recycling of Amberlyst®-15(H) using **1a** in moist MeCN at 80 °C for 6 h; % of yield was yield of isolated product **3a**.

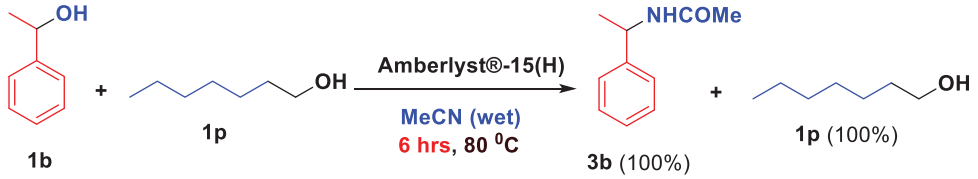


Scheme 3. Reaction of substituted secondary benzylic alcohols with wet acetonitrile under optimized condition.

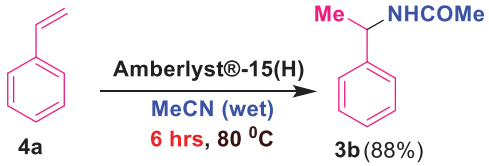


Scheme 4. Reaction of *tert*-butanol with alkyl/aryl nitriles.

and **3h** with 87% and 83% yields respectively. Hydrolyzable functional group -COOMe also survived in the present protocol to produce **3f** in 84% yield. The reaction gave quite impressive results with α-tetralol molecule forming **3k** with 85% yield. α-Hydroxyketone also reacted under this protocol and formed **3l** (82%) which is



Scheme 5. Intermolecular competition experiment (1).



Scheme 6. Reaction of styrene with wet acetonitrile under optimized condition.

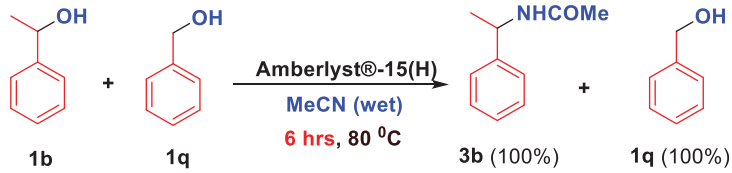
otherwise difficult to prepare. TBDMS group also survived under this procedure without any O-Si bond cleavage and **3 m** was obtained in 83% yield. When benzhydrol (**1a**) was reacted with benzonitrile and 4-methylbenzonitrile as a reagent in place of acetonitrile using toluene as the solvent it produced **3n** and **3o** respectively with satisfactory yield. No such reaction took place with aromatic or aliphatic primary alcohols where the substrates were recovered unchanged. When a mixture of equimolecular amounts of **1a** and benzyl alcohol was reacted under the optimized condition, only **1a** was converted to **3a** selectively leaving benzyl alcohol totally unaffected. Even with dialkyl secondary alcohol the reaction was inefficient to react under this protocol. Therefore this protocol is very much selective for only secondary alcohols where the aromatic ring is connected to the carbinol carbon. *tert*-Butanol responded efficiently under the present protocol (Scheme 4) giving N-tert-butyl-amides (**6a–c**) without any cleavage of any C-C bonds.

To substantiate the selectivity between aromatic and aliphatic alcohols, the competition reaction was carried out under optimized condition at 80 °C with equimolar mixtures of 1-phenylethanol (**1b**) and 1-heptanol (**1p**) where the product **3b** was obtained as expected from **1b**; leaving **1p** intact (Scheme 5). Absence of any signal at δ 3.24 ppm in ^{1}H NMR spectrum of the reaction mixture further confirmed the fact that the aliphatic –$\underline{CH_2}$OH has not been transformed into –$\underline{CH_2}$NHCOCH$_3$.

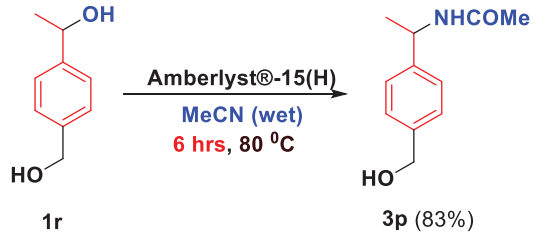
As a continuity of this theme, styrene (**4a**) was subjected to the optimized condition at 80 °C and produced N-(1-phenylethyl)-acetamide (**3b**) as the sole product (Scheme 6).

Equimolecular mixture of 1-phenylethanol (**1b**) and benzyl alcohol (**1q**), under optimized condition at 80 °C produced **3b** exclusively as the product obtained from **1b** leaving behind **1q** unaffected (Scheme 7).

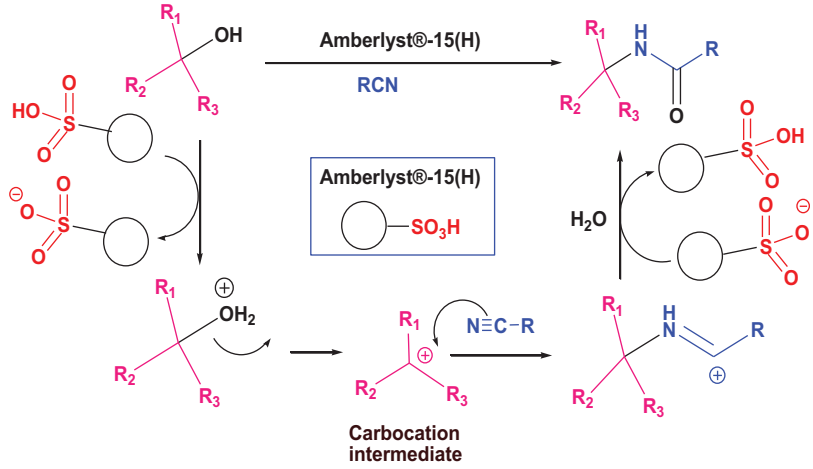
Intramolecular completion experiment with the substrate **1r** (containing both the aromatic primary and secondary carbinol moieties in the same molecule) under this protocol, produced **3p** exclusively (Scheme 8) with 83% yield. Excellent and subtle chemoselectivity was thus conclusively substantiated as the most important attribute of the present Amberlyst®-15(H)-catalyzed protocol.



Scheme 7. Intermolecular competition experiment (2).



Scheme 8. Intramolecular competition experiment.



Scheme 9. Proposed mechanism for the reaction.

Both ^{1}H and ^{13}C NMR spectroscopic studies confirmed the occurrence of **3p**. A doublet at δ 1.46 in ^{1}H NMR (δ 21.8 in ^{13}C NMR) and a singlet at δ 1.96 in ^{1}H NMR (δ 23.6 in ^{13}C NMR) established the presence of one alkyl-methyl and one acetamino-methyl moieties respectively. A singlet at δ 4.51 in ^{1}H NMR (δ 71.9 in ^{13}C NMR) indicated the unperturbed benzylic primary carbinol moiety.

The aforesaid observations indicate that this subtle chemoselectivity might originate due to preferential formation of the relatively more stable carbocationic intermediate. The result obtained in the study delineated in Scheme 6 also indicated towards the involvement of carbocationic intermediate. Furthermore, when the reaction was carried out using enantiopure *R*-1-phenylethanol under the optimized reaction condition, the product **3b** was obtained as a racemic mixture. This observation also supported

the formation of planar carbocation during the course of the reaction. On the basis of the above-mentioned outcomes, a plausible mechanistic scheme has been put forward (Scheme 9) involving the formation of carbocation through acid-catalyzed dehydration of alcohol with concomitant nucleophilic attack by nitrile followed by another nucleophilic attack by water to end up with the product amide. This mechanism also accounts for the catalytic role of Amberlyst®-15(H) in terms of Bronsted acidity and recyclability. No reaction took place with highly substituted triphenylmethanol due to lower stability of propeller-shaped triphenylmethyl carbocation as well as increased steric crowding.

Conclusion

In conclusion, commercially available Amberlyst®-15(H) has been effectively utilized as an air stable and recyclable heterogeneous inexpensive solid acid catalyst for the construction of C–N bond through chemoselective formation of diversely N-substituted amides using benzylic secondary alcohols as well as aliphatic tertiary alcohols and alkyl/aryl nitriles under environmentally acceptable conditions without any necessity of anhydrous and inert environment. Use of reagents, solvents and catalyst of negligible toxicity, mild reaction conditions, tolerance of various sensitive moieties, excellent chemoselectivity, wide substrate scope, high atom economy, formation of the most innocuous by-product (namely water), procedural simplicity, good yields and recyclability of the catalyst are the outstanding features of the present method with greater applicability compared to many existing protocols.

Experimental

A. To a mixture of benzhydrol **1a** (184 mg, 1.0 mmol) and wet MeCN **2a** (4 mL) the catalyst Amberlyst®-15(H) (50 mg) was added. The reaction mixture was stirred for 6 hours at 80 °C till the reaction was complete (monitored with TLC). Then the reaction mixture was cooled to room temperature, excess MeCN was removed under reduced pressure, the catalyst was filtered out keeping a cotton plug on a funnel and washed repeatedly by ethyl acetate (3 × 10 mL) to dissolve and collect the product. The product was thoroughly washed with water (2 × 10 mL) to remove any unused MeCN. The aqueous reaction mixture was then repeatedly extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with water (3 × 10 mL) and dried over anhydrous Na_2SO_4. The crude product was obtained by removal of the solvent under reduced pressure and purified by filtration chromatography on a short column of silica gel using 1–4% ethyl acetate-hexane as eluent to afford **3a**[21] (198 mg, Yield 88%, mp143–144 °C).

B. To a mixture of *tert*-butanol **5** (74 mg, 1.0 mmol), and PhCN **2b** (103 mg, 1.0 mmol) in 4 mL toluene, the catalyst Amberlyst®-15(H) (50 mg) was added. The reaction mixture was stirred for 6 hours at 80 °C till the reaction was complete (monitored with TLC). Then the reaction mixture was cooled to room temperature, excess toluene was removed under reduced pressure, keeping a cotton plug on a funnel the catalyst was filtered out and washed repeatedly by ethyl acetate (3 × 10 mL) to dissolve and collect the product. The product was thoroughly washed with water (2 × 10 mL). The aqueous reaction mixture was then repeatedly extracted with ethyl acetate (3 × 5 mL).

The combined organic extracts were washed with water (3 × 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure furnished the product **6b**[29] (152 mg, Yield 86%, mp132–133 °C) without any necessity of further purification.

Supporting information

This part contains experimental procedure, physical characteristics as well as spectral (^1H and ^{13}C NMR) and HRMS/analytical data (wherever applicable) for the products. This material can be found via the "Supplementary Information" section of this article's webpage.

Acknowledgements

S. N. thanks DST-INSPIRE, India for senior research fellowship. Financial support from UGC-CAS-II program in Chemistry and RUSA program 2.0 at Jadavpur University as well as Infrastructural support from DST-FIST program are gratefully acknowledged. The authors express sincere gratitude to Ms. P. Das of Indian Institute of Chemical Biology for necessary assistance.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Poster – 1 (Picture)

National Seminar on "*Indian Chemical Industries: Retrospect and Prospect*"

DEPARTMENT OF CHEMISTRY

Jogesh Chandra Chaudhuri College

February 27, 2017

Synthesis of alkyl and aryl esters from the corresponding alcohols in aqueous medium using TBHP/TBAI as an efficient catalyst

Sneha Nandy[a], Avishek Ghatak[b], Asit Kumar Das[a], Dibyendu Chakraborty[a] and Sanjay Bhar[a,*]

[a] Department of Chemistry, Organic Chemistry Section, Jadavpur University, Kolkata-700032, India

[b] Department of Chemistry, Dr. A. P. J. Abdul Kalam Govt. College, Kolkata- 700157 , India. (Formerly Government General Degree College, NewTown, Rajarhat)

Reaction of benzyl alcohol using different catalysts and oxidants in aqueous medium

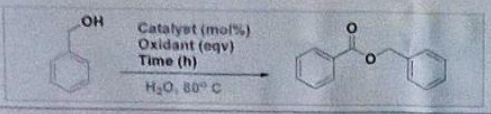
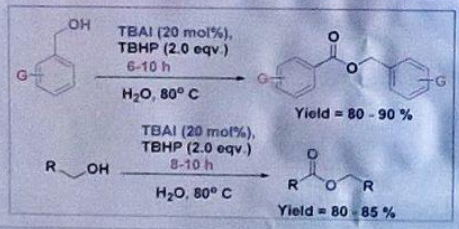


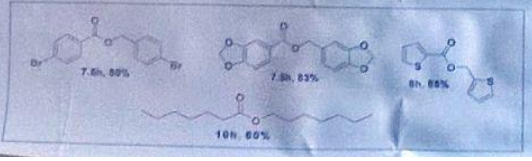
Table 1. Optimization of the oxidation reaction of benzyl alcohol using different catalysts and oxidants

Entry	Catalyst	Mole %	Oxidant	Molar Eqv.	Time (h)	Yield of 2a (%)
1	KI	10	H_2O_2	1	8	-
2	KI	10	H_2O_2	2	10	-
3	I_2	10	H_2O_2	1	10	-
4	I_2	10	H_2O_2	2	10	Trace
5	TBAI	10	TBHP	1	6	65
6	TBAI	15	TBHP	2	8	73
7	TBAI	20	TBHP	2	8	86
8	TBAI	15	TBHP	3	8	74
9	TBAI	20	TBHP	3	10	69
10	TBAI	30	TBHP	2	10	72

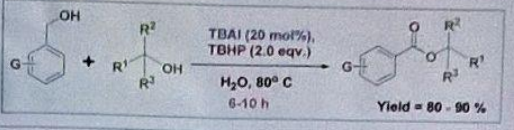
TBHP: tert-Butylhydroperoxide , TBAI: Tetrabutylammonium iodide

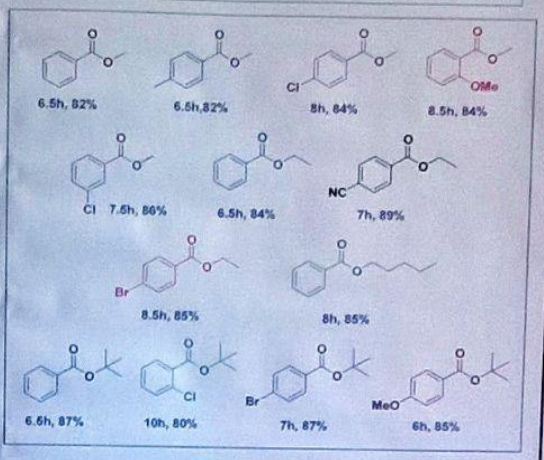
Synthesis of aryl esters and alkyl esters through oxidation reaction in aqueous medium using TBHP and TBAI



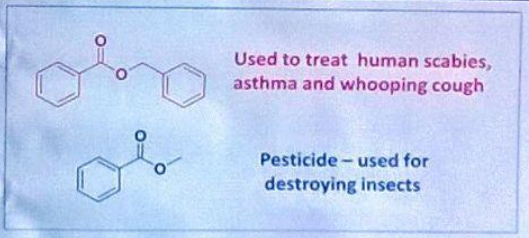


Reaction between substituted benzyl alcohols and alkanols in the presence of TBHP and TBAI in aqueous medium





Representative examples of biologically active aryl esters



Acknowledgment: S.N. thanks DST-INSPIRE, New Delhi, Government of India for junior research fellowship and other financial support.

A one-day UGC Sponsored National Level Seminar

on

Indian Chemical Industries: Retrospect and Prospect

Organized by

Department of Chemistry, Jogesh Chandra Chaudhuri College, Kolkata-700 033

(NAAC Reaccredited B++ , 2016)

In collaboration with

New Alipore College, Kolkata-700 053

Certificate of Participation

This is to certify that Sri/ Smt/ Dr./ Prof. Sneha Nandy

of Jadavpur University Kolkata has participated/ presented a paper/ poster/ chaired / invited talk entitled Synthesis of alkyl and aryl ..... an efficient catalyst in the seminar held at Jogesh Chandra Chaudhuri College Auditorium, 30 Prince Anwar Shah Road, Kolkata-700 033 on February 27, 2017.

Dr. Pankaj Kumar Roy	**Dr. Avijit Saha**	**Dr. Saswati Chatterjee**
Principal	Convener	Joint Convener
Jogesh Chandra Chaudhuri College	Jogesh Chandra Chaudhuri College	New Alipore College

Poster – 1 (Certificate)

Poster – 2 (Abstract)

P27. C–N bond formation in wet acetonitrile using Amberlyst®-15(H) as a catalyst

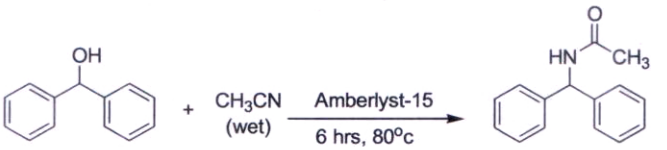
Sneha Nandy[a], Asit Kumar Das[b] and Sanjay Bhar[a,*]

[a] Department of Chemistry, Jadavpur University, Kolkata-700032, India.

[b] Department of Chemistry, Krishnath College, Murshidabad-742101, India.

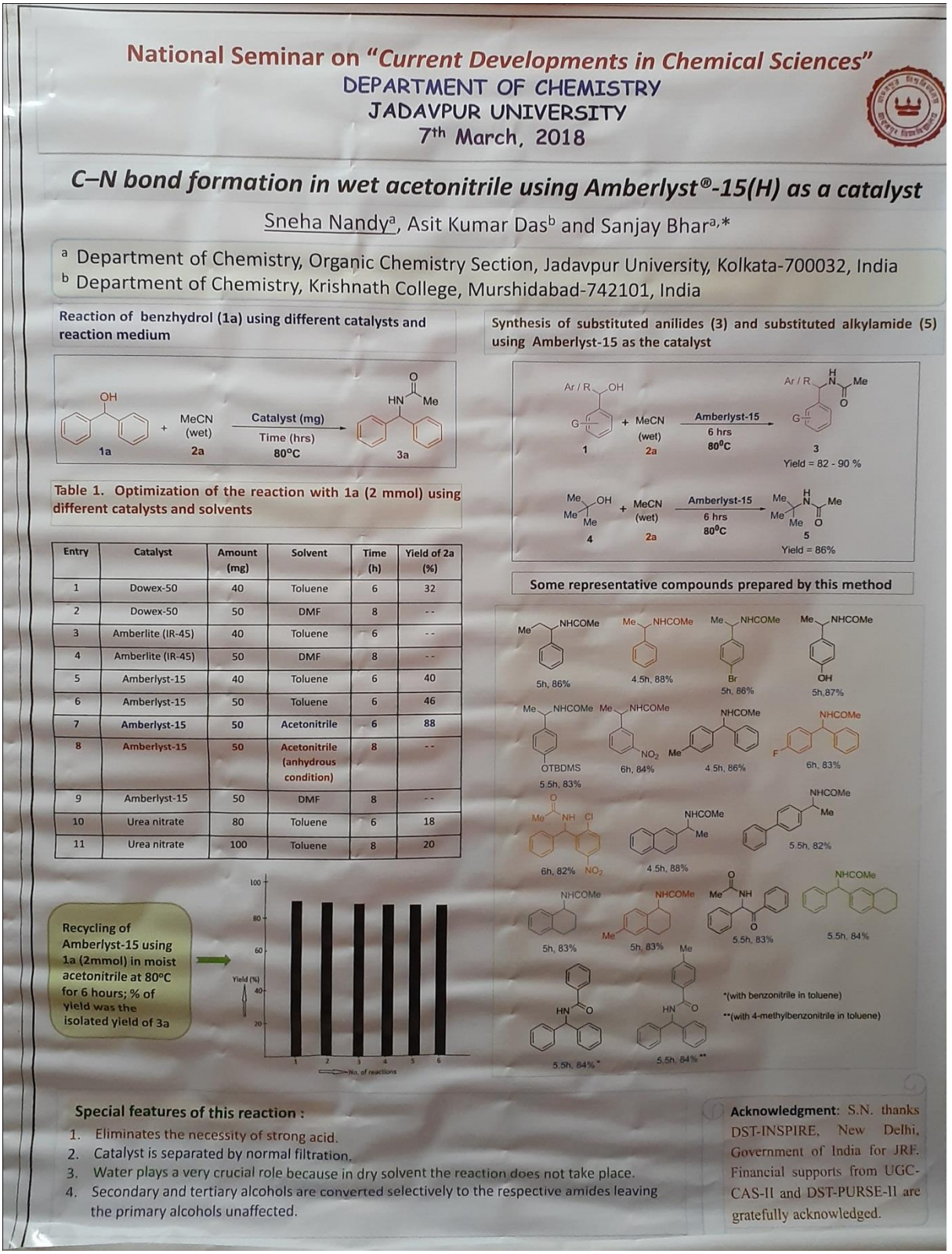
E-mail: sanjaybharin@yahoo.com ; sanjay_bhar@chemistry.jdvu.ac.in

Development of an efficient protocol to obtain C–N bond in aliphatic frameworks using easily accessible reagents as well as mild and eco-compatible experimental conditions constitutes a formidable challenge towards the synthetic organic chemists. Ritter reaction, often used to obtain substituted amides from alcohols, demands a strong acid catalyst which sometimes poses environmental threats. Resins bearing acidic sites offer the advantages not only due to the subtle catalytic attributes but also from the standpoint of operational simplicity with reference to the ease of catalyst separation. We report herein the catalytic application of Amberlyst®-15(H) in moist acetonitrile for the formation of C–N bond through the Ritter reaction of the alcohols with wide structural variation. The reactions neither occur in anhydrous acetonitrile nor in water alone, wet acetonitrile is the suitable reaction medium where the amount of water is very crucial for optimum performance. This study leads to the advent of an utilatarian and eco-compatible protocol for this important synthetic operation using easily accesible substrates. Detailed results of this investigation will be presented.



Yield = 88%

Poster – 2 (Picture)



National Seminar on "*Current Developments in Chemical Sciences*"
DEPARTMENT OF CHEMISTRY
JADAVPUR UNIVERSITY
7th March, 2018

C–N bond formation in wet acetonitrile using Amberlyst®-15(H) as a catalyst

Sneha Nandy[a], Asit Kumar Das[b] and Sanjay Bhar[a,*]

[a] Department of Chemistry, Organic Chemistry Section, Jadavpur University, Kolkata-700032, India
[b] Department of Chemistry, Krishnath College, Murshidabad-742101, India

Reaction of benzhydrol (1a) using different catalysts and reaction medium

Table 1. Optimization of the reaction with 1a (2 mmol) using different catalysts and solvents

Entry	Catalyst	Amount (mg)	Solvent	Time (h)	Yield of 2a (%)
1	Dowex-50	40	Toluene	6	32
2	Dowex-50	50	DMF	8	--
3	Amberlite (IR-45)	40	Toluene	6	--
4	Amberlite (IR-45)	50	DMF	8	--
5	Amberlyst-15	40	Toluene	6	40
6	Amberlyst-15	50	Toluene	6	46
7	Amberlyst-15	50	Acetonitrile	6	88
8	Amberlyst-15	50	Acetonitrile (anhydrous condition)	8	--
9	Amberlyst-15	50	DMF	8	--
10	Urea nitrate	80	Toluene	6	18
11	Urea nitrate	100	Toluene	8	20

Recycling of Amberlyst-15 using 1a (2mmol) in moist acetonitrile at 80°C for 6 hours; % of yield was the isolated yield of 3a

Synthesis of substituted anilides (3) and substituted alkylamide (5) using Amberlyst-15 as the catalyst

Some representative compounds prepared by this method

Special features of this reaction :

1. Eliminates the necessity of strong acid.
2. Catalyst is separated by normal filtration.
3. Water plays a very crucial role because in dry solvent the reaction does not take place.
4. Secondary and tertiary alcohols are converted selectively to the respective amides leaving the primary alcohols unaffected.

Acknowledgment: S.N. thanks DST-INSPIRE, New Delhi, Government of India for JRF. Financial supports from UGC-CAS-II and DST-PURSE-II are gratefully acknowledged.

National Seminar on

CURRENT DEVELOPMENTS IN CHEMICAL SCIENCES (CDCS-2018)

(Wednesday, March 7, 2018)

under

Centre for Advanced Studies II Program

Organized by

Department of Chemistry, Jadavpur University, Kolkata 700 032

This is to certify that Sneha Nandy *of* Jadavpur University *has participated/presented a poster in the seminar organized by the Department of Chemistry, Jadavpur University, Kolkata 700 032 on Wednesday, March 7, 2018.*

Date: 07-03-2018
Place: Kolkata

SAUBHIK HALDAR P. Mahata **PARTHA MAHATA**

Conveners

Poster – 2 (Certificate)

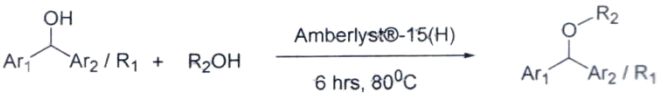
Poster – 3 (Abstract)

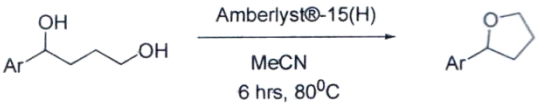
C–O BOND FORMATION USING AMBERLYST®-15(H) AS A RECYCLABLE CATALYST

S. Nandy, T. K. Dinda and S. Bhar*

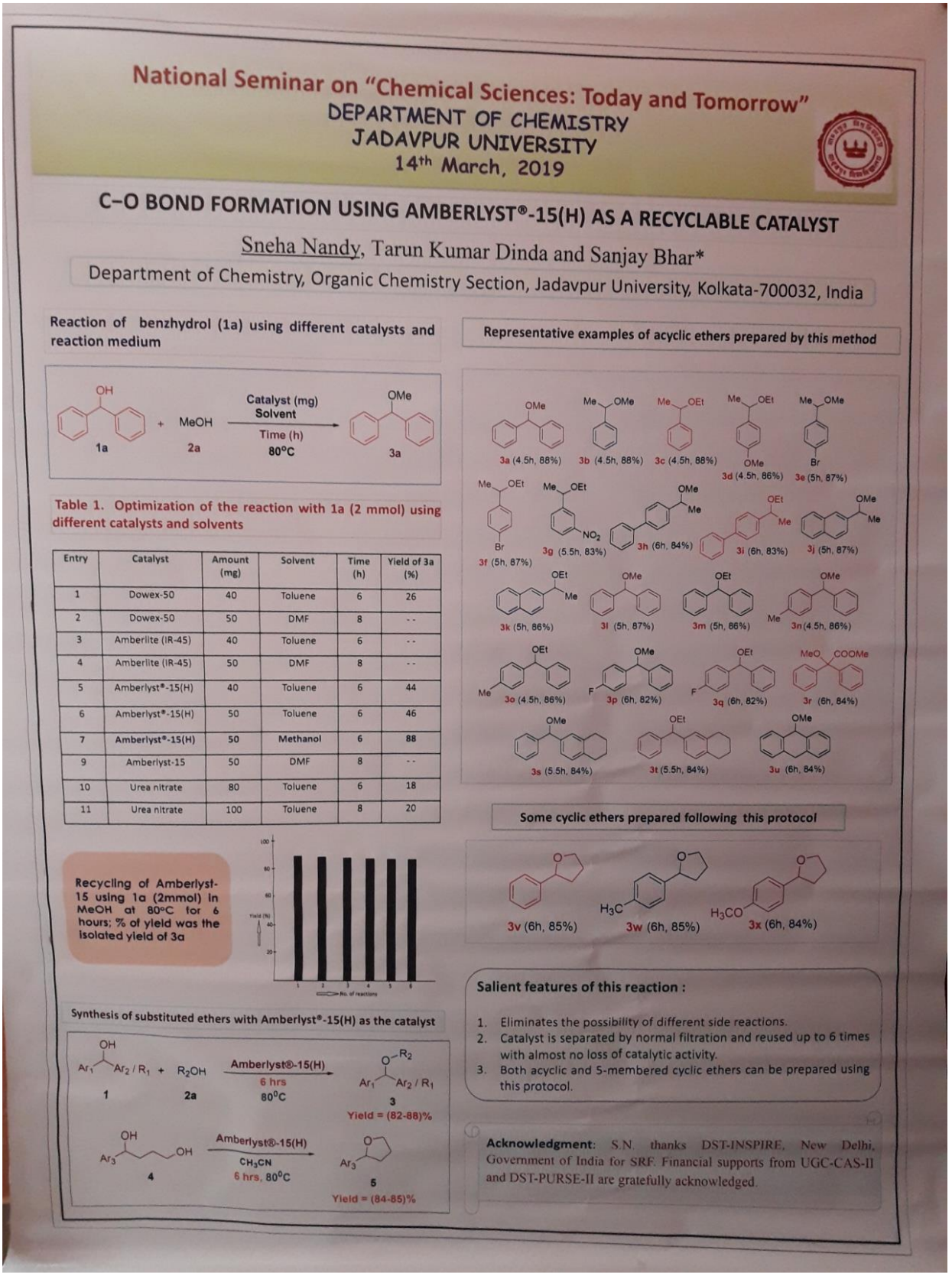
Department of Chemistry, Jadavpur University, Kolkata-700032, India.
e-mail: sanjay.bhar@jadavpuruniversity.in; Phone: +918697179547

Development of an efficient protocol to generate C-O bond in aliphatic framework using easily accessible reagents as well as mild and eco-friendly experimental conditions constitutes a formidable challenge towards the synthetic organic chemists all over the globe. Resins bearing acidic sites offer the advantages not only due to its subtle catalytic attributes but also for its operational simplicity with reference to the ease of isolation and reuse of the catalyst. We report herein the catalytic application of Amberlyst®-15(H) for the formation of C-O bond with a wide structural variation. With the help of this method both acyclic and cyclic ethers were prepared starting from the corresponding secondary alcohols through intermolecular as well as intramolecular etherification reaction. This exploration led to the development of a highly utilitarian and eco-compatible protocol for the construction of important structural motifs. Detailed results of this investigation will be presented.





Poster – 3 (Picture)



National Seminar on "Chemical Sciences: Today and Tomorrow"
DEPARTMENT OF CHEMISTRY
JADAVPUR UNIVERSITY
14th March, 2019

C–O BOND FORMATION USING AMBERLYST®-15(H) AS A RECYCLABLE CATALYST

Sneha Nandy, Tarun Kumar Dinda and Sanjay Bhar*
Department of Chemistry, Organic Chemistry Section, Jadavpur University, Kolkata-700032, India

Reaction of benzhydrol (1a) using different catalysts and reaction medium

Table 1. Optimization of the reaction with 1a (2 mmol) using different catalysts and solvents

Entry	Catalyst	Amount (mg)	Solvent	Time (h)	Yield of 3a (%)
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3	Amberlite (IR-45)	40	Toluene	6	--
4	Amberlite (IR-45)	50	DMF	8	--
5	Amberlyst®-15(H)	40	Toluene	6	44
6	Amberlyst®-15(H)	50	Toluene	6	46
7	**Amberlyst®-15(H)**	**50**	**Methanol**	**6**	**88**
9	Amberlyst-15	50	DMF	8	--
10	Urea nitrate	80	Toluene	6	18
11	Urea nitrate	100	Toluene	8	20

Recycling of Amberlyst-15 using 1a (2mmol) in MeOH at 80°C for 6 hours; % of yield was the isolated yield of 3a

Synthesis of substituted ethers with Amberlyst®-15(H) as the catalyst

Representative examples of acyclic ethers prepared by this method

Some cyclic ethers prepared following this protocol

Salient features of this reaction :

1. Eliminates the possibility of different side reactions.
2. Catalyst is separated by normal filtration and reused up to 6 times with almost no loss of catalytic activity.
3. Both acyclic and 5-membered cyclic ethers can be prepared using this protocol.

Acknowledgment: S.N. thanks DST-INSPIRE, New Delhi, Government of India for SRF. Financial supports from UGC-CAS-II and DST-PURSE-II are gratefully acknowledged.

National Seminar on

CHEMICAL SCIENCES: TODAY AND TOMORROW (CSTT-2019)

(Thursday, March 14, 2019)

under

Centre for Advanced Studies II Program

Organized by

Department of Chemistry, Jadavpur University, Kolkata 700 032

This is to certify that SNEHA NANDY *of* Dept. of Chemistry JADAVPUR UNIVERSITY *has delivered an invited talk /participated/ presented a poster in the seminar organized by the Department of Chemistry, Jadavpur University, Kolkata 700 032 on Thursday, March 14, 2019.*

Date: 14-03-2019
Place: Kolkata

Partha Roy
Co-Convener

Swapan Kumar Bhattacharya
Convener

Poster – 3 (Certificate)

Poster – 4 (Abstract)

References:

1. Donaire, J.-G.; Martin, R. *J. Am. Chem. Soc.* **2013**,*13*,9350-9353
2. Nandi, S.; Jana, R. *Manuscript under preparation*

P-017

Amberlyst®-15(H) – a versatile and recyclable catalyst for organic transformations

Sneha Nandy,Asit Kumar Das and Sanjay Bhar*
Department of Chemistry, Jadavpur University, Kolkata-700032, INDIA
e-mail: sanjay.bhar@jadavpuruniversity.in

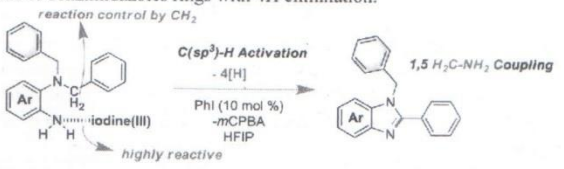
Development of efficient and eco-compatible protocols to obtain carbon-heteroatom bonds in aliphatic frameworks constitutes a formidable challenge towards the synthetic organic chemists. Several reactions have been implemented to obtain C-N and C-O bonds but most of them experience several disadvantages in terms of accessibility, cost, toxicity and lack of selectivity. Resins bearing acidic sites offer the advantages not only due to their subtle catalytic attributes but also from the standpoint of operational simplicity with reference to the ease of catalyst separation. Commercially availableAmberlyst®-15(H) has been utilised efficiently as an air-stable, heterogeneous and inexpensive solid acid catalyst which is easily separated by filtration and successively recycled with marginal loss of catalytic activity. The catalyst is utilized in different solvent systems for the formation of C–N as well as C-O bonds starting from alcohols with a wide structural variation. Moreover, differently substituted conjugated dienes have been synthesized in excellent yield through the cleavage of cyclopropane ring. Mild reaction conditions, tolerance of various sensitive moieties, excellent chemoselectivity, high atom economy and efficient functioning of the catalyst along with good recyclability contribute to the outstanding features of the newly developed reactions from our group compared to many of the existing methods.

P-018

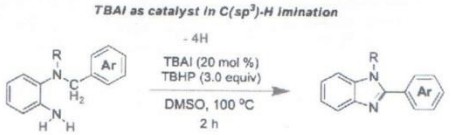
Intramolecular C(sp3)-H Imination towards Benzimidazoles using Iodine Reagents

Sudip Sauand Prasenjit Mal*
School of Chemical Sciences, National Institute of Science Education and Research (NISER), HBNI, Bhubaneswar, PO Bhimpur-Padanpur, Via Jatni, District Khurda, Odisha 752050, India
Email id: sudip.sau@niser.ac.in

The C(sp3)–H bonds are thermodynamically more stable and generally less reactive than the C(sp2)–H bonds. The known methods available for the activation of non-prefunctionalized C–H bonds are mainly based on either as metal initiated or by radical mediated pathway. The present works describe application of iodine reagents for conversion of unactivated C(sp3)-H bond of a benzylic group to imine functionality for the synthesis of benzimidazoles rings with 4H elimination.



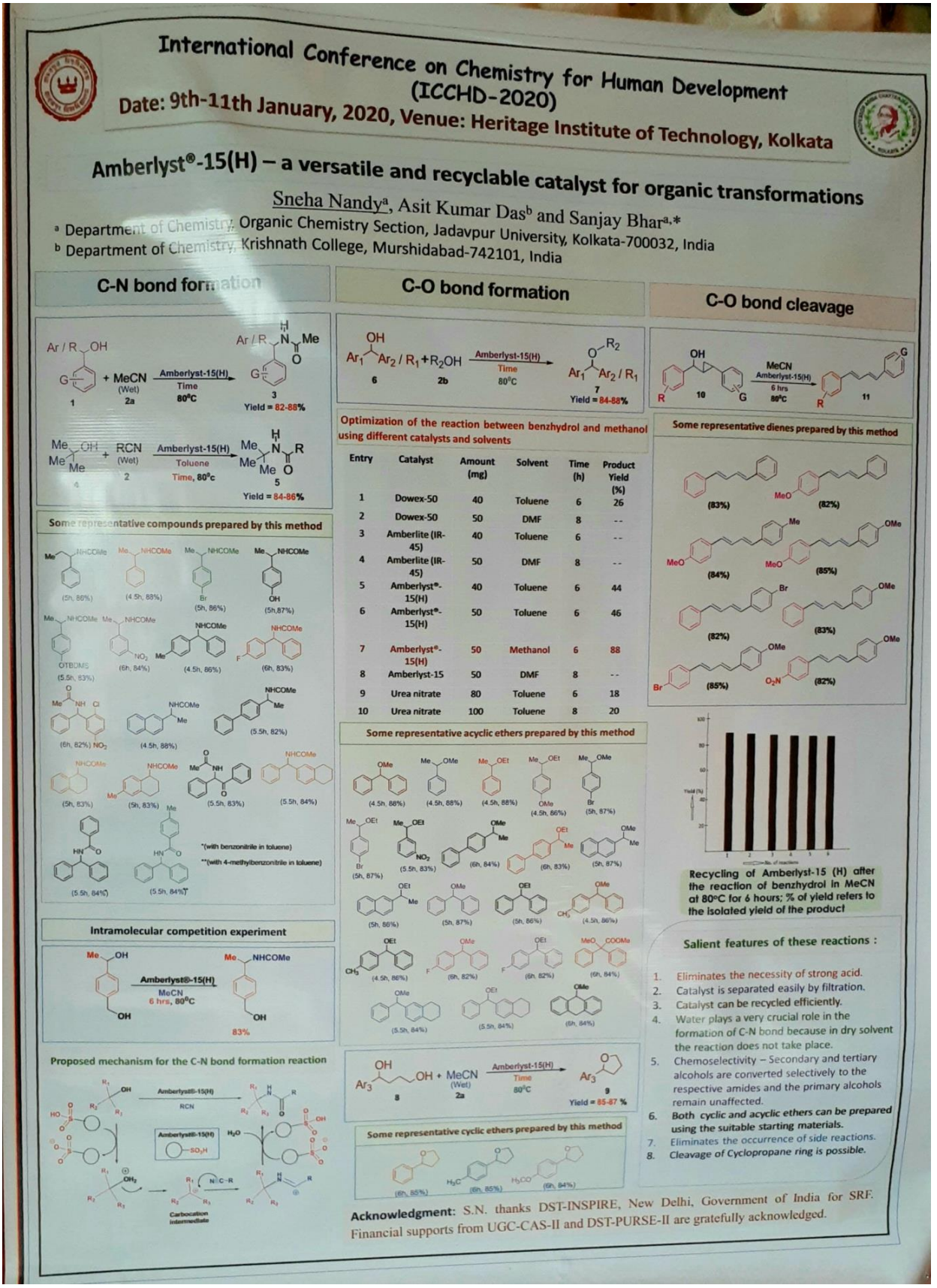
Chem. Commun. **2019**, *55*, 2066.



Eur. J. Org. Chem. **2019**, 4105.

References.

Poster – 4 (Picture)



International Conference on Chemistry for Human Development (ICCHD-2020)

January 9–11th, 2020

Certificate

ICCHD 2020

This is to Certify that ~~Prof/Dr./Mr.~~/Mrs. Sneha Nandy

of JU

has participated and presented a Paper (~~Oral~~/Poster) Delivered Talk in the International Conference on Chemistry for Human Development (ICCHD-2020) held at Heritage Institute of Technology, Kolkata

Convenor

Prof. Dilip Kumar Maiti
Convener, ICCHD-2020
Professor Asima Chatterjee
Foundation, Kolkata

Poster – 4 (Certificate)