
3d-Metal Salts and their Pincer-Complexes for Catalytic Value-Addition of Alcohols to Hydrogen and Speciality Chemicals

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by

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*Dedicated
To
My Parents*



Do not boast about tomorrow, for you do not know what a day may bring.

-Proverbs 27:1





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Abbreviation

°C	Degree Celsius	psi	Pound per square inch
r.t.	Room temperature	m/z	Mass to charge ratio
h	Hours	THF	Tetrahydrofuran
equiv.	equivalent	KIE	Kinetic isotopic effect
NHC	<i>N</i> -heterocyclic carbene	TON	Turn over number
RDS	rate determining step	TOF	Turn over frequency
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine	TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
J	joule	Vs	Versus
Kg	Kilogram	KHMDS	Potassium hexamethyldisilazane
LOHCs	Liquid Organic Hydrogen Carrier	DFT	Density functional theory
EG	Ethylene glycol	terpy	terpyridine
GLY	Glycerol	ca.	around
LA	Lactic acid	TS	Transition state
DHA	Dihydroxyacetone	ImNHC	imidazol-2-ylidene
PLA	Poly(lactic acid)	1,2,3-tz-N	1,2,3-triazole-N
PDO	Propanediol	tzNHC	1,2,3-triazol-5-ylidene
via	through	MPV	Meerwein-Ponndorf-Verley
EPR	Electron Paramagnetic Resonance	ORTEP	Oak Ridge Thermal Ellipsoid Plot
MS	Mass spectrometry	CCDC	Cambridge Crystallographic Data Center
HRMS	High-resolution mass spectrometry	GC	Gas chromatography
Hz	Hertz	g	Grams
MHz	Megahertz	mg	milligram
GHz	Gigahertz	mmol	millimole
NMR	Nuclear Magnetic Resonance	mL	milliliter
<i>J</i>	Spin – spin coupling constant	W	watt
s	Singlet	t	Triplet
d	Doublet	q	Quartet
dd	Doublet of Doublet	m	Multiplate
ddd	Doublet of Doublet of Doublet	bs	Broad singlet
δ	Chemical shifts	K	Kelvin
EDG	Electron donating group	EWG	Electron withdrawing group
IPA	Isopropanol		



Abstract

The contents of the present thesis entitled “*3d-Metal Salts and their Pincer-Complexes for Catalytic Value-addition of Alcohols to Hydrogen and Speciality Chemicals*” have been divided into five chapters based on the results achieved from the experimental work carried out during the entire course of the PhD research program.

Chapter I provides a concise overview of the literature regarding transition metal salts, coordination compounds, organometallic complexes with a special focus on pincer-metal complexes and organic transformations catalysed by them. The dehydrogenative coupling of alcohols and aqueous reforming of alcohols using transition metal salts and pincer-metal complexes is also reviewed. The chapter winds up by defining the scope of the current thesis.

Chapter II demonstrates an efficient β -alkylation of secondary alcohols with primary alcohols catalyzed by commercially available $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its corresponding pincer-Cr complex $\text{Ph}_2\text{NNN}(\text{CrCl}_3)$. High yields (ca. 90%) of the β -alkylated product was obtained with a selectivity of 91% at very low loadings (0.005 mol%) of the pincer-chromium catalyst based on *bis*(imino-pyridine) under microwave conditions in the presence of 5 mol% NaO^tBu . The reaction mechanism was probed on the basis of control experiments.

Chapter III illustrates the potential of commercially available first-row, 3d transition metal salt chromium (III) chloride (0.4 mol%) in catalyzing the selective α -alkylation of nitriles with benzyl alcohol in excellent yields (ca. 99%) in the presence of 30 mol% KO^tBu at 140 °C after 24 h using conventional heating in air. The reaction was found to reach completion within 2 h under microwave heating conditions, with comparable yields (ca. 93%). Detailed mechanistic studies are suggestive of a sole contribution from the alcoholysis path in the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed α -alkylation of benzyl nitrile with benzyl alcohol with β -hydride elimination as the RDS having a rate-determining barrier of 28.6 kcal/mol.

Chapter IV deals with the net transfer dehydrogenation of glycerol (GLY) to lactic acid (LA) catalyzed by commercially available first-row transition metal salt $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its corresponding pincer complexes based on *bis*(imino)pyridine ligands ($(\text{R}^2\text{NNN})\text{CrCl}_3$; R = Ph, Cy, ^iPr and ^tBu) in the presence of a sacrificial hydrogen acceptor, acetone. The pincer-Cr complex, $(\text{Cy}^2\text{NNN})\text{CrCl}_3$ (0.5 mol%) was found to efficiently bring about the catalytic net transfer dehydrogenation of glycerol in presence of 1.1 equivalents of NaOH, at 160 °C to

afford 94% lactic acid at 98% selectivity along with another value added product isopropanol (IPA). Thorough mechanistic investigations have suggested the homogeneous molecular nature of the Cr(II) active species in the reaction course.

Chapter V describes the role of readily available, inexpensive, environmentally benign and earth-abundant base metal salt cobaltous chloride (0.5 mol%) which successfully catalysed the dehydrogenative conversion of glycerol to lactic acid in an acceptorless fashion as well as under transfer dehydrogenation conditions using acetone as a sacrificial acceptor at 160 °C in the presence of various bases. Up to 75% conversion of glycerol to lactic acid (33%), ethylene glycol (14%) and formic acid (27%) was observed in addition to hydrogen, under the acceptorless conditions, whereas a maximum of 93% lactic acid with 96% selectivity along with isopropanol was obtained in the presence of acetone as a sacrificial hydrogen acceptor in a sealed vessel. Mechanistic investigations shed light on the homogeneous nature of the reaction mixture involving Co(II) as the active species.



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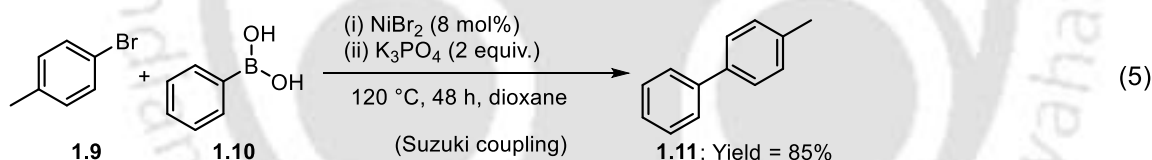
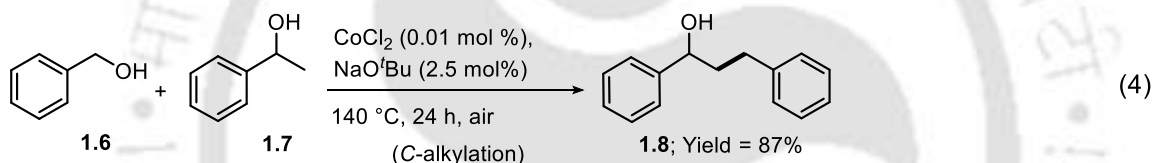
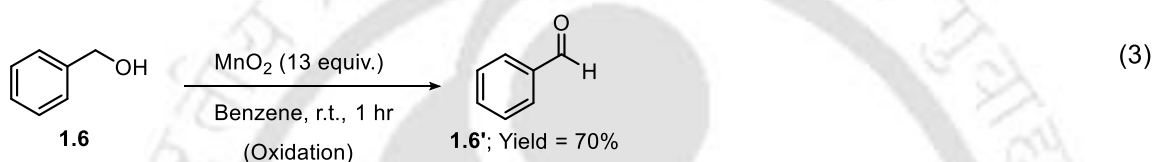
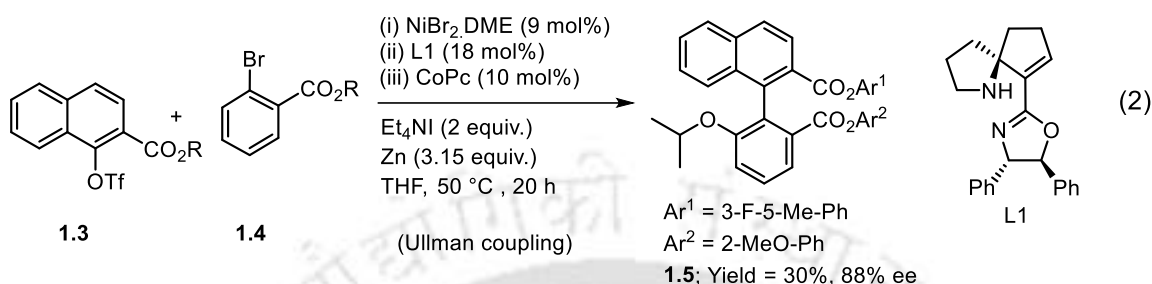
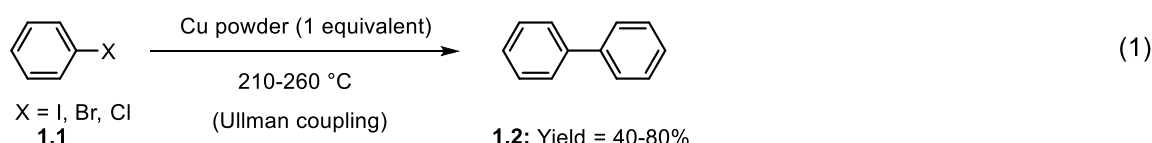
Chapter- I

Transition Metal Salts and their Complexes as Catalysts for Organic transformations





1.1. Transition metal salts



Scheme 1.1. Transition metal catalysed reactions such as 1) Ullmann coupling^{2a} using Cu powder 2) Ullman coupling catalysed by NiBr₂.DME^{2d} 3) Oxidation^{1g} of alcohols catalysed by MnO₂ 4) C-alkylation³ catalysed by CoCl₂ 5) Suzuki coupling^{2e} catalysed by NiBr₂.

The ionic compounds which are comprised of a transition metal cation and an anion are termed as transition metal salts.^{1a-e} The partially filled *d*-orbitals and the electronic configuration of transition metal centre imparts unique properties to these metal salts, such as they are coloured (owing to d-d transitions), they own magnetic properties and moreover they possess variable oxidation states.^{1a-e} These facts together make transition metal salts more attractive and have garnered special attention in the field of catalysis. The transition metals occur in nature as ores in the form of halides, oxides or as an alloy with other metals.^{1a-e} They can act as a reducing

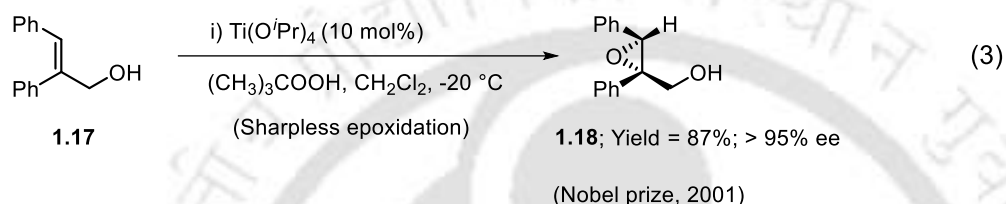
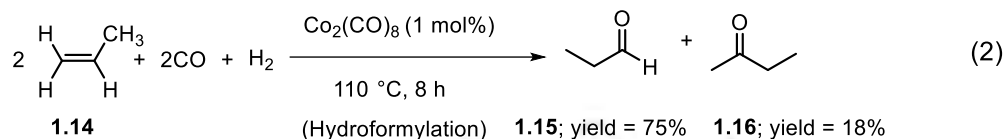
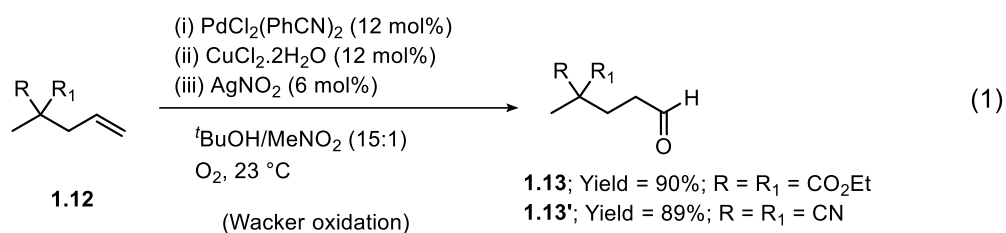
agent,¹ an oxidising agent,¹ hence, can act as a catalyst in different hydrogenation,¹ⁱ oxidation^{1g-h} and coupling reactions.^{1f,2-4}

Representative examples of different coupling reactions have been given in Scheme 1.1. One such classical reaction is Ullman coupling of aryl halides catalysed by copper salt. The traditional Ullmann coupling of two aryl halides in the presence of copper was reported by Ullman in 1901 (equation 1, Scheme 1.1).^{2a} This reaction can follow radical mechanism or ionic mechanism to give homo-coupled biaryl as the product.^{2b-c} Recent advances in Ullmann reaction showed, asymmetric Ullmann coupling is evolving as an important tool in the field of catalysis.^{2c} A recent report by Tu, demonstrated the synthesis of highly enantioselective asymmetric biaryls in the presence of NiBr₂.DME and spirocyclic pyrrolidine oxazoline ligand L1 (equation 2, Scheme 1.1).^{2d} In 1968, Goldman reported an oxidation reaction, where, he utilised simple transition metal salt manganese dioxide to oxidise alcohol to aldehyde at room temperature (equation 3, Scheme 1.1).^{1g} Transition metal salts continue to be very productive in various catalytic reactions such as alcohol alkylation³ (equation 4, Scheme 1.1) and Suzuki coupling^{2e} (equation 5, Scheme 1.1). The transition metal salts act as versatile precursors to coordination complexes and organometallic complexes.

1.2. Co-ordination compound

The inorganic compounds which can retain their characteristic properties in solid state as well as in a solution are known as coordination compounds.^{1a-e} They are composed of a complex ion (positively or negatively charged) and a counter ion (cation or anion) e.g. [Co(NH₃)₆]Cl₃, [Cu(NH₃)₄]SO₄, K₄[Fe(CN)₆].^{1a-e} A complex ion consists of a metal atom in the centre which has a group of neutral molecules or ions in its surroundings. For example, in [Cu(NH₃)₄]SO₄, [Cu(NH₃)₄]²⁺ is a complex ion where a central metal atom copper is surrounded by four neutral molecules of ammonia and SO₄²⁻ as a counter anion.^{1a-e} The ligands form coordinate bonds with the central metal atom by donating their lone pair to the vacant orbital of the metal atom. Coordination compounds are coloured, magnetic, and can take part in both outer and inner-sphere electron transfer reactions owing to the presence of unpaired electrons.^{1a-e}

Haemoglobin (a coordination complex of iron(II) ion with a porphyrin ring), cobalamin or vitamin B12 (a coordination complex of cobalt(III) ion with a corrin ring), chlorophyll (a coordination complex of magnesium(II) ion with a porphyrin ring) are some examples of naturally occurring coordination compounds.^{1a-e} Coordination compounds show high catalytic

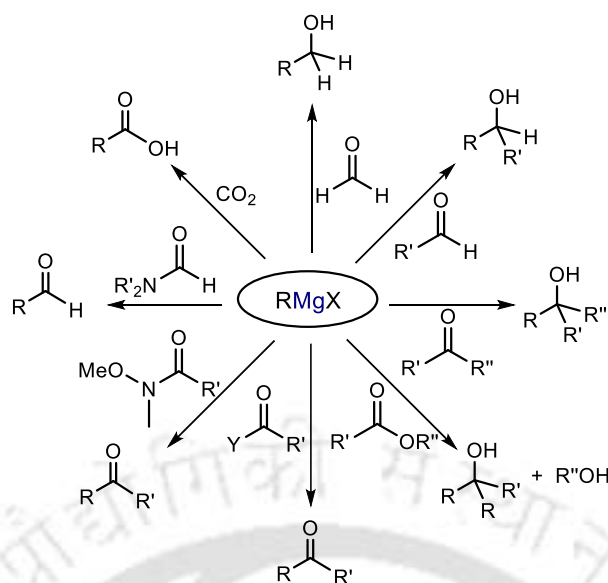


Scheme 1.2. Coordination compounds catalysed 1) Wacker oxidation^{4d} 2) hydroformylation reaction^{4e} 3) Sharpless epoxidation.^{4f}

activity. Wacker oxidation,^{4b-d} hydroformylation^{4e} and Sharpless epoxidation^{4f-g} are few famous examples of reactions catalysed by coordination compounds. In 1959, Wacker and Hoechst developed the well-known Wacker process, for the oxidation of ethene to acetaldehyde in the presence of $\text{PdCl}_2 \cdot \text{CuCl}_2$, CO and H_2 .^{4b-c} This process is widely adapted for the industrial synthesis of chloroform,^{4c} acetic acid^{4c} and acetic anhydride.^{4c} In 2016, Grubbs and Stoltz have reported the Tsuji–Wacker oxidation of terminal olefins to aldehydes in the presence of $\text{PdCl}_2(\text{PhCN})_2/\text{CuCl}_2 \cdot 2\text{H}_2\text{O}/\text{AgNO}_2$ under aerobic conditions (equation 1, Scheme 1.2).^{4d} Another important example is the hydroformylation reaction (oxo process), where, an alkene is allowed to react with carbon monoxide and H_2 to generate an aldehyde. In 1987, Moretti reported such hydroformylation reaction in the presence of $\text{Co}_2(\text{CO})_8$ and obtained the corresponding aldehyde in 75% yield (equation 2, Scheme 1.2).^{4e} Sharpless epoxidation of allylic alcohols was a breakthrough in the field of asymmetric synthesis (equation 3, Scheme 1.2). Barry Sharpless was awarded the Nobel prize in 2001 for this astounding discovery.^{4f}

1.3. Organometallic complex

A co-ordination compound is named as an organometallic compound, if it has atleast a metal-carbon bond or a metal-hydrogen bond or a metal phosphorous bond.^{1a-e} In 1827, the first organometallic compound Zeise's salt ($\text{K}[\text{Pt}(\text{C}_2\text{H}_4)\text{Cl}_3]$) was reported by William Zeise. The



Scheme 1.3. Various organic transformations mediated by a Grignard reagent.

most versatile organometallic compound, Grignard's reagent (RMgX , R is alkyl or aryl group, $\text{X} = \text{Cl, Br, I}$) was discovered by Victor Grignard in 1899. This discovery proved to be the turning point in the field of organic synthesis related to carbonyl chemistry (Scheme 1.3).^{1a-e} In 1972, Kumada utilised a Grignard reagent and coupled it with alkyl, vinyl and aryl halides to achieved the C-C cross coupled product.^{5-6a} The Kumada cross-coupling reaction have opened the door for other historic cross-coupling reactions. Later, in 1963, Ziegler Natta catalyst (a combination of $\text{Et}_3\text{Al} + \text{TiCl}_4$) bagged the Nobel prize for its application in highly stereo- and regio-selective polymerization of α -olefins (Figure 1.1).^{6c-d} Another such path-finder is the discovery of ferrocene (first sandwich compound) which introduced a new area in the field of organometallic chemistry. Later, Grubbs, Chauvin and Schrock introduced alkene metathesis catalysed by transition metal and received Nobel prize for this great achievement (Figure 1.1). The cross coupling reactions with alkyl halides catalysed by Pd brought Nobel prize to Heck, Negishi and Suzuki for their wonderful contribution towards organometallic chemistry. There are some exceptional compounds where even a presence of a metal carbon bond does not make it an organometallic complex but rather considered as inorganic compounds such as carbides (CaC_2), cyanides (NaCN).^{1a-e} Also, there are exceptional cases, where there is no metal carbon bond but they are considered as organometallic compound, owing to the fact that they form metal carbon bond in the catalytic cycle, such an example is Wilkinson catalyst $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ which forms a metal carbon bond in the catalytic cycle of hydrogenation of alkenes where at one stage the alkene is coordinated to metal.^{1a-e} Also, phosphorous has a diagonal relationship

with carbon, so the compounds having a metal-P or metal-H qualify and demonstrate similar reactivity as organometallic compounds and can take part in reactions such as oxidative addition, reductive elimination, migratory insertion, transmetallation.

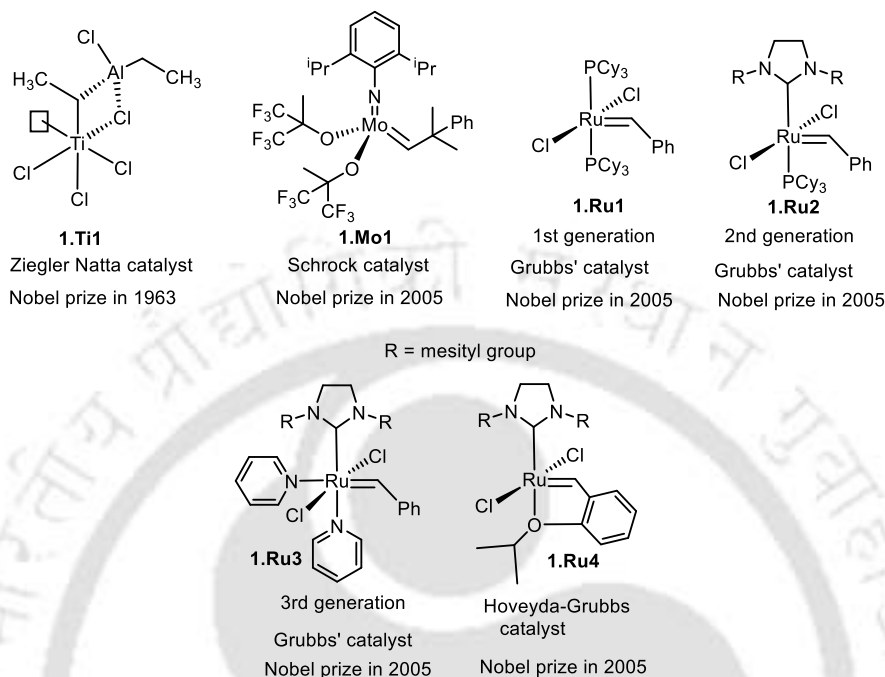


Figure 1.1. Organometallic complexes for polymerization^{6c-d} and olefin metathesis.^{4d,4h}

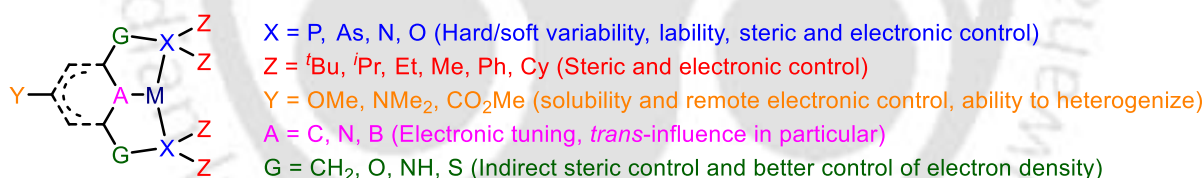


Figure 1.2. General representation of a pincer-metal complex.

In 1970s, a special class of organometallic complex based on ^tBu₄PCP ligand was introduced to the scientific world by Shaw, which was later termed as “Pincer” by Van-Koten⁷ based on its crab like structure. It is basically, a terdentate chelating ligand bound to a metal centre in meridional fashion. These rigid chelating pincer ligand renders high thermal stability to the pincer-metal complex (Figure 1.2). These ligands can effectively control electronic and steric properties of the pincer-metal complex.⁷ Pincer complexes with ECE backbone (E = neutral donors) acquires high thermal stability owing to the metal-C σ -donation and also donation from the neutral donors.⁸ Bulkiness of the substituents in the donor atoms also sheds impact on the

thermodynamic stability.⁹ Among the donor atoms the common heteroatoms are N, P, S and O. Donor atoms can be neutral or anionic.⁸⁻¹⁰

In the past few decades, pincer-metal complexes have acquired weight in the area of homogeneous catalysis owing to the great thermal stability and reactivity, provided by the rigid pincer framework.^{11a-c,15,31,34} There are several review articles which have addressed the chemistry and catalytic applications of pincer-metal complexes based on precious as well as 3d-base metals such as Ru,^{12a} Pd,^{12b} Ir,^{12c,15} Mn,^{12d,29} Fe,^{12d} Co^{29,34} and Ni.³¹ They showcase excellent activity towards several challenging organic transformations such as dehydrogenation of alkane,^{11b} reduction of carbon dioxide,^{10,11d} olefins,^{10,11d} nitrile,^{10,11d} and alkynes,^{10,11d} cross coupling reactions,^{28,31} and dehydrogenation of alcohols.^{11e,89}

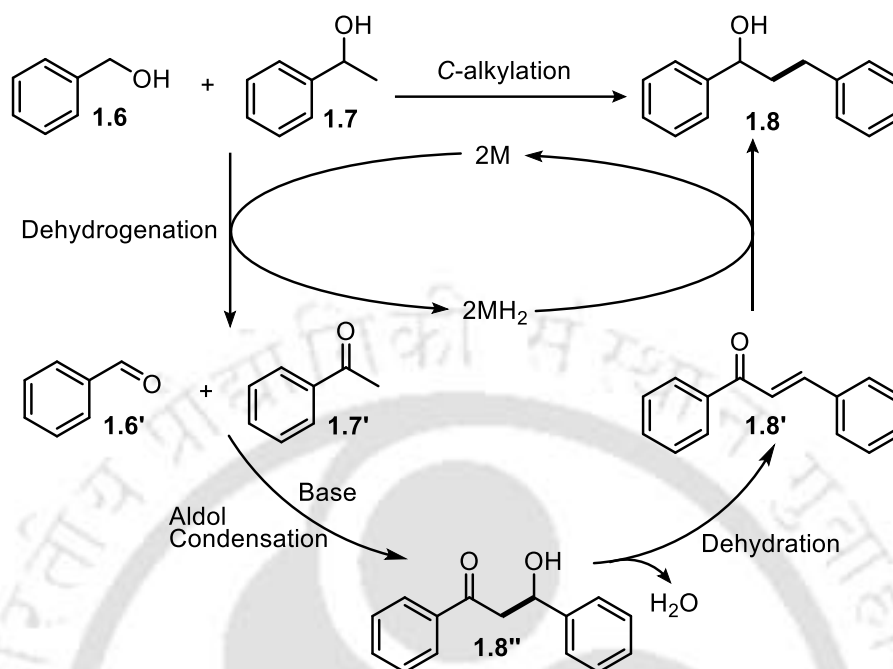
In the current thesis, the dehydrogenative coupling of alcohols and alcohol reforming leading to speciality chemicals and H₂, catalysed by homogeneous catalytic systems based on transition metal salts and pincer-metal complexes have been reviewed. Alcohols from easily available biomass serve as an important starting material in various fields of organic synthesis. They are available at a low price and possess low toxicity.^{11f} They can be obtained from numerous renewable feedstocks such as biomass and carbohydrates^{11g} and they can also be easily synthesized.^{11f}

1.4. β -alkylation of alcohols

One of the most implemented organic transformation in various industrial fields including fuel-chemicals, pharmaceuticals, fine chemicals and agrochemicals is the carbon-carbon bond formation.¹³ Traditional synthesis of C-C bond required activation of C-H or C-X (X = Cl, Br and I) bond catalysed by transition metals which leads to the generation of toxic by-products.¹⁴⁻¹⁶ In the context of green chemistry, the “hydrogen-borrowing” strategy stands out to be more environment friendly compared to the traditional methodologies based on the fact that water is generated as the sole by-product. Typically, the transition metal catalysed C-alkylation of alcohols follows a mechanism (Scheme 1.4) which involves the following steps: i) dehydrogenation of the alcohol ii) a base mediated condensation of the resulting carbonyl compounds to yield α,β -unsaturated carbonyls followed by iii) catalytic hydrogenation of the α,β -unsaturated carbonyl compounds.^{11h}

The homogeneous β -alkylation of secondary alcohols with primary alcohols have been widely explored using various transition metal salts, organometallic complexes and pincer complexes

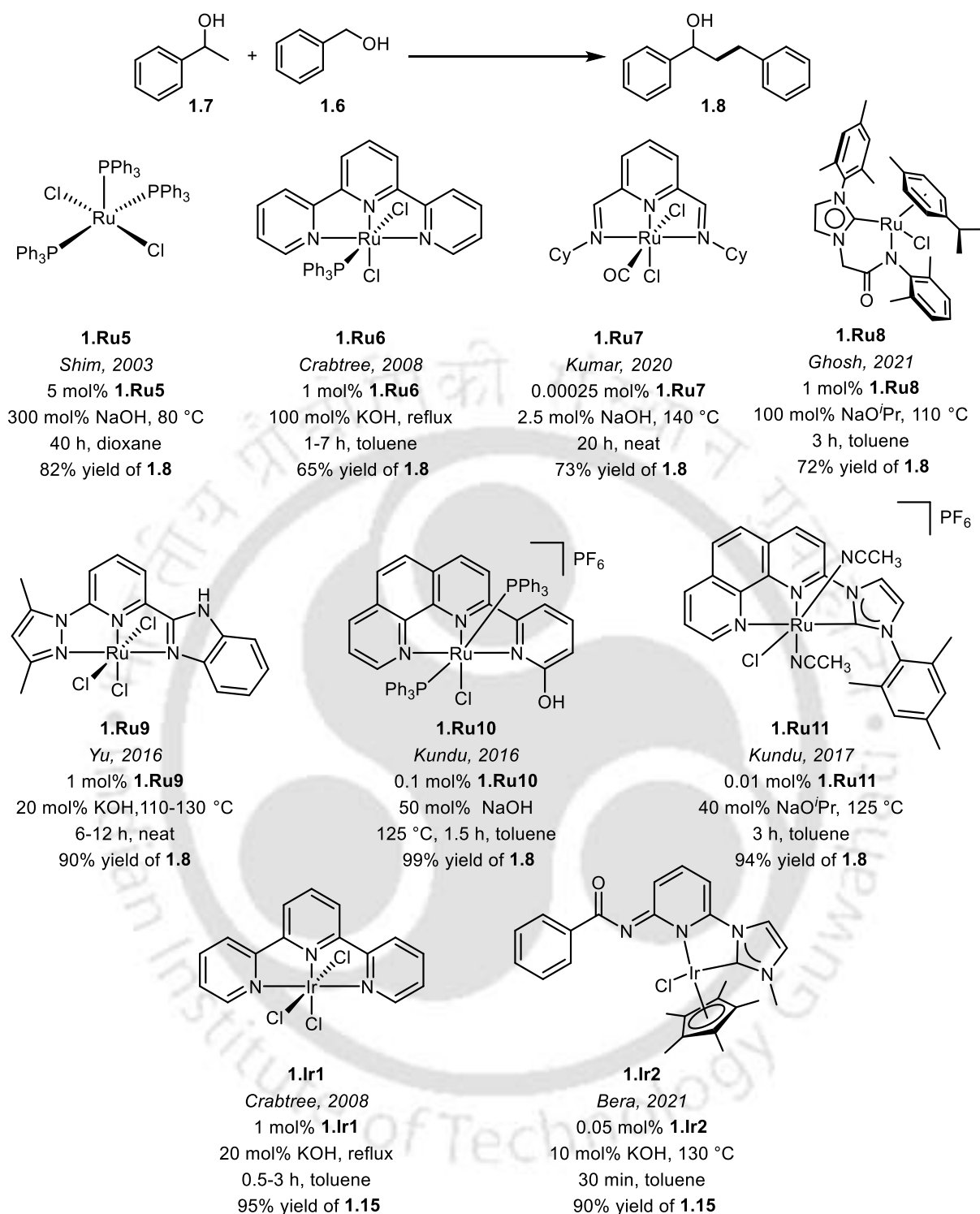
based on precious transition metals like Ir,¹⁷⁻²⁶ Rh,²⁷ Ru,²⁸ as well as earth abundant, more environment friendly base metals such as Mn,²⁹⁻³⁰ Co,²⁹ Ni,³⁰⁻³¹ and Cu.³⁰



Scheme 1.4. General mechanistic representation of the transition metal catalysed C-alkylation.

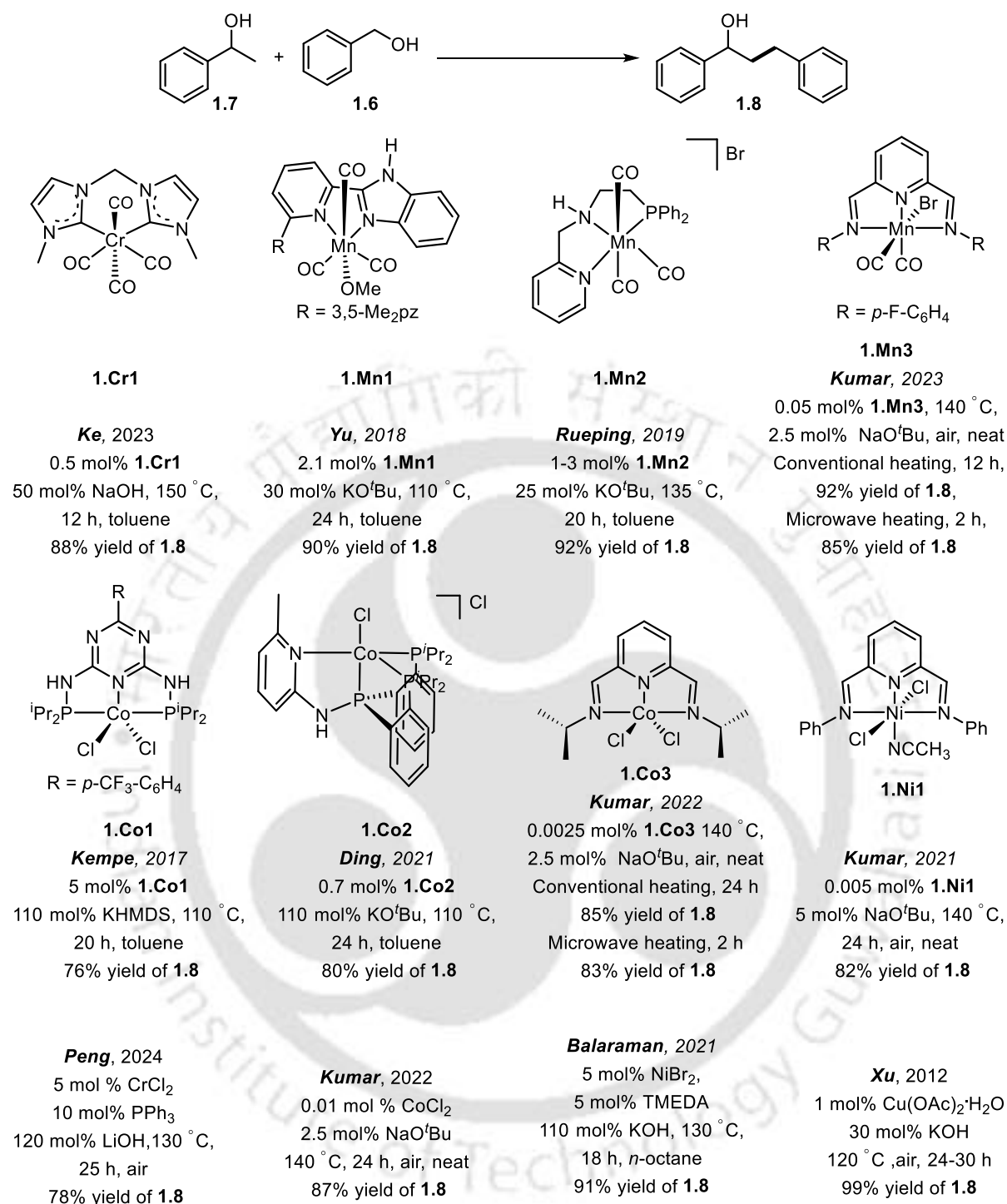
In this regard, Shim was the first to demonstrate the β -alkylation of secondary alcohols with primary alcohols utilizing a simple organometallic complex, dichloro tris(triphenylphosphine)ruthenium(II) **1.Ru5**.³² Other than Shim, Sun employed commercially available and inexpensive organometallic complex, ferrocenecarboxaldehyde (5 mol%) to catalyse the β -alkylation of secondary alcohols with primary alcohols.³³

Among the organometallic complexes, the cross-coupling of alcohols have been well explored using pincer ligated metal complexes which can be considered as a special class of organometallic compounds.^{28, 31, 34} As seen from the reports by Crabtree²⁵ and Ghosh³⁵, the pincer complexes **1.Ru6** and **1.Ru8** were functional under milder reaction conditions (1 equivalent of base) than the simple organometallic complex **1.Ru5** which catalysed the reaction in the presence of 3 equivalents of base (Scheme 1.5). Later, Yu³⁶ and Kundu³⁷ reported **1.Ru9**, **1.Ru10** and **1.Ru11** which worked at lower base loading of 20-50 mol%. Whereas, **1.Ru7** synthesised by Kumar achieved highest TON of 372000, at a catalyst loading of 0.00025 mol% in presence of only 2.5 mol% NaOH (Scheme 1.5).³⁸ The Ir(III)-NHC complex **1.Ir2** has shown high reactivity under mild conditions (Scheme 1.5).³⁹



Scheme 1.5. The homogeneous catalysts based on precious metals reported for β -alkylation of 1-phenyl ethanol with benzyl alcohol.¹⁷⁻²⁸

We have seen that the β -alkylation of secondary alcohols with primary alcohols has been well explored using highly efficient pincer complexes based on noble metals,²⁸ but in the recent



Scheme 1.6. The homogeneous catalysts based on 3d-metals reported for the β -alkylation of 1-phenyl ethanol with benzyl alcohol.^{29-31, 34, 40}

times, the researchers have emphasised on the utilization of cheaper, less toxic, more environment friendly and highly abundant 3d-metal based complexes instead of noble metals.²⁸ In this regard, β -alkylation of secondary alcohols with primary alcohols have been reported

Table 1.1. Comparative summary table for β -alkylation of secondary alcohols with primary alcohols

Catalyst	Activity (TON)	E-factor
1.Ru5	16.4	14
1.Ru6	65	2
1.Ru7	372,000	0.2
1.Ru8	72	12
1.Ru9	90	0.2
1.Ru10	990	19
1.Ru11	9400	13
1.Ir1	65	2
1.Cr1	176	10
1.Mn1	43	2
1.Mn2	76	4
1.Mn3	1840	0.13
1.Co1	15	13
1.Co2	114	32
1.Co3	34,000	0.23
1.Ni1	16,400	0.2
CoCl ₂	8700	0.2
NiBr ₂	18	8

using pincer-complexes based on first-row transition metals such as Cr,⁴⁰ Mn,²⁹ Co³⁴, Ni,³¹ and Zn⁴¹. Starting with chromium, the first one in the series of the reported 3d-metals, Ke reported the β -alkylation of secondary alcohols with primary alcohol catalysed by a Cr(0) complex **1.Cr1** which gave up to 88% of the cross-coupled product (Scheme 1.6).⁴² There are three catalysts reported for the manganese catalysed C-alkylation, namely **1.Mn1**⁴³, **1.Mn2**⁴⁴ and **1.Mn3**⁴⁵ which have shown excellent reactivity towards the β -alkylation of secondary alcohols with primary alcohols (Scheme 1.6).

The complexes **1.Co1**⁴⁶ and **1.Co2**⁴⁷ both required stoichiometric amount of base where as **1.Co3**⁴⁸ reported by Kumar catalysed the β -alkylation of alcohols at a catalyst loading of 2.5 mol% (Scheme 1.6). Kumar reported that cobaltous chloride (0.01 mol %) efficiently achieves

the catalytic β -alkylation of alcohols with high yields (up to 87%) and unprecedented turnovers (ca. 8700) in the presence of only 2.5 mol % of NaO^tBu.³ Kumar also explored this transformation utilizing NNN pincer-Ni(II) complex **1.Ni1** based on *bis*(imino)pyridine ligands and obtained a very high TONs (up to 18400) (Scheme 1.6).⁴⁹

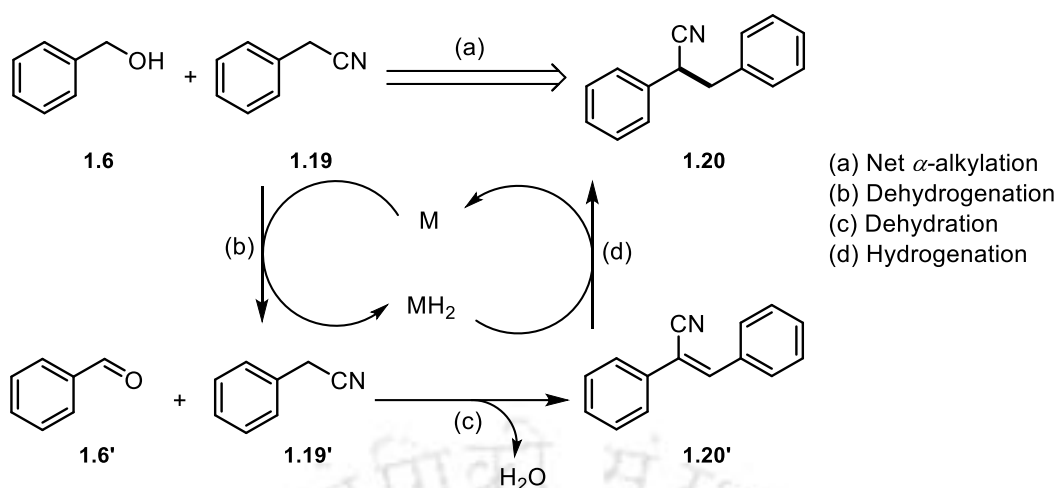
So far, we have seen that the β -alkylation of alcohols can be catalysed by organometallic complexes as well as pincer complexes. There are very few reports wherein simple base metal salts like CrCl₂,⁵⁰ CoCl₂,³ NiBr₂⁵¹ and Cu(OAc)₂⁵² have been utilised to catalyse this reaction where excellent yields were obtained (Scheme 1.6). It is also seen in the independent reports by Crabtree,⁵³ Gunanathan,⁵⁴ Jhonson and Wendt⁵⁵ that β -alkylation of secondary alcohols with primary alcohols can be mediated only in presence of a base albeit at high loadings (sub-stoichiometric or stoichiometric).

In conclusion, the coupling of C-C bond via the β -alkylation of secondary alcohols with primary alcohols is an important organic transformation and it finds its application in various industries including medicinal, biofuel and fine chemicals.¹³ Researchers have explored this transformation using simple metal salts, organometallic complexes and pincer complexes based on transition metals and few of them have been discussed in this chapter. Recently, there are significant advancements in employing earth abundant, less toxic metals for the catalytic β -alkylation of alcohols.^{29-31, 34, 40} The detailed discussion of the same is covered in Chapter-II.

1.5. Catalytic α -alkylation of nitriles

Similar to the C-alkylation, C-C bond formation in organic chemistry can also be accomplished by α -alkylation of nitriles and the resulting nitrile functionality can act as a versatile candidate which can be converted into amides,^{56a-b} aryl ketones,^{56a,56c} amines^{56a,56d} and oxazolines.^{56a,56e} In a transition metal catalysed α -alkylation of nitriles, the first step is the dehydrogenation of alcohol to corresponding aldehyde, which undergoes condensation with a nitrile to give rise to an unsaturated nitrile along with a water molecule, followed by transition metal catalysed hydrogenation of the unsaturated nitrile to give the α -alkylated nitrile (Scheme 1.7). Researchers have widely explored the α -alkylation of nitriles catalysed by noble metals such Ru,⁵⁷⁻⁶² Ir,⁶³⁻⁶⁶ Rh⁶⁷ and Os.⁶⁸

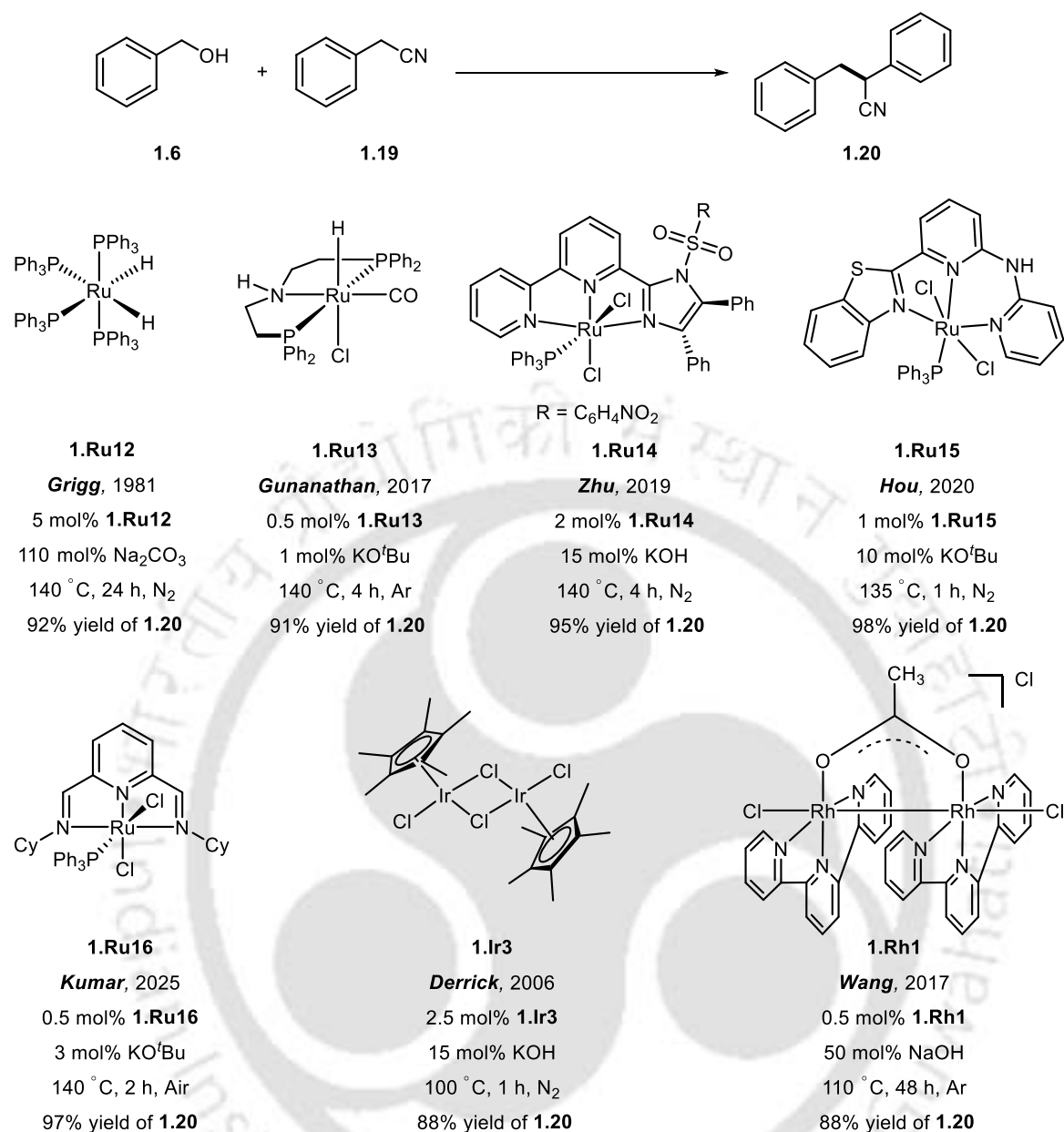
The first report of the ruthenium catalysed α -alkylation of nitriles came from Grigg where an organometallic complex, RuH₂(PPh₃)₄ **1.Ru12** (5 mol%) was utilised to catalyse the



Scheme 1.7. General mechanism followed in α -alkylation of nitriles.

α -alkylation of nitriles to afford 92% yield of the α -alkylated nitrile in presence of 110 mol% Na_2CO_3 , which can be considered as high base loading (Scheme 1.8).⁵⁸ Further reports were based on pincer-metal complexes. Gunanathan designed a PNP-Ru pincer complex **1.Ru13** and investigated its activity experimentally in presence of only 1 mol% KO^tBu which is the lowest base loading reported till now (Scheme 1.8)⁵⁹ whereas, Li with his computational studies, supported the mechanism reported by Gunanathan,⁵⁹ where the RDS had a barrier of 23.9 kcal/mol.⁶⁹ Kumar utilised phosphine free NNN-Ru complex **1.Ru16** (0.5 mol%) for the α -alkylation of nitriles which afforded 99% yield of the α -alkylated product in the presence of very low KO^tBu loading of 3 mol% at 140 °C, in 2 hours in air (Scheme 1.8).⁵⁷ Zhu⁶⁰ and Hou⁶² have also reported NNN pincer-Ru complex catalysed α -alkylation of nitriles.

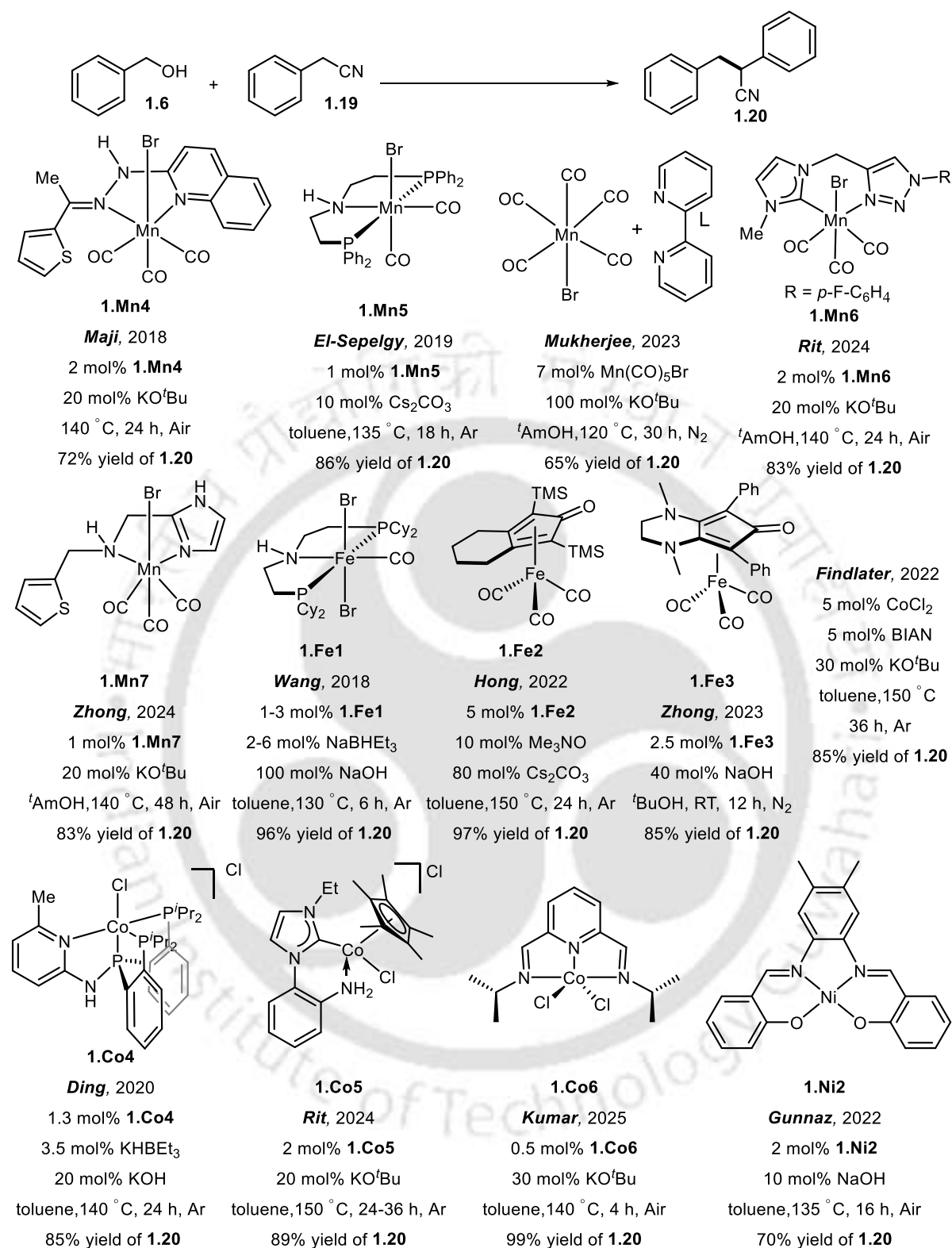
Derrick utilised iridium complex **1.Ir3** (2.5 mol%) to catalyse the α -alkylation of nitriles and achieved 93% of the α -alkylated product in presence of 15 mol% KOH at 100 °C, in 1 hour under an atmosphere of nitrogen (Scheme 1.8).⁶³ Recently, Xu employed the same catalyst **1.Ir3**, but interestingly they could obtain the α -alkylated arylacetone nitrile or arylacetamide selectively by only changing the base. In the presence of K_2CO_3 (20 mol%) they witnessed the formation of α -alkylated arylacetone nitrile whereas 20 mol% KO^tBu generated arylacetamide (Scheme 1.8).⁶⁵ Wang accomplished the α -alkylation of nitriles by treating nitriles in presence of alcohols in presence of 0.5 mol% rhodium catalyst **1.Rh1**, 50 mol% NaOH in 48 h at 110 °C under an atmosphere of Ar (Scheme 1.8).⁶⁷ While other Ru and Ir complexes accomplished the transformation in a very short duration of 1-4 h, the Rh catalyst **1.Rh1** took comparatively longer duration of 48 h to complete the reaction. Recently, the researchers have emphasized on the utilization of catalytic systems based on 3d metals (Scheme 1.8) for such transformations.⁷⁰



Scheme 1.8. The homogeneous catalysts based on precious metals reported for the α -alkylation of nitriles.^{57-68,102}

In this context, Mn(I) complexes **1.Mn4-1.Mn7** have been well explored for this transformation and they worked well in combination with 10-20 mol% base (Scheme 1.9). The complexes **1.Mn4-1.Mn7** were found to show metal-ligand cooperativity in the catalytic cycle and hence followed an outer-sphere mechanism (Scheme 1.9).¹⁰³⁻¹⁰⁶

Compared to the Mn(I) complexes, both the iron complexes **1.Fe1**¹⁰⁷ and **1.Fe2**¹⁰⁸ were found to be active for this reaction in the presence of stoichiometric amounts of base. Amongst all other reports, where the reaction was performed at higher temperatures, the report by Zhong



Scheme 1.9. The homogeneous catalysts based on 3d metals reported for α -alkylation of nitriles.⁷¹⁻⁸⁴

was an exception where the α -alkylation of nitriles was accomplished in the presence While, Cp*Co(III) afforded 77% yield of the α -alkylated nitriles in presence stoichiometric amount of

Table 1.2. Comparative summary table for α -alkylation of nitriles.

Catalyst	Activity (TON)	E-factor
1.Ru15	98	5
1.Ru16	194	10
1.Ir3	35	2
1.Rh1	176	19
1.Mn4	36	12
1.Mn5	86	6
1.Mn6	41	24
1.Mn7	83	
Mn(CO) ₅ Br	9	21
1.Fe1	96	27
1.Fe2	19	10
1.Fe3	34	10
1.Co4	65	26
1.Co5	44	20
1.Co6	198	9
CoCl ₂	17	11
1.Ni2	35	13

of **1.Fe3** at room temperature aided by blue light and could achieve 85% yield of the desired product after 12 h under an atmosphere of N₂ (Scheme 1.9).⁷⁷

base (Scheme 1.9),⁷⁸ *i*PrPPN^HPyMe-Co(I) **1.Co4** complex by Ding (Scheme 1.9)⁷⁹ and the bifunctional NHC-Co(III) complex **1.Co5** designed by Rit, successfully catalysed the α -alkylation of nitriles in the presence of 20 mol% base (Scheme 1.9).⁸⁰ Very recently, Kumar treated nitriles and benzyl alcohols in presence of 0.5 mol% **1.Co6**, 30 mol% KO^tBu at 140 °C under open air conditions and accomplished the α -alkylation of nitriles within 4 hours which led to 99% yield of the α -alkylated product.⁸¹ The only report based on Ni(II) complex **1.Ni2** supported with a tetradentate N₂O₂ schiff-base ligand came from Gunnaz and co-workers, where 88% yield of **3.4** was achieved in the presence of 2 mol% complex, 10 mol% NaOH, at 135 °C, in air (Scheme 1.9).⁸²

Besides organometallic complexes and pincer complexes, commercially available base metal

salts have also been found to be active for this transformation. In this regard, Mukherjee utilised commercially available $\text{Mn}(\text{CO})_5\text{Br}$ (7 mol%) **3.Mn4** to catalyse the α -alkylation of nitriles and obtain a yield of 89% in presence of 10 mol% bidentate NN ligand at 120 °C in 30 hours under N_2 (Scheme 1.9).⁸³ Findlater also employed commercially available cobaltous chloride and achieved 88% yield of the desired product at a catalyst loading of 5 mol% combined with 5 mol% BIAN ligand, 30 mol% KO^tBu at 150 °C, in 36 h under Ar (Scheme 1.9).⁸⁴ In a similar vein, Vougioukalakis chose a combination of 5 mol% CuCl_2 and 5 mol% TMEDA which in the presence of 30 mol% KO^tBu afforded 99% of **3.4** at 140 °C under an atmosphere of argon (Scheme 1.9).⁸⁵

So far, we have seen, the homogeneous α -alkylation of nitriles have been carried out utilizing commercially available salts, organometallic complexes that include pincer complexes. Pincer complexes based on precious metals have been well explored. And among the pincer complexes based on base metals, manganese, iron and cobalt have been more explored. There is only one report with ONNO tetradentate nickel complex. Interestingly, 3d metal salts have also shown good reactivity. A quick glimpse of these reports have been given in this chapter. The detailed discussion of the same is covered in Chapter-III.

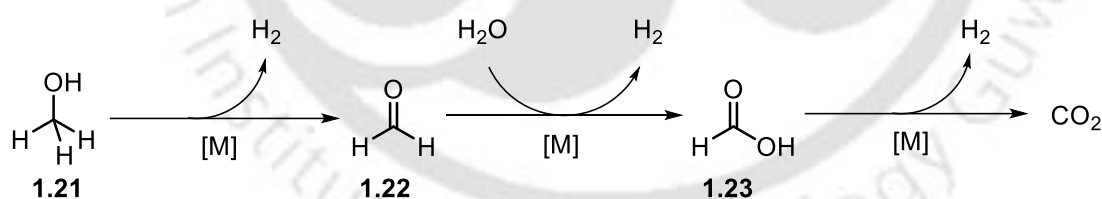
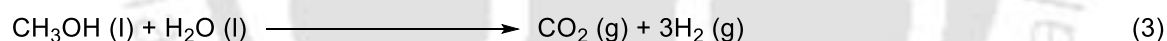
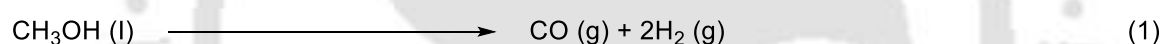
1.6. Alcohol reforming

The spontaneous depletion of fossil fuels owing to the increased demand of energy consumption, is a concern of utmost importance. This rising crisis have led the scientific community to explore alternative pathways to generate green fuel, like, hydrogen.^{86a} The use of hydrogen (a clean fuel), which is an efficient energy carrier (120 MJ/Kg) and has a low volumetric energy density, would also help to eliminate the hazardous consequences of burning fossil fuels.^{86b-c} Advancement in the hydrogen production has some drawbacks, such as difficulty in storage and transportation, due to the low volumetric energy density.^{86d-f} They also require cautious handling and needs to be stored in expensive high-pressure compression cylinders.^{86d-f} The liquid organic hydrogen carriers (LOHCs, small organic molecules), on the other hand can serve as an alternate source of hydrogen, which are quite easier to handle. The dehydrogenation of LOHCs can produce hydrogen on demand.^{86g} Hence, alcohol reforming is emerging as a promising method and is gaining a significant importance in recent times. In this process, the alcohols are converted into other value-added products through catalytic reactions. There are different types of alcohol reforming techniques, such as, steam reforming,^{86h} partial oxidation,⁸⁷ autothermal reforming,⁸⁸ dehydrogenation of alcohols.^{89-91a}

Discussing each topic in detailed is out of the scope of this thesis. We are more delighted to discuss briefly about the homogeneous dehydrogenative transformations of alcohols, where, the alcohols are dehydrogenated to the corresponding aldehydes or ketones along with the release of H_2 .^{89-91a} In this regard, the pincer complexes have been well explored as they can be cost-effective and selective towards hydrogen generation.

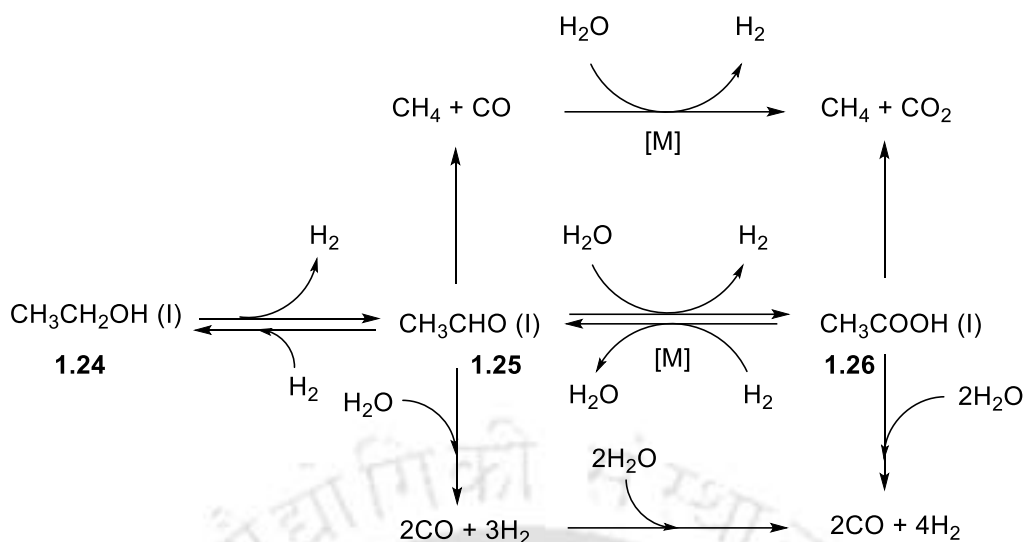
1.6.1. Aqueous reforming of (m)ethanol

Alcohols could serve as starting materials for hydrogen generation. High risks associated with the storage of hydrogen in the form of gas or liquid has stirred the idea of producing “on-demand” hydrogen by direct dehydrogenation of LOHCs along with the generation of value-added products.^{86g} In this regard, the homogeneous catalysts, like pincer-complexes have achieved a great height in the field of aqueous reforming of (m)ethanol.^{91b} Dehydrogenation of methanol can produce carbon monoxide and hydrogen, but CO can cause harm to the fuel cells (Scheme 1.10).^{91c} On contrary, the dehydrogenative aqueous reforming of methanol leads to the generation of hydrogen and carbon-dioxide (Scheme 1.10), making it more suitable for hydrogen production.



Scheme 1.10. General mechanism for aqueous reforming of methanol.

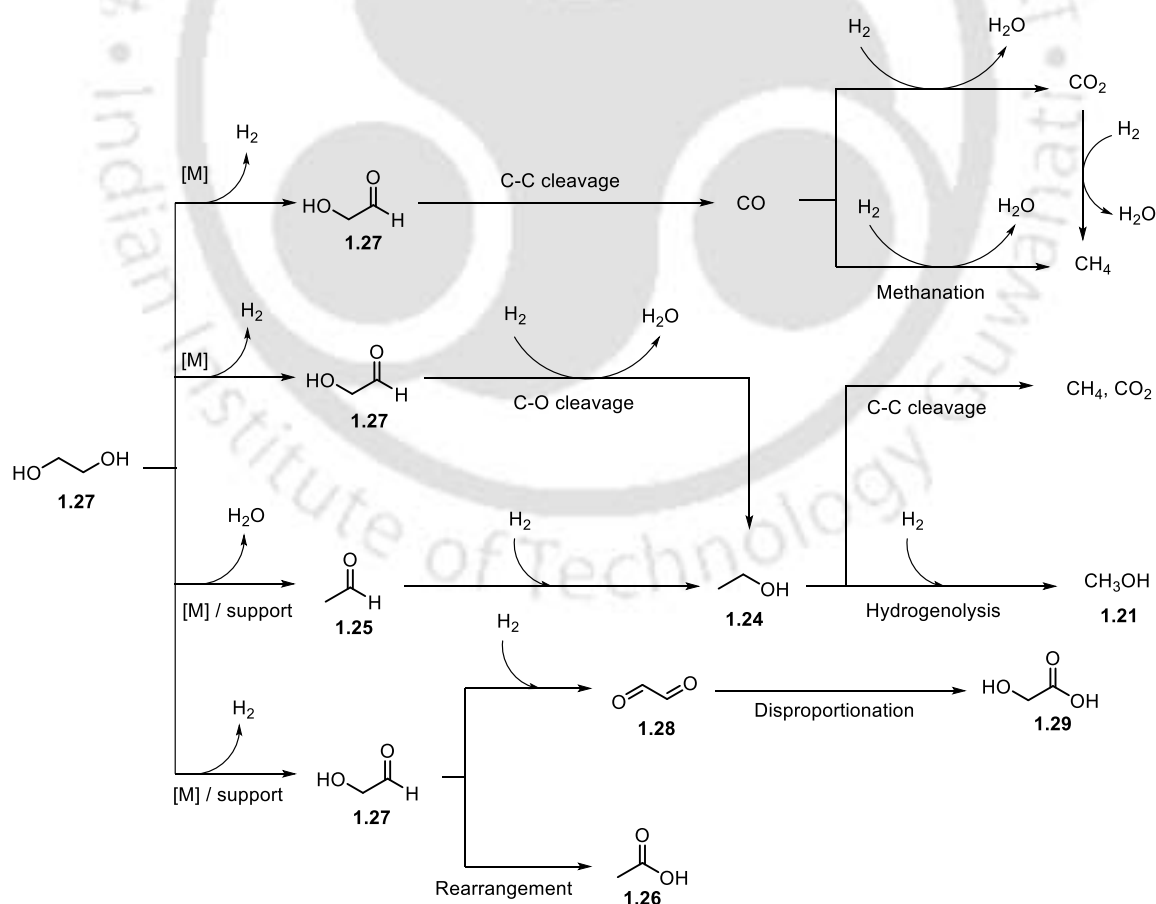
There are various reports, where in pincer-complexes based on precious metals such as Ru,⁹⁰ Ir^{91d} have been utilised to catalyse this dehydrogenative transformation with 26-96% yield of hydrogen at 100% selectivity towards CO_2 . Pincer-complex based on 3d-base metals such as Fe^{91e-f} and Mn^{91g} have also shown 100% selectivity towards CO_2 . Ethanol also serves as a good candidate for the production of hydrogen, as it has 13 wt% of hydrogen output and it is produced in large scale from biomass fermentation.^{91h-j} Aqueous reforming of ethanol produces acetic acid along with green hydrogen (Scheme 1.11).^{91k} Very similar to the examples with



Scheme 1.11. General scheme for aqueous reforming of ethanol.

methanol reforming, homogeneous pincer-catalysts based on precious metals such as Ru^{91a,92a-b} and Ir^{92c} have found greater success for the aqueous reforming of ethanol.

1.6.2. Aqueous reforming of ethylene glycol



Scheme 1.12. General scheme for aqueous reforming of ethylene glycol.

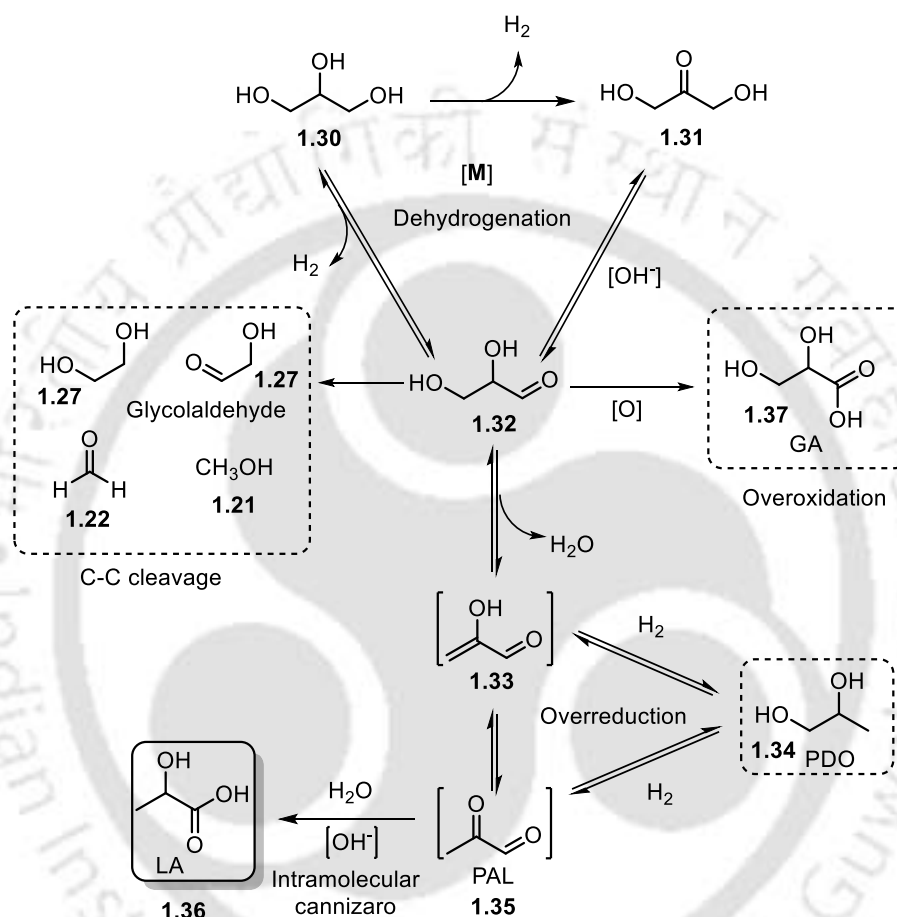
Ethylene glycol (EG) is a simple vicinal diol which have a high H₂ storage capacity of 6.5 wt%.^{92d} The aqueous reforming of ethylene glycol produces green hydrogen along with glycolic acid (Scheme 1.12). It has been widely explored using heterogeneous catalysts^{92e} but the homogeneous reforming of EG still needs further study.⁸⁹ In the context of homogeneous reforming of EG, pincer complexes have enjoyed great success. Pincer complexes based on precious metal such as Ru^{92f-i,136} and pincer complex based on 3d-metal Mn^{92j,136} have been reported for this transformation.

1.6.3. Dehydrogenative transformation of glycerol to lactic acid and hydrogen

Higher rate of increased consumption of natural fossil-fuel reserves is the sole reason for the increased demand of biodiesel production.⁹³ Biodiesel production is limited by the fact that it produces glycerol (GLY) as a waste in quantitatively large scale.⁹³ Glycerol is also generated in significant amount from various industries including cellulose hydrogenolysis⁹⁴⁻⁹⁵ and fermentation⁹⁶ processes which leads to the high accumulation of glycerol globally. Strikingly, Glycerol turns out to be a great starting material for various forms of speciality chemicals such as dihydroxyacetone (DHA), lactic acid (LA) and propanediol.⁹⁷⁻¹⁰⁹ The presence of hydroxyl groups in glycerol provides it the ability to serve as a great hydrogen source, additionally it can serve as a solvent in plethora of transition metal catalysed reactions.^{93, 110-115} LA has a wide array of applications in various industries such as pharmaceutical, cosmetics, food, green solvent production and polylactic acid production (PLA).¹¹⁶⁻¹¹⁷ Conventional ways for the transformation of GLY to LA involves bacterial fermentation via bioconversion¹¹⁸ and heterogeneous catalysis.^{89, 94, 108, 119-131} Challenges involved in these conventional routes includes endurance of bacteria under the harsh reaction parameters as well as they are accompanied by complex product separation steps.¹³¹

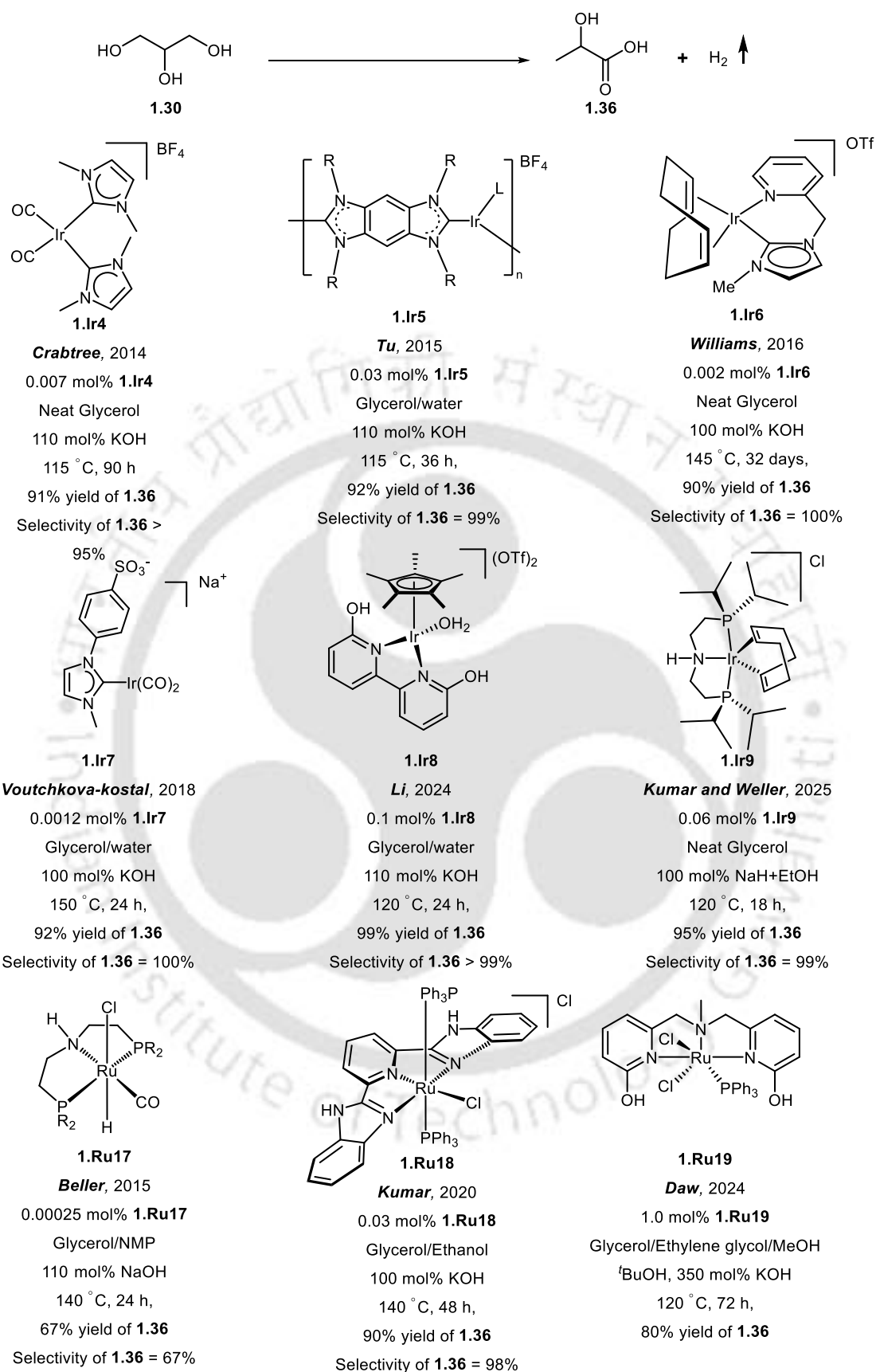
The heterogeneous catalysts operate under higher temperature and harsh reaction conditions compared to homogeneous catalysts. Under harsh reaction conditions, there are possibilities of overoxidation of glyceraldehyde (GAL) which can lead to glyceric acid (Scheme 1.13), C-C cleavage of GAL can generate ethylene glycol (EG), glycolaldehyde, formaldehyde and methanol, and overreduction of GAL can give rise to propanediol (PDO) (Scheme 1.13).¹⁶¹ But, the heterogeneous catalysts are advantageous if we consider their recyclability and ease of recovery from the reaction mixture. On the contrary, homogeneous catalysis can be executed under milder reaction parameters resulting in increased reactivity with better selectivity.^{89, 122, 132-145} The homogeneous acceptorless transformation of glycerol to LA was first introduced by

Crabtree, where Ir(I)-NHC complex **1.Ir4** was utilised to obtain LA in 90% yield at a high selectivity of 95% with a turnover number of 30100 (Scheme 1.14).¹³² This reaction was accomplished at a very low catalyst loading of 0.003 mol% under solvent-free conditions. They have proposed that the reaction is initiated via dehydrogenation of glycerol to glyceraldehyde and dihydroxyacetone intermediates which undergoes a series of organic transformations (dehydration, tautomerism and Cannizzaro reaction) in the presence of base to give LA.¹⁶¹

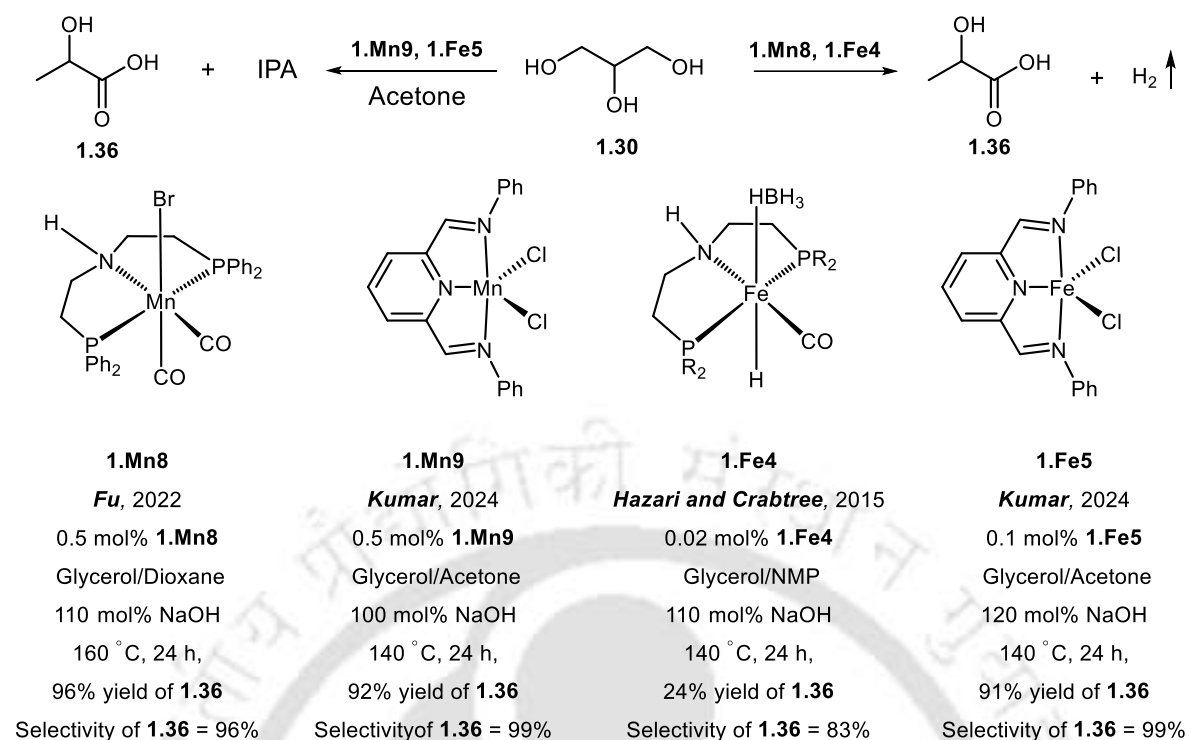


Scheme 1.13. General mechanism for the acceptorless dehydrogenative transformation of glycerol to lactic acid catalysed by transition metal complexes.

Tu developed a copolymer based Ir-NHC complex **1.Ir5** to accomplish this transformation which afforded 98% yield of LA with turnover numbers of 3266 (Scheme 1.14). The catalyst was active up to 31 cycles without any loss in the reactivity. In the reaction, the transformation of glycerol to LA involved oxidative dehydrogenation of glycerol followed by a series of organic reactions.¹³³ In a report by Williams, the highest TONs of 1057172 was obtained in the acceptorless dehydrogenation of glycerol to LA catalysed by Ir(I) complex **1.Ir6** supported by bidentate(pyridylmethyl)imidazolium carbene ligand (Scheme 1.14). The reaction was carried



Scheme 1.14. The homogeneous catalysts based on precious metals reported for acceptorless dehydrogenation of glycerol to lactic acid. ^{132-137, 143-145}



Scheme 1.15. The homogeneous catalysts based on 3d metals reported for transformation of glycerol to lactic acid.¹³⁸⁻¹⁴¹

out under solvent-free conditions.¹³⁴ Voutchkova-Kostal accomplished this transformation under microwave heating conditions in presence of Ir(I), Ir(III) and Ru(II) NHC complexes based on highly charged sulfonate moieties and achieved 45592 TONs (Scheme 1.14). This may be attributed to the fact that under microwave reaction conditions, the rate of efficiency of heating is higher as compared to that of conventional heating.¹³⁵ In a recent study, Li could achieve 99% yield of LA at 99% selectivity in presence of a water-soluble piano-stool iridium complex **1.Ir8** (Scheme 1.14).¹⁴³ Very recently, Kumar and Weller have obtained 96% yield of LA at 99% selectivity with 65000 turnover numbers, in presence of PNP-Ir complex **1.Ir9**. The N-H bond in the ligand coordinated to the complex participates in the reaction hence it follows an outer-sphere mechanism.¹⁴⁴

Beller gave the first report on Ru catalysed glycerol to LA transformation, where a PNP pincer-Ru complex **1.Ru17** afforded 67% yield of LA (270000 TONs) with a selectivity of 67% (Scheme 1.14). They have extended their work to dehydrogenate ethylene glycol and D-sorbitol to generate green hydrogen in the presence of 1.5 M KOH.¹³⁶ Next report on pincer-Ru catalysed glycerol to LA transformation came from Kumar. They have demonstrated that the NNN pincer-Ru complex **1.Ru18** based on *bis*(benzimidazole-2-yl)pyridine ligands resulted in conversion of GLY to LA with an yield of 90% at a selectivity of 98% (Scheme

1.14).¹³⁷ Daw have synthesized LA from a mixture composed of glycerol, ethylene glycol and methanol in a ratio of 1:1:5. LA was obtained in a yield of 78% in a reaction catalysed by NNN-pincer Ru complex **1.Ru19** (Scheme 1.14).¹⁴⁵ The dehydrogenative transformation of glycerol to lactic acid has been well explored utilizing the catalytic systems based on Ir^{132-135,143-144} and Ru.^{136-137,145} However, researchers in recent days are more indulged in replacing precious metals with cheap, easily available, 3d metals for the dehydrogenative transformation of glycerol to LA.

Table 1.3. Comparative summary table for dehydrogenative transformation of glycerol to lactic acid

Catalyst	TON	Stability	E-factor
1.Ir4	13000	-	0.9
1.Ir5	3067	Up to 31 cycles	1
1.Ir6	4557487	-	3
1.Ir7			
1.Ir8	990	-	0.81.
1.Ir9	1650	Up to 8 cycles	0.8
1.Ru17	268000	-	2
1.Ru18	3000	-	0.8
1.Mn8	192	-	
1.Mn9	184	-	1
1.Fe4	1200	-	12
1.Fe5	910	-	2

Hazari and Crabtree were the pioneers to report the transformation of glycerol to LA catalysed by a complex based on 3d-metal. They have accomplished the reaction in presence of a PNP-pincer-Fe complex **1.Fe4** and achieved 20% glycerol conversion at 80% selectivity towards LA with TONs of 880 (Scheme 1.15).¹³⁸ Fu then employed a pincer-Mn complex **1.Mn8** which was highly reactive towards acceptorless transfer dehydrogenation of glycerol to LA giving a very high yield of LA (96%) at 96% selectivity (Scheme 1.15).¹³⁹ Besides 3d metal catalysed acceptorless dehydrogenation of glycerol, there are only two reports of transfer dehydrogenation catalysed by 3d metals. In one of the recent reports by Kumar, 0.5 mol% (Ph_2NNN)MnCl₂ **1.Mn9** was utilised to accomplish the transfer dehydrogenative transformation of glycerol to LA where LA was obtained in 92% yield at a selectivity of 99%

(Scheme 1.15).¹⁴⁰ The same group have reported the transfer dehydrogenative transformation of glycerol to LA catalysed by NNN-Fe complex **1.Fe5** based on *bis*(imino)pyridine ligand where 91% yield of LA was obtained at 99% selectivity (Scheme 1.15).¹⁴¹

The homogeneous dehydrogenative conversion of glycerol to lactic acid is presently being carried out via hydrogen-borrowing strategy to synthesize lactic acid which plays an important role in industries related to pharmaceutical, food, cosmetics.

1.7. Summary

Transition metal salts were found to actively catalyse challenging organic transformations. Besides catalysis, they also serve as the precursor to different coordination compounds, organometallic complexes including the special class of pincer complexes. Organometallic complexes are well known for catalysing various coupling reactions such as Kumada, Heck, Sonogashira, Suzuki-Miyaura and Negishi coupling reactions which require toxic alkyl halides as alkylating agents. But the protocols in which alkyl halides can be replaced by alcohols are considered as more greener approach. These approaches are well accomplished in the presence of a special class of organometallic complexes known as “pincer complexes”. In 1976, Moulton and Shaw, introduced the concept of pincer-metal complexes to the scientific world. These complexes play an important role in catalysing various organic transformations. These complexes are typically highly active for catalysing various (de)hydrogenative reactions such as C-alkylation, α -alkylation of nitriles and transformation of glycerol to LA as well. Recently, the pincer chemistry have flourished in various fields of catalysis but providing a thorough description on every field is currently out of the scope of this thesis. We have provided some representative examples of organic transformations catalysed by transition metal salts, coordination compounds, organometallic complexes with a special focus on pincer complexes. The state-of-the-art of these organic transformations have been discussed in greater details in the introduction section of chapters II-IV.

1.8. Objective of the current thesis

We have seen simple salts specially based on noble transition metals are capable of executing various organic transformations. For instance, some famous named reactions such as Suzuki coupling,¹⁴⁶ Heck coupling and ¹Sonogashira coupling¹⁴⁷ reactions are catalysed by a variety of palladium salts. On the other hand, first row transition metals have also enjoyed some success beginning with the seminal report on hydroformylation reaction is catalysed by

Co₂(CO)₈. Coordination compounds, organometallic compounds and pincer complexes are capable of bringing about challenging transformations like hydrogenation,¹⁵ dehydrogenation,¹⁵ coupling reaction,¹⁵ bond activation¹⁵ and many more. Considering the fact that alcohols are abundantly available from renewable sources such as biomass, global research is focused on their use as a substitute of conventional carbon sources (such as toxic alkyl halides as alkylating agents) in chemical industries and petrochemical industries. Accordingly, the current thesis sets upon to investigate the alcohol dehydrogenation reactions and associated tandem reactions while attempting to address the following questions:

1. Can we move away from precious metals and accomplish the transformations of alcohols using earth-abundant, easily available and cheap 3d-metal salts?
2. Would it be possible to generate pincer complexes of these 3d-metals using easy to synthesize bis(iminopyridine) pincer ligands?
3. How do the activity of the 3d-metal salts compare with their corresponding bis(iminopyridine) pincer complexes towards catalytic alcohol dehydrogenative transformations?

1.9. References

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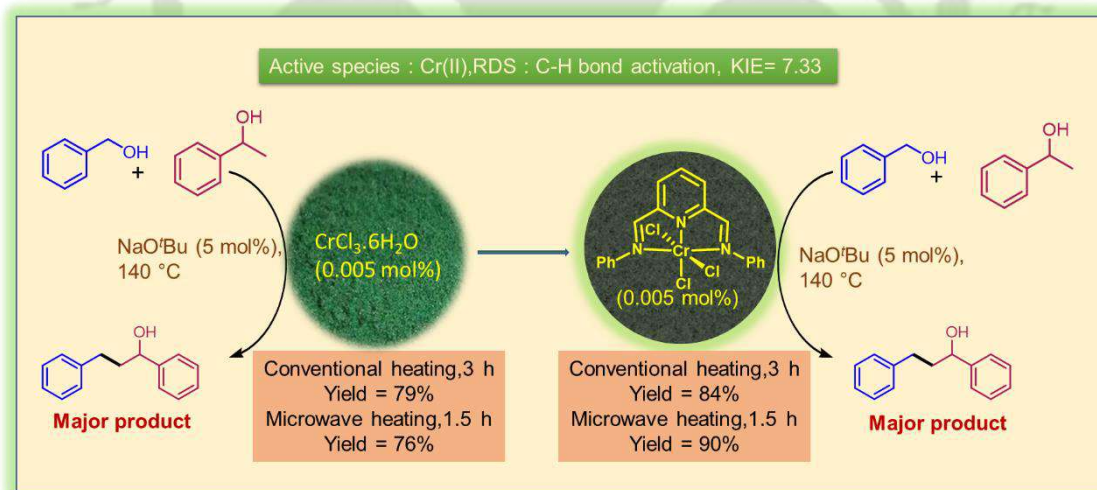
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Chapter- II

The β -Alkylation of Secondary Alcohols with Primary Alcohols Catalysed by Chromium(III) Chloride and its Bis(iminopyridine) Pincer Complex

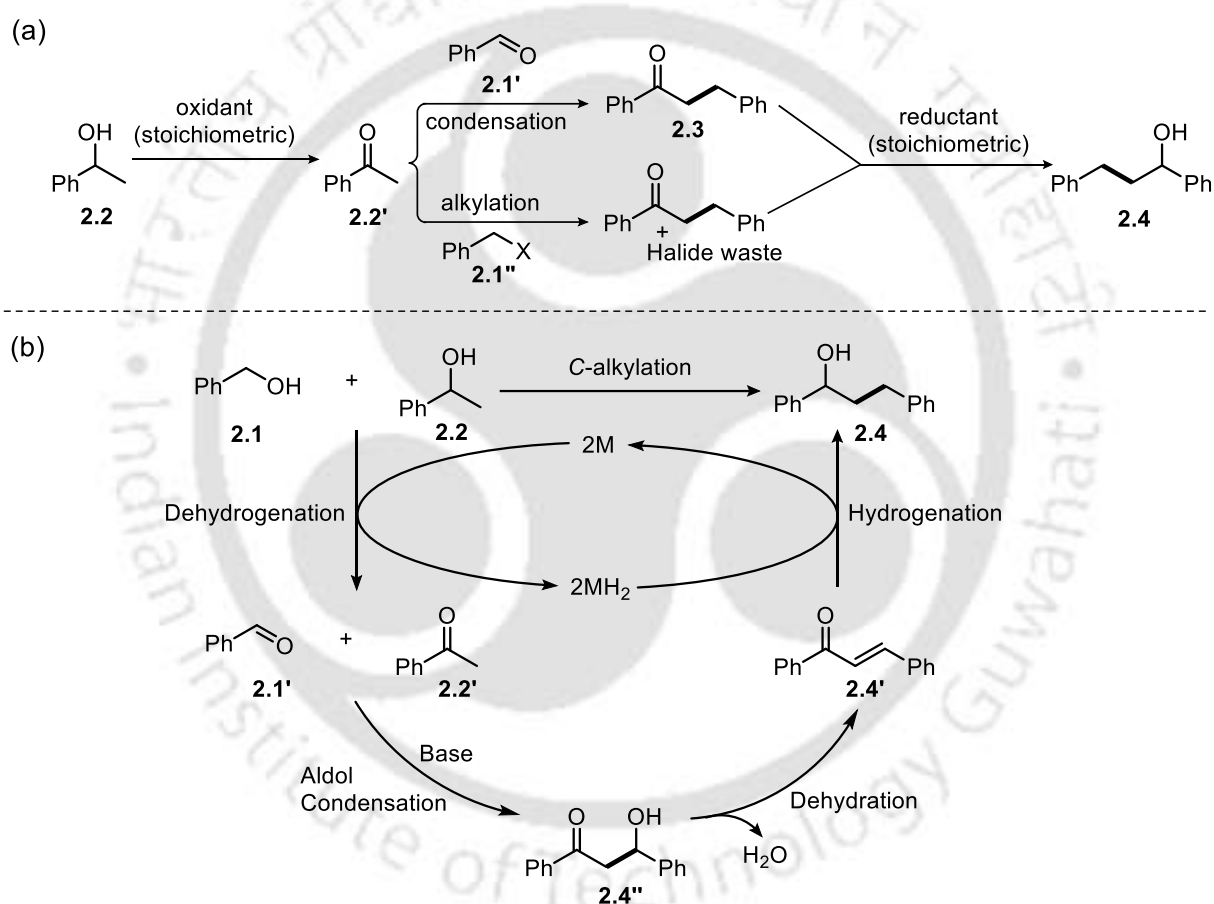


The content of this chapter has been adapted from “Guerbet-Type β -alkylation of Secondary Alcohols Catalysed by Chromium Chloride and its Corresponding NNN Pincer Complex” by Narjinari, H.; Tanwar, N.; Kathuria, L.; Jasra, R. V.; Kumar, A. *Catal. Sci. Technol.*, **2022**, 12, 4753–4762.



2.1. Introduction

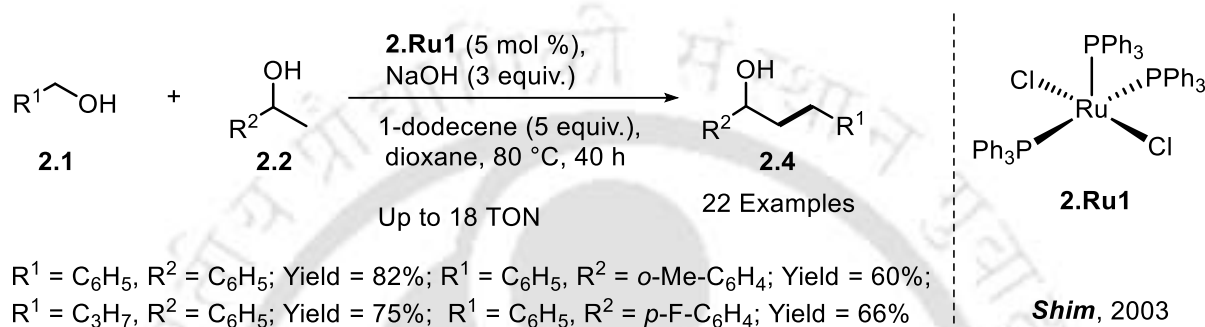
Alcohols play an important role in various organic reactions and in diverse industries including pharmaceutical,¹ cosmetics,¹ fuel,² food¹ and preservatives.¹⁻² Alcohols also serve as a sustainable feedstock and acts as a substitute for carbon sources in industries related to petrochemicals.¹⁻² The traditional methodology employed for synthesizing β -alkylated alcohols involve a synthetic pathway consisting of multiple steps (Scheme 2.1a). This pathway is accompanied with waste³⁻⁵ generation in stoichiometric amount and demands costly and toxic reagents, and strong bases.³⁻⁵ Hence, establishing a greener and alternative synthetic pathway for the formation of C-C bond is a concern of utmost importance.



Scheme 2.1. (a) Traditional pathways of the formation of β -alkylated alcohols using either alcohols or alkyl halides as alkylating agents.³⁻⁵ (b) General mechanism involved in β -alkylation of alcohols using alcohols as an alkylating agent.

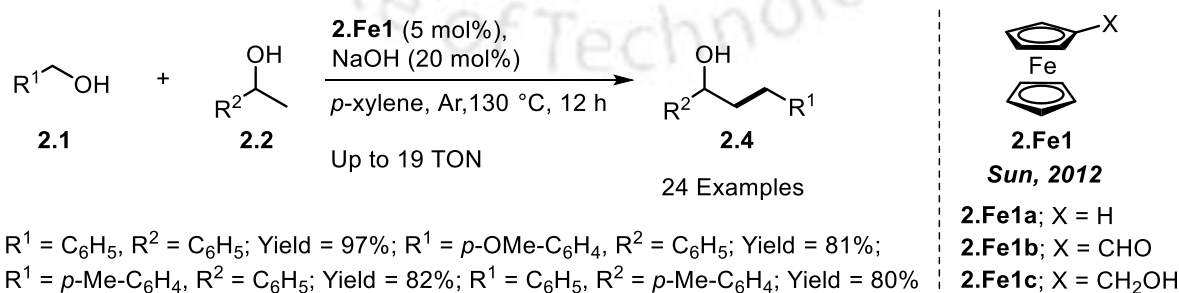
In this context, the C–C bond formation involving transition metal-catalysed β -alkylation of alcohols has fetched plenty of attention. From the point of view of designing environmentally benign process, the transition-metal catalysed acceptorless dehydrogenative coupling of

alcohols to synthesize higher β -alkylated alcohols is indeed quite fascinating. This protocol generally proceeds via the following steps: i) transition metal catalysed dehydrogenation of both alcohols (primary and secondary) to their corresponding carbonyl compounds ii) an uncatalysed aldol condensation of the resulting carbonyl compounds to the corresponding α,β -unsaturated ketones and iii) transition metal catalysed hydrogenation of the α,β -unsaturated ketones to the β -alkylated alcohols (Scheme 2.1b). In the whole tandem process, water is the sole by-product.

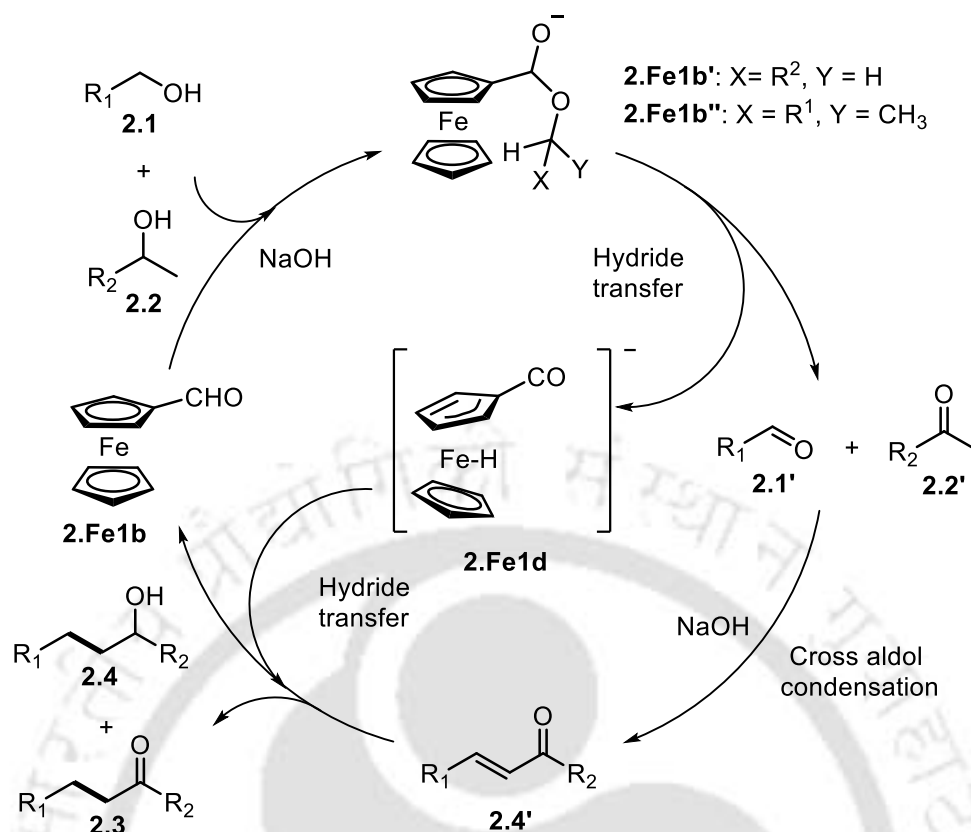


Scheme 2.2: $RuCl_2(PPh_3)_3$ catalysed β -alkylation of alcohols reported by Shim.¹⁰

Accordingly, the hydrogen-borrowing strategy which is functional even under mild reaction conditions has proven to be a more preferable strategy in tandem organic transformations. Precious noble metals have been employed to explore various tandem organic transformations, one such example being the dehydrogenation of alcohols.⁶⁻⁸ The dehydrogenation of alcohols have been broadly surveyed under aerobic conditions but under this condition the reactions were limited with some constraints, such as, deactivation of the active metal-hydride species (i.e MH_2 ; Scheme 2.1b) in the presence of air.⁹⁻¹⁰

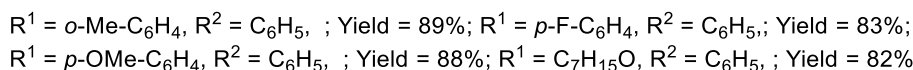


Scheme 2.3: The catalytic β -alkylation of alcohols reported by Sun using complexes based on ferrocene derivatives.¹¹



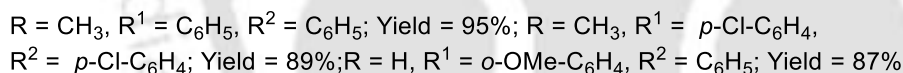
Scheme 2.4. Proposed mechanism for the β -alkylation of alcohols catalysed by the ferrocene derivative **2.Fe1b**.¹¹

In this regard, Shim was the pioneer to utilize 5 mol% of a simple organometallic complex dichloro *tris*(triphenylphosphine)ruthenium(II) (**2.Ru1**) to demonstrate the catalytic β -alkylation of secondary alcohols with primary alcohols in the presence of 3 equivalents NaOH in 1-dodecene at 80 °C that led to 82 % yield of the product **2.4** after 40 h.¹⁰ This protocol selectively afforded regioselective β -alkylation of a variety of secondary and primary alcohol derivatives which included functional groups such as aryl methyl, alkyl methyl, cyclic carbinols, alkyl methyl carbinols.¹⁰ In 2012, Sun utilized commercially available and inexpensive organometallic complex ferrocenecarboxaldehyde **2.Fe1** to catalyse the β -alkylation of secondary alcohols with primary alcohols. It is the first report on an iron mediated β -alkylation of secondary alcohols with primary alcohols. Using the protocol formulated, β -alkylated alcohols were obtained in 97% yield in the presence of 5 mol% of ferrocenecarboxaldehyde and 20 mol% NaOH, in *p*-xylene, at 130 °C after 12 h. (Scheme 2.3).¹¹ The developed synthetic protocol is generic in nature and the ferrocenecarboxaldehyde catalysed β -alkylation of various substrates were conveniently achieved.



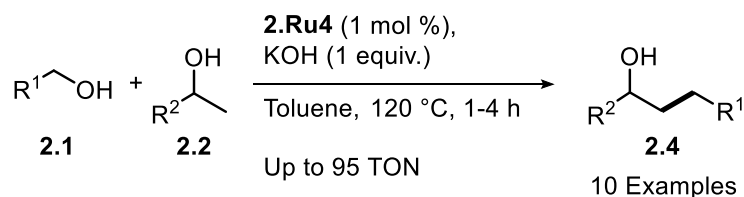
Scheme 2.5: The pincer-Ru catalysed β -alkylation of alcohols reported by Achard.⁹

From a mechanistic point of view, (Scheme 2.4) initially, the alkoxy anions of **2.1** or **2.2** does a nucleophilic attack on the aldehyde group of **2.Fe1b** in the presence of base leading to the generation of an active hydride species **2.Fe1d** along with the extrusion of aldehyde and ketone. These aldehyde and ketone undergoes cross aldol-condensation in the presence of a base to form an α,β -unsaturated ketone which is followed by the transfer of hydride from **2.Fe1d** to the α,β -unsaturated ketone leading to the β -alkylated product.¹¹

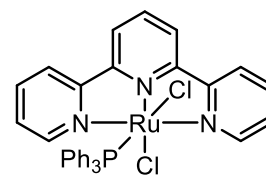


Scheme 2.6: The pincer-Ru catalysed β -alkylation of alcohols reported by Gelman.¹²

In 2017, Achard demonstrated the **2.Ru2** (0.5 mol%) catalysed the β -alkylation of alcohols in the presence of NaOH (10 mol%), in toluene, at 150 °C, after 16 h of reaction to yield of 89 % of the α -alkylated ketone along with the formation of a trace amount of β -alkylated alcohol (Scheme 2.5). The reaction follows an inner sphere mechanism similar to the general scheme shown in Scheme 2.1b.⁹ In 2013, Gelman and co-workers reported an efficient and selective synthesis of β -alkylated ketones *via* cross-coupling of secondary alcohols with primary/secondary alcohols. Gelman reported the C-alkylation of two secondary alcohols catalysed by **2.Ru3** (2 mol%) in presence of KOH (1 equivalent), in xylene, at 130 °C after 24 h where yields up to 95 % could be achieved (Scheme 2.6).¹² The ligand-metal cooperation is presumed to be involved in the catalytic cycle which operates *via* dehydrogenation and hydrogenation pathway to achieve a maximum of 48 turnovers (TON).¹²



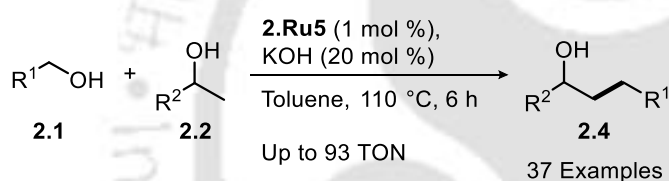
$\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 65% ; $\text{R}^1 = p\text{-Cl-C}_6\text{H}_4$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 56%;
 $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = \text{C}_3\text{H}_7$; Yield = 84% ; $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = p\text{-Cl-C}_6\text{H}_4$; Yield = 66 %

**2.Ru4**

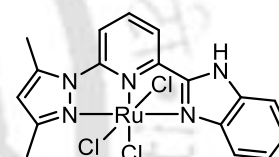
Crabtree, 2008

Scheme 2.7: The pincer-Ru catalysed β -alkylation of alcohols reported by Crabtree.¹³

In 2008, Crabtree reported the β -alkylation of secondary alcohols with primary alcohols based on terpyridine (terpy) pincer-ruthenium catalyst **2.Ru4**. Crabtree employed **2.Ru4** (1 mol%) in presence of KOH (1 equivalent), in toluene, at 120 °C within 1-4 h and achieved up to 84% yield of the β -alkylated alcohol (Scheme 2.7). They have proposed a similar inner-sphere mechanism as general mechanism shown in Scheme 2.1a which involves dehydrogenation, condensation and hydrogenation with water as the sole by-product.¹³



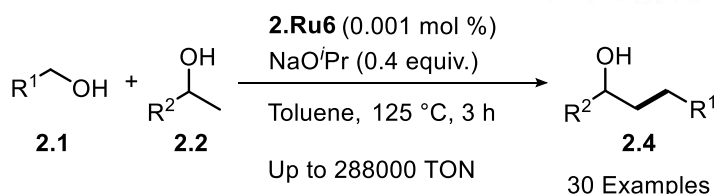
$\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 90%; $\text{R}^1 = o\text{-Me-C}_6\text{H}_4$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 91%;
 $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = o\text{-Me-C}_6\text{H}_4$; Yield = 93%; $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = p\text{-Cl-C}_6\text{H}_4$; Yield = 82%

**2.Ru5**

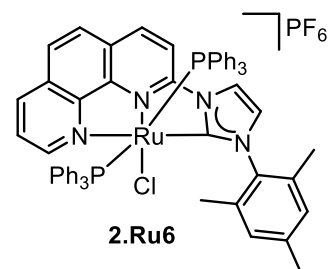
Yu, 2016

Scheme 2.8: The pincer-Ru catalysed β -alkylation of alcohols reported by Yu.¹⁴

In 2016, Yu reported the atom-economical β -alkylation of secondary alcohols with primary alcohols through a hydrogen-borrowing pathway which followed an inner-sphere mechanism and achieved up to 93 TONs. Yu used **2.Ru5** (1 mol%) achieved up to 93% yield of β -alkylated product in the presence of KOH (20 mol%), in toluene, at 110 °C in 6 h (Scheme 2.8).¹⁴

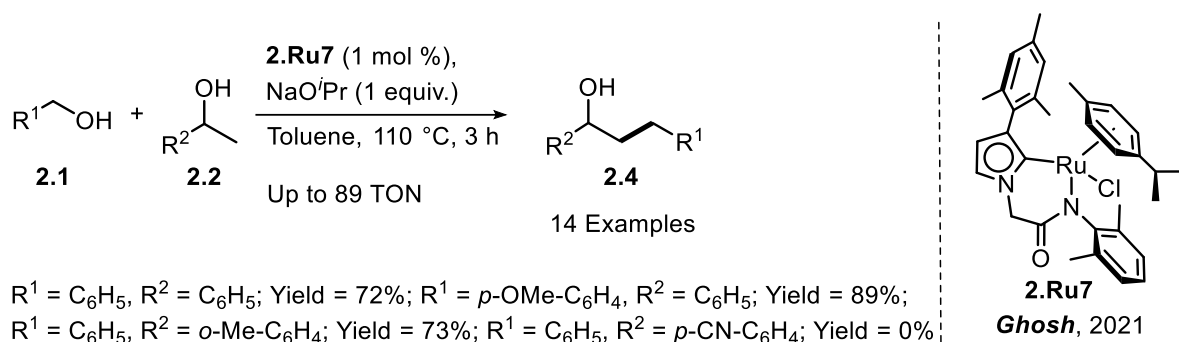


$\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 94% ; $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = p\text{-Me-C}_6\text{H}_4$; Yield=95%;
 $\text{R}^1 = p\text{-Me-C}_6\text{H}_4$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 94% ; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 88%

**2.Ru6**

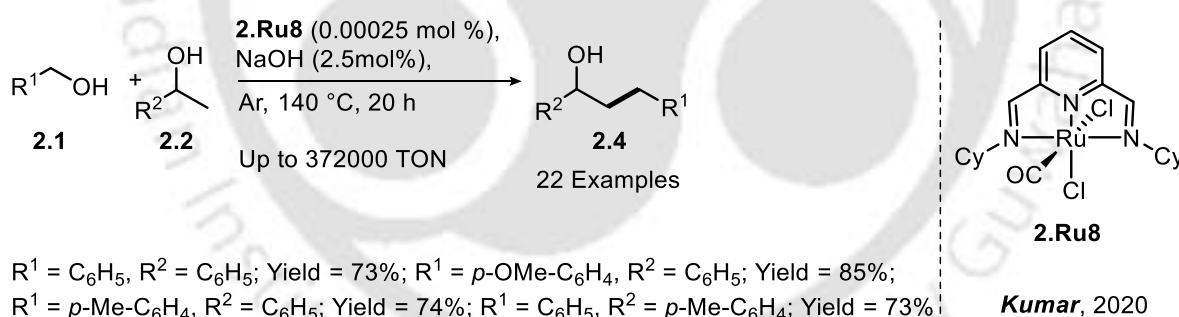
Kundu, 2018

Scheme 2.9: The pincer-Ru catalysed β -alkylation of alcohols reported by Kundu.¹⁵



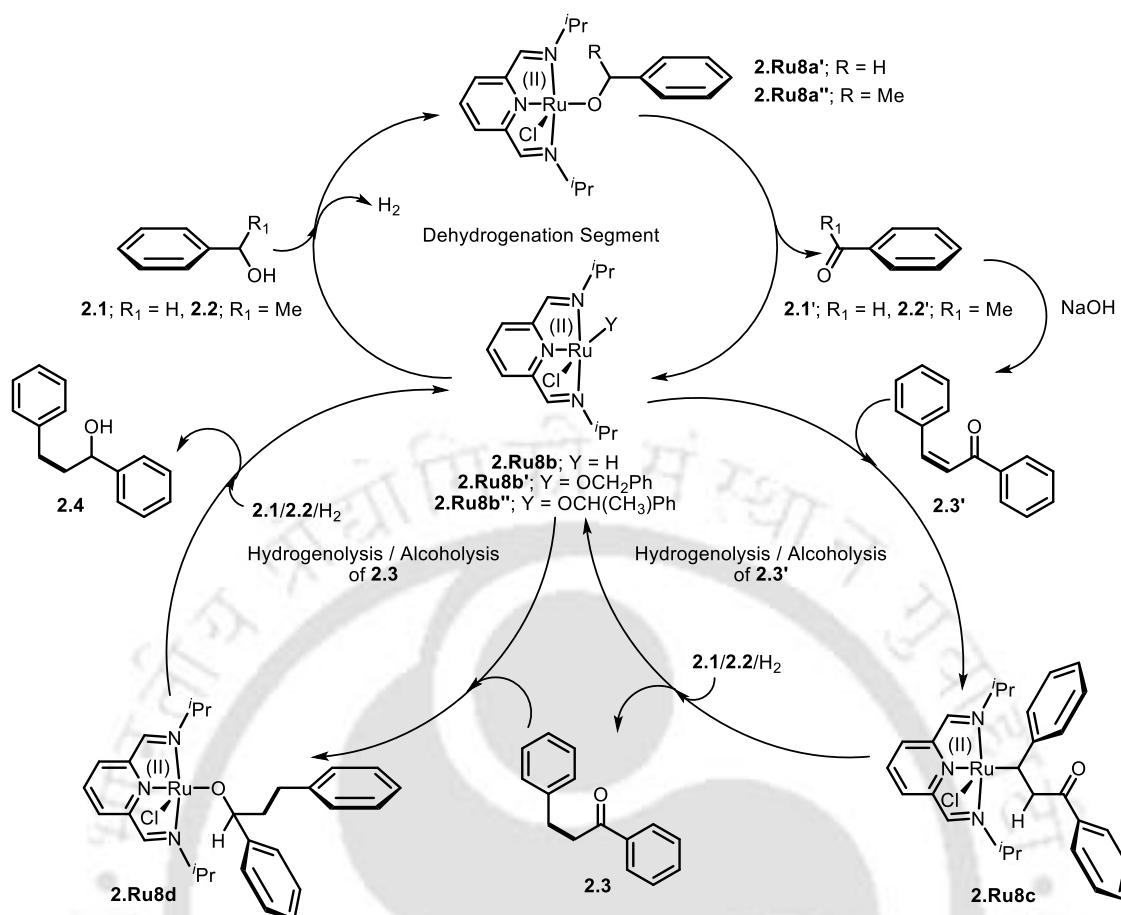
Scheme 2.10: Half-sandwich Ru complex for the catalytic β -alkylation of alcohols reported by Ghosh.¹⁶

In 2018, Kundu reported pincer-ruthenium catalysts based on very electron rich phenanthroline based NHC and pyridine based NNC ligands for the β -alkylation of secondary alcohols with primary alcohols. Upon using a significantly low catalyst loading of 0.001 mol%, the NHC ligand-based NNC pincer-ruthenium complex **2.Ru6** provided a very high turnover of 288000 for the β -alkylation reaction with 95% yield of β -alkylated alcohol in presence of NaOⁱPr (0.4 equivalents), in toluene at 125 °C after 3h (Scheme 2.9). The reaction follows the hydrogen auto-transfer mechanism.¹⁵



Scheme 2.11: The pincer-Ru catalysed β -alkylation of alcohols reported by Kumar.¹⁷

In 2021, Ghosh and co-workers reported an amido-functionalized ruthenium-carbene complex **2.Ru7** catalysed β -alkylation of secondary alcohols with primary alcohols. Ghosh demonstrated that **2.Ru7** (1 mol%) afforded up to 89% yield of the β -alkylated product in presence of NaOⁱPr (1 equivalent), toluene at 110 °C after 3h (Scheme 2.10). The progress of this one-pot tandem transformation proceeded via a partial hydrogenation of the α,β -unsaturated ketone to entirely hydrogenated β -alkylated alcohol.¹⁶

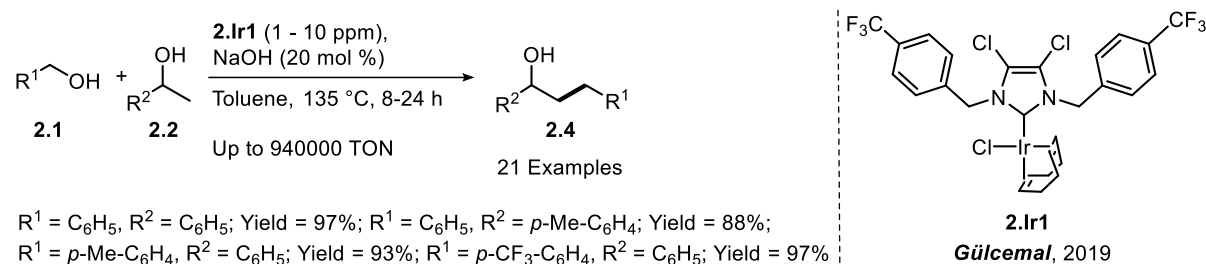


Scheme 2.12. Proposed mechanism for the pincer-ruthenium catalysed β -alkylation of alcohols by Kumar.¹⁷

In 2020, Kumar has reported the β -alkylation of 1-phenyl ethanol alcohol with benzyl alcohol that is catalysed by phosphine-free NNN pincer-ruthenium carbonyl complexes based on *bis(imino)pyridine* ligands. The highest TON of 372000 was achieved with the complex **2.Ru8** (0.00025 mol%) under solvent free condition in the presence of very low base loading (2.5 mol%) at 140 °C after 20 h of reaction (Scheme 2.11). The reaction proceeded *via* an inner sphere mechanism (Scheme 2.12) which was supported by DFT studies. DFT studies revealed that the β -hydride elimination step with a release of a molecule of acetophenone as RDS with a barrier of 21.71 kcalmol⁻¹.¹⁷

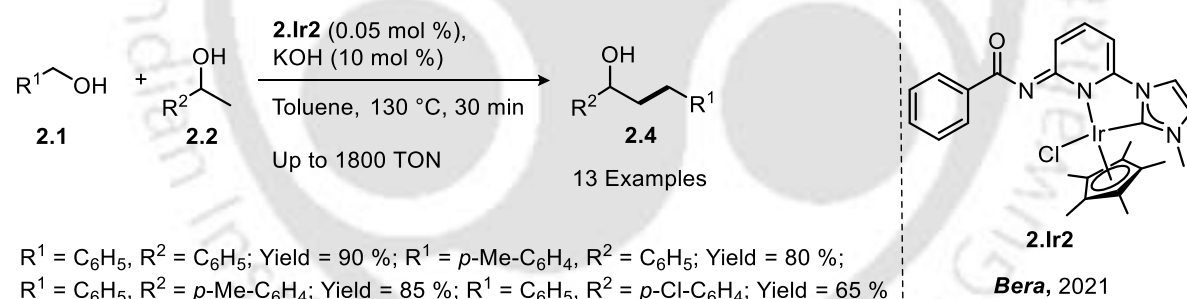
In 2019, Gülcemal reported the imidazol-2-ylidene ligand-based iridium(I) **2.Ir1** catalysed β -alkylation of secondary alcohols with primary alcohols. This simple catalytic system provided the β -alkylated alcohols (including cholesterol derivatives) with good yields under a very low loading of the catalyst **2.Ir1**. The catalyst **2.Ir1** achieved up to 940000 TON with a catalytic

amount of NaOH or KOH under aerobic conditions via hydrogen-borrowing strategy (Scheme 2.13).¹⁸

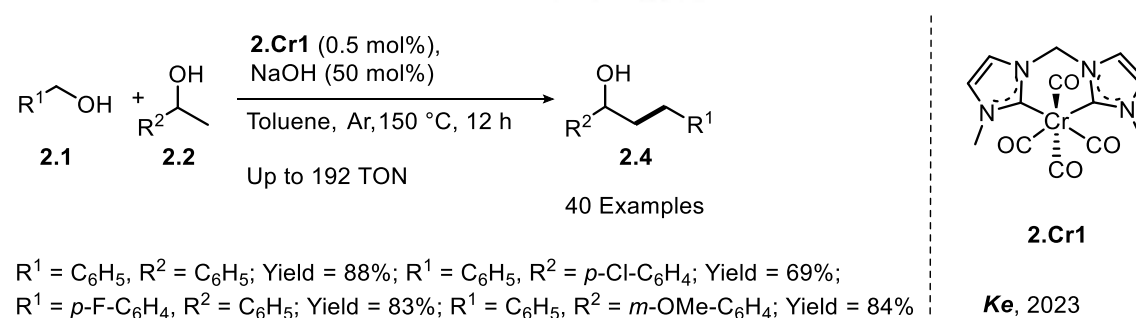


Scheme 2.13: The NHC-Ir catalysed β -alkylation of alcohols reported by Gülcemal.¹⁸

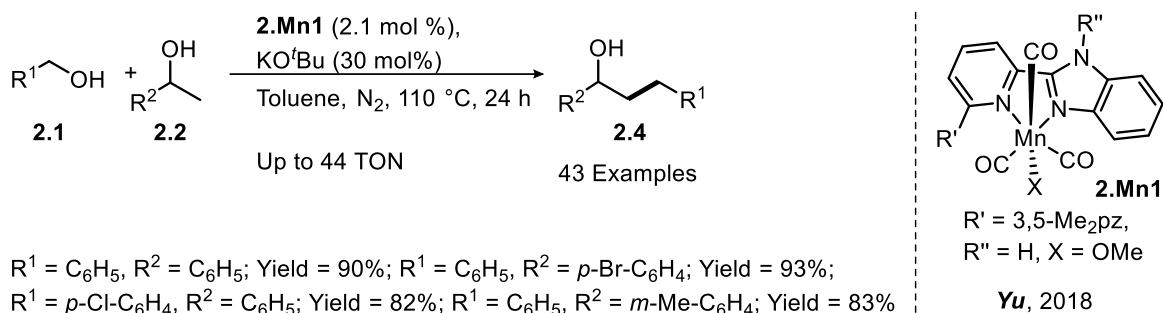
In 2021, Bera reported Ir(III)-*N*-heterocyclic carbene **2.Ir2** catalysed β -alkylation of secondary alcohols with primary alcohols. The complex **2.Ir2** demonstrated remarkable activity due to pyridyl(benzamide)-functionalized NHC backbone, which involves dearomatization/aromatization of pyridine backbone during catalysis. The catalyst **2.Ir2** (0.05 mol%) has demonstrated a wide range of substrate scope under low KOH loading (10 mol%) at 130 °C within 30 minutes of reaction (Scheme 2.14). The mechanistic studies suggests that the outer-sphere mechanism with metal-ligand co-operativity is more favourable than the inner-sphere mechanism.¹⁹



Scheme 2.14: Half-sandwich Ir complexes for the catalytic β -alkylation of alcohols reported by Bera.¹⁹

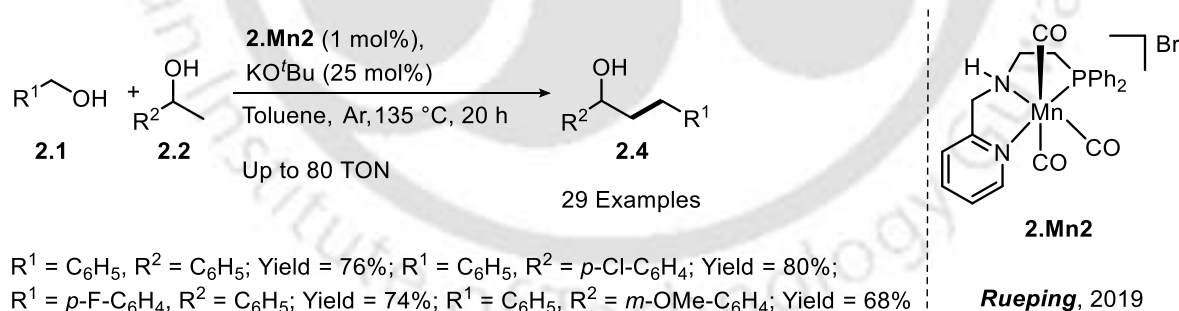


Scheme 2.15. The Cr catalysed β -alkylation of alcohols reported by Ke.²⁰



Scheme 2.16: The Mn catalysed β -alkylation of alcohols reported by Yu.²¹

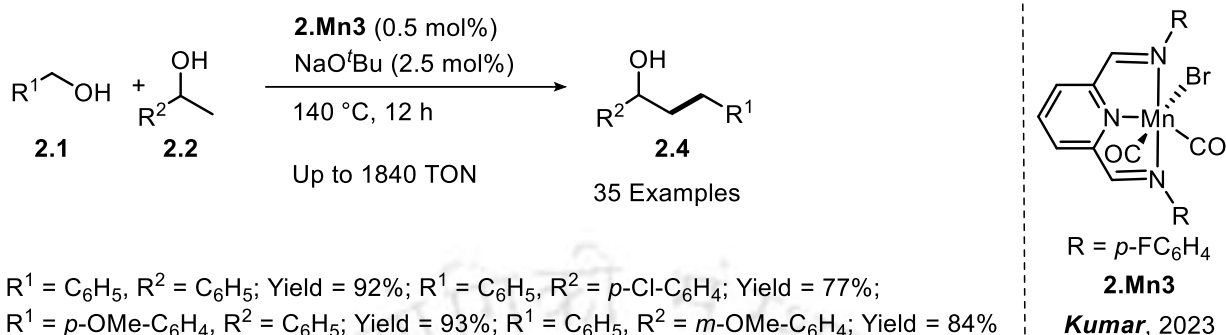
In 2023, Ke have utilised highly active Cr(0) catalyst to overcome the alkoxide-trap, an obstacle encountered in the β -alkylation of secondary alcohols with primary alcohols. Here, the catalyst **2.Cr1** (0.5 mol%) afforded up to 88% of the β -alkylated product in presence of NaOH (50 mol%) at 150°C after 12 hours of reaction under an argon atmosphere (Scheme 2.15). Based on the computational studies, they have proposed an inner sphere mechanism for the Cr(0) catalysed β -alkylation of alcohols.²⁰ In 2018, Yu was the first one to report the Mn-catalysed β -alkylation reaction. About 2.1 mol% of the phosphine-free Mn(I) complexes bearing a pyridyl-supported pyrazolyl-imidazolyl ligand were employed for the direct β -alkylation of secondary alcohols by primary alcohols (43 examples) to yield up to 92% of the β -alkylated product in the presence of KO^tBu (30 mol%) at 110°C with water as the sole by product (Scheme 2.16).²¹



Scheme 2.17: The pincer-Mn catalysed β -alkylation of alcohols reported by Rueping.²²

In 2019, Rueping have utilised Mn(I) complex **2.Mn2** bearing a PNN pincer ligand and developed a protocol to achieve the β -alkylation of secondary alcohols by primary alcohols through double hydrogen auto-transfer. They have obtained 99% conversion using 1 mol% of **2.Mn2** catalyst in presence of KO^tBu (25 mol%) at 135°C and a broad range of substrates (29 examples) were converted into higher-value alcohols in good yields (Scheme 2.17). Thorough

mechanistic investigations showed that the reaction proceeds via hydrogen auto-transfer pathway and demonstrated the pivotal role played by the non-innocent ligand in the catalytic pathway.²²



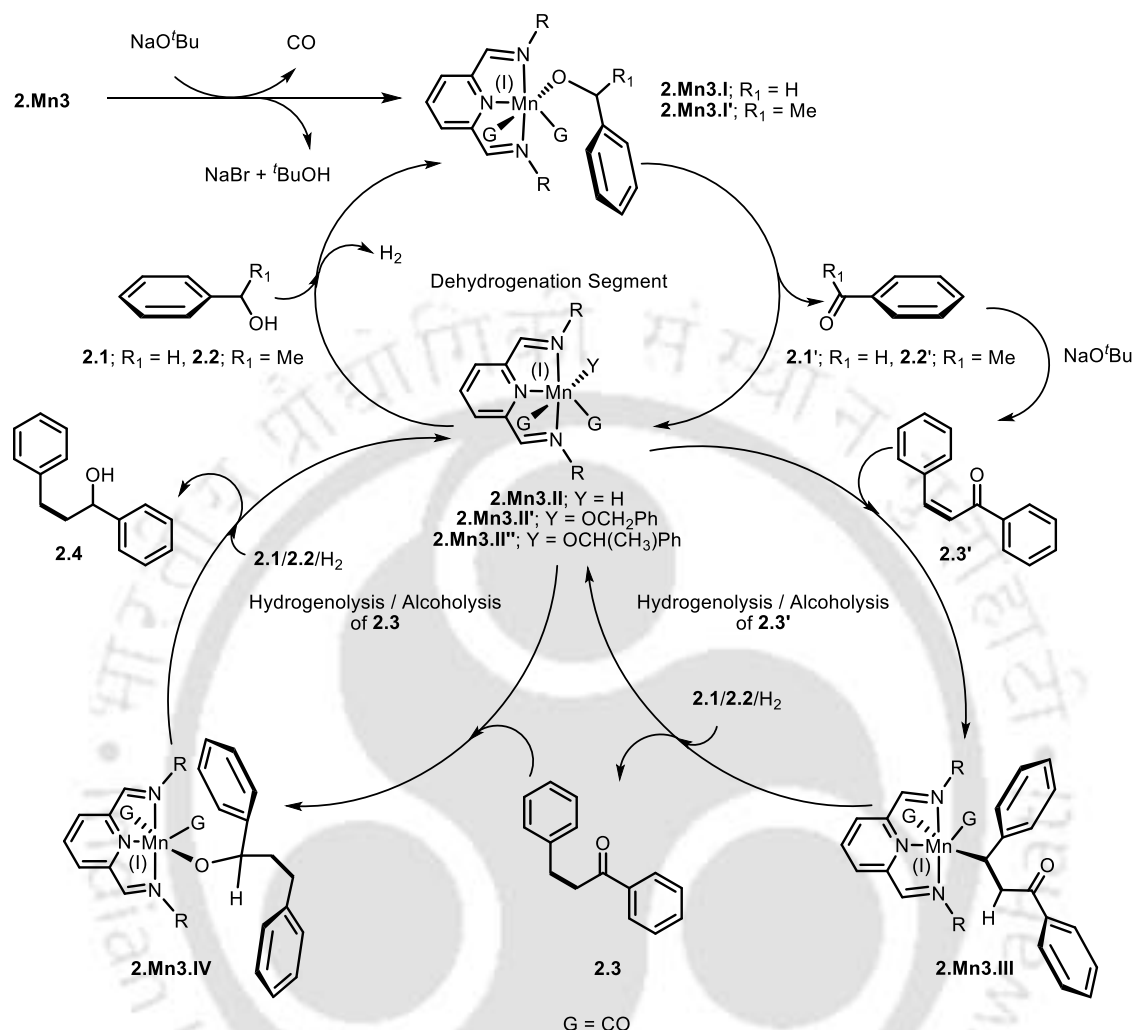
Scheme 2.18: The pincer-Mn catalysed β -alkylation of alcohols reported by Kumar.²³

In 2023, Kumar have employed pincer-Mn(I) complex **2.Mn3** based on *bis*(imino) pyridine ligands for catalysing the β -alkylation of secondary alcohols by primary alcohols (35 examples) at 0.05 mol% catalyst loading in presence of 2.5 mol% of NaOtBu under both conventional (12h) and microwave heating (2h) (Scheme 2.18). The catalyst $p\text{-FC}_6\text{H}_4\text{NNNMn}(\text{CO})_2\text{Br}$ (**2.Mn3**) has given maximum yield of 92% (1840 TON) under conventional heating while yield of 85% (1700 TON) was obtained under microwave conditions.²³

They have proposed two different mechanisms based on Mn(I) and Mn(0) species. The Mn(I) catalysed mechanism initiates via conversion of a *tris* carbonyl bidentate-Mn(I) complex **2.Mn3** to a *bis* carbonyl tridentate-Mn(I) species (**2.Mn3.I/2.Mn3.I'**) in the presence of **2.1/2.2** and NaOtBu with the release of one molecule of NaBr (Scheme 2.19). The species **2.Mn3.I** or **2.Mn3.I'** undergoes β -hydride elimination to give rise to a hydride species (**2.Mn3.II/2.Mn3.II'/2.Mn3.II''**) with an extrusion of **2.1'/2.2'**. The carbonyl compounds **2.1'** and **2.2'** undergoes aldol condensation in presence of base and generates the species **2.3'**. The M-H bond of **2.Mn3.II/2.Mn3.II'/2.Mn3.II''** undergoes σ -bond metathesis with the O-H bond of **2.1/2.2** and regenerates the alkoxide species **2.Mn3.I/2.Mn3.I'** along with an extrusion of H_2 .²³

The insertion of **2.3'** into M-H bond of **2.Mn3.I/2.Mn3.I'** gives **2.Mn3.III** which again undergoes σ -bond metathesis in presence of H_2 or **2.1/2.2** with a release of **2.3** giving back **2.Mn3.II/2.Mn3.II'/2.Mn3.II''**. The species **2.3** undergoes insertion followed by

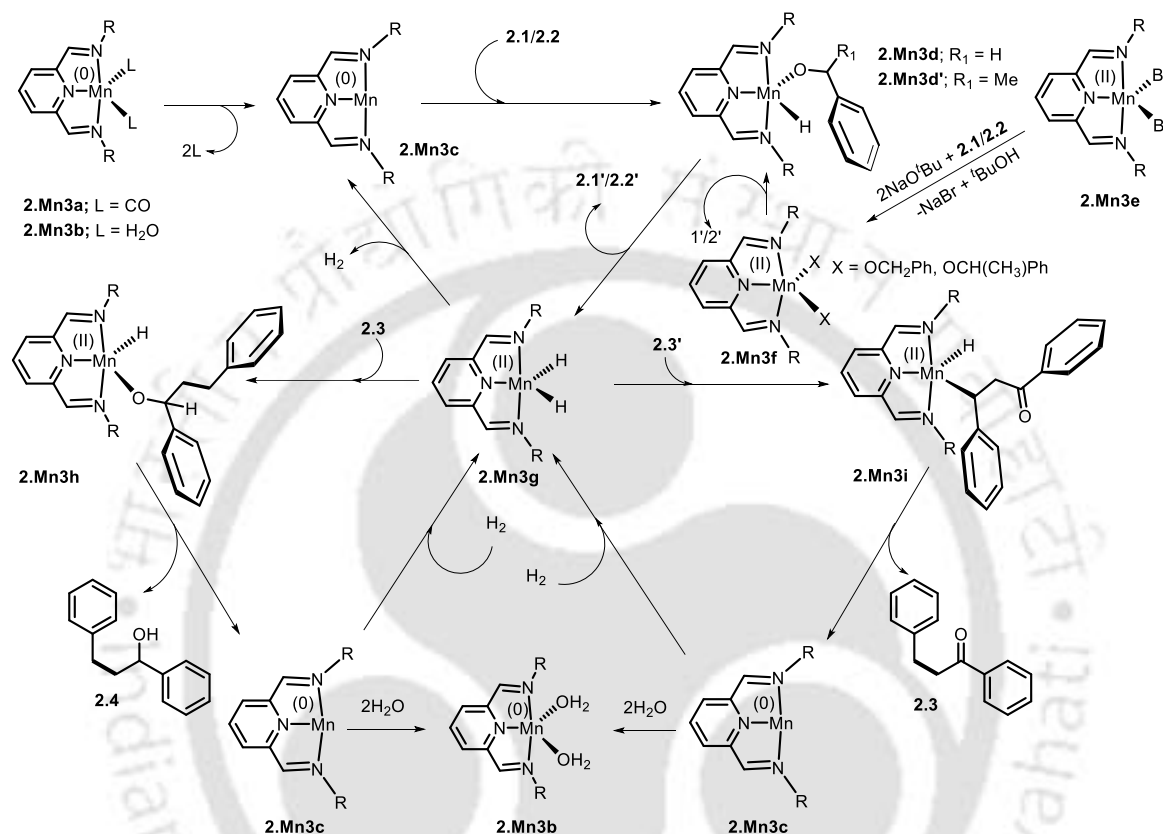
hydrogenolysis/alcoholysis to generate the product **2.4** along with regeneration of **2.Mn3.II/2.Mn3.II'/2.Mn3.II''** (Scheme 2.19).²³



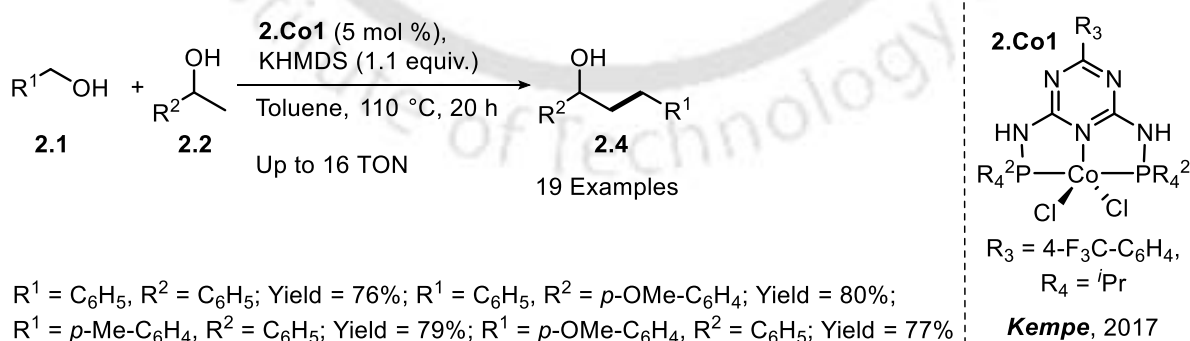
Scheme 2.19. Proposed mechanism for the pincer-manganese catalysed β -alkylation of alcohols by Kumar.²³

In the mechanistic cycle catalysed by the Mn(II)/Mn(0) couple, the Mn(0) complex **2.Mn3b** converts to Mn(II) alkoxide–hydride species **2.Mn3d/2.Mn3d'** via Mn(0) species **2.Mn3c** (Scheme 2.20). It is followed by a β -hydride elimination from **2.Mn3d/2.Mn3d'** and results in the generation of **2.1'** and **2.2'** leading to the formation of a Mn(II) dihydride species **2.Mn3g** (Scheme 2.20). Alternatively, a sequential salt metathesis at Mn(II) dibromide complex **2.Mn3e** in the presence of **2.1/2.2** and NaO^tBu, followed by β -hydride elimination can also give rise to the dihydride species **2.Mn3g** (Scheme 2.20). The **2.Mn3g** undergoes reductive elimination and regenerates the Mn(0) species **2.Mn3c**. A Mn(0) species **2.Mn3c** is generated

after a sequential insertion of **2.3'** into the Mn-H bond of the dihydride species **2.Mn3g** and reductive elimination of **2.3** from **2.Mn3i** (Scheme 2.20). After which H₂ undergoes oxidative addition at **2.Mn3c** and regenerates the Mn(II) dihydride species **2.Mn3g**. The hydrogenation of **2.3** to **2.4** follows similar steps such as insertion followed by reductive elimination (Scheme 2.20).²³



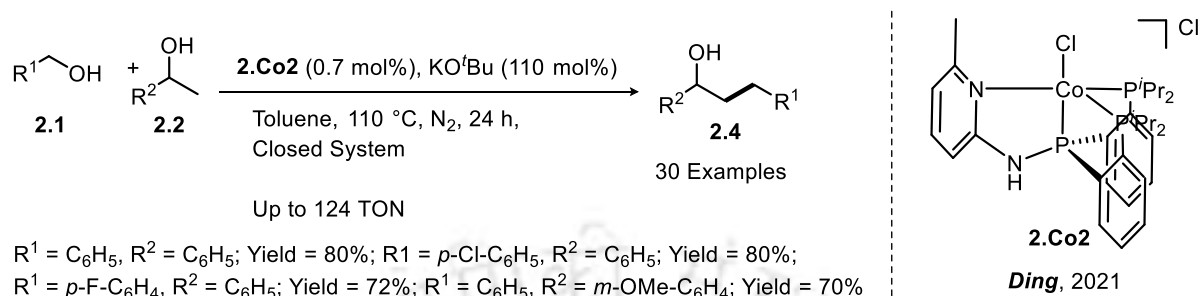
Scheme 2.20. Proposed mechanism for the pincer-manganese catalysed β -alkylation of alcohols by Kumar.²³



Scheme 2.21: A PNP-pincer Co catalysed β -alkylation of alcohols reported by Kempe.²⁴

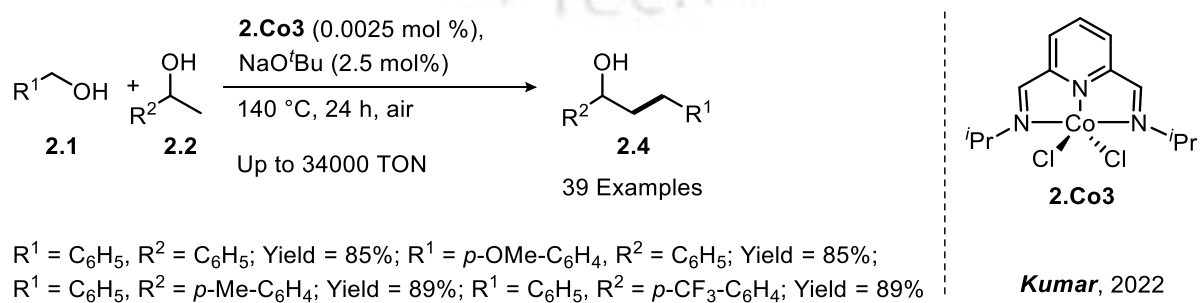
In 2017, Kempe first reported the Co-catalysed β -alkylation of alcohols using a PN₅P pincer-Co complex **2.Co1** (5 mol %) in the presence of 1.1 equivalents of KHMDS (potassium

hexamethyldisilazane) to get up to 90% yield of the β -alkylated product (Scheme 2.21). The catalyst system based on **2.Co1** was applicable to a broad range of substrates. Notably, the β -alkylation was driven by **2.Co1** based on a hydrogen auto-transfer strategy.²⁴

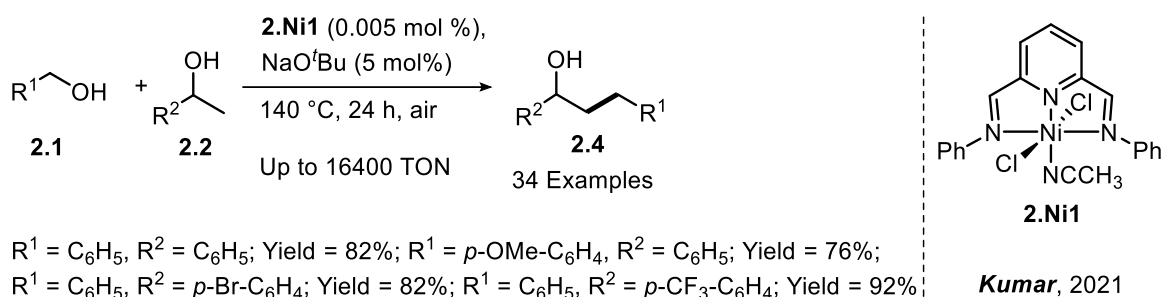


Scheme 2.22: A terdentate Co complex for the catalytic β -alkylation of alcohols reported by Ding.²⁵

In 2021, Ding group reported a Co catalyst (0.7 mol %) supported by a $i\text{PrPPN}^{\text{H}}\text{Py}^{\text{Me}}$ terdentate ligand for the β -alkylation of alcohols in up to 80% yield at 110 °C at a very high loading (110 mol %) of KO^tBu (Scheme 2.22). This protocol also followed the hydrogen-borrowing strategy. Also, the deuterium labelling experiments indicated a KIE of 1.65 which points to the fact that α -C-H bond breaking of benzyl alcohol is quite slow.²⁵ In 2022, Kumar reported NNN pincer-Co complex **2.Co3** (0.002 mol%) for the catalytic β -alkylation of 1-phenyl ethanol with benzyl alcohol in the presence of 2.5 mol % of NaO^tBu at 140 °C which rendered up to 85% yield (ca. 34000 TON at 1417 TOF h⁻¹) of the β -alkylated product (Scheme 2.23). The corresponding reaction under microwave conditions (140 °C at 75 W) was complete in only 2 h with a comparable yield (83%, 33200 TON) and far better TOF (16600 TOF h⁻¹). They have reported a KIE of 6.14 which indicated that β -hydride elimination step is involved in the RDS of the which proceeded through an inner-sphere mechanism involving a hydrogen- borrowing strategy.²⁶

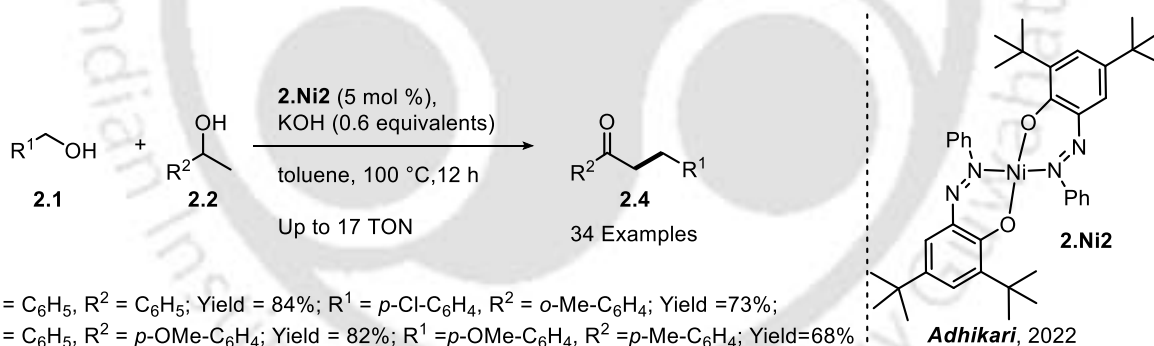


Scheme 2.23: A NNN pincer-Co complex for the catalytic β -alkylation of alcohols reported by Kumar.²⁶



Scheme 2.24: A NNN pincer-Ni complex for the catalytic β -alkylation of alcohols reported by Kumar.²⁷

In 2021, Kumar reported the β -alkylation of various primary alcohols with secondary alcohols catalysed by NNN pincer-Ni(II) complex **2.Ni1** based on bis(imino)pyridine ligands. Very high TONs (up to 18400) were observed for the alkylation of 1-phenyl ethanol with benzyl alcohol catalysed by 0.005 mol% of (^{Ph}NNN)NiCl₂(CH₃CN) (**2.Ni1**) in the presence of 5 mol% NaO^tBu at 140 °C after 24 h (Scheme 2.24). The reaction follows a similar mechanism as shown in Scheme 2.19 which involved salt metathesis, β -hydride elimination, aldol condensation, sequential insertion and hydrogenolysis/alcoholysis. Based on the kinetic studies the aldol-condensation step was suggested to be the RDS.²⁷

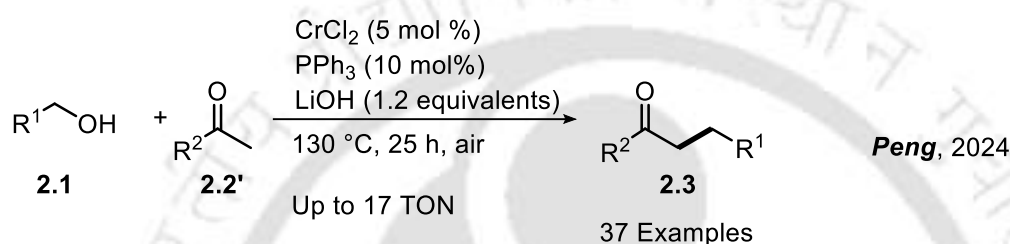


Scheme 2.25: A bidentate Ni complex for the catalytic β -alkylation of alcohols reported by Adhikari.²⁸

In 2022, Adhikari demonstrated the dehydrogenative cross-coupling of primary and secondary alcohols to yield α -alkylated ketones using nickel azo-phenolate catalyst. The Ni(II) catalyst **2.Ni2** demonstrated a wide substrate scope of primary alcohols including challenging aliphatic alcohols where they obtained up to 68% yield (Scheme 2.25). They have anticipated that a sequence of catalytic transformations involving dehydrogenation of alcohols, followed by aldol-condensation of the dehydrogenated product and hydrogenation of the resulting olefin

gave the final product enone and but the quenching of the reaction in the presence of a radical quencher TEMPO is suggestive of a radical mechanism.²⁸

In 2024, Peng have reported chromium(II) chloride (5 mol%) catalysed β -alkylation of alcohols in presence of PPh_3 (10 mol%) and LiOH (1.2 equivalents) at 130°C in 25 hours and reached up to 85% yield of the desired product (Scheme 2.26). This protocol also follows a sequential dehydrogenation of alcohols to their corresponding aldehydes which undergoes condensation to give rise to the α,β -unsaturated ketone. A sequential insertion of the α,β -unsaturated ketone in the hydride species followed by σ -bond metathesis in the presence of hydrogen generates the α -alkylated ketone.²⁹



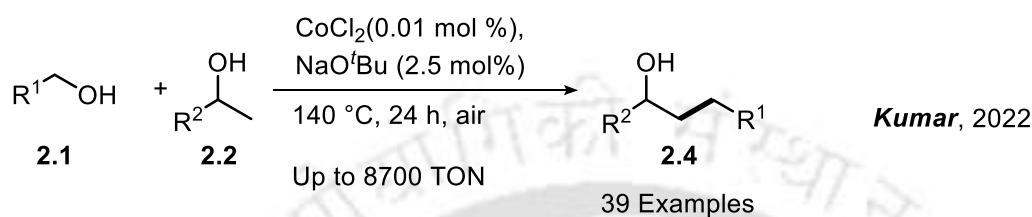
$\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 78%; $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = p\text{-OMe-C}_6\text{H}_4$; Yield = 84%;
 $\text{R}^1 = p\text{-OMe-C}_6\text{H}_4$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 80%; $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = p\text{-Me-C}_6\text{H}_4$; Yield = 85%

Scheme 2.26. Chromium catalysed β -alkylation of alcohols reported by Peng.²⁹

In 2022, Kumar reported that cobaltous chloride (0.01 mol %) efficiently achieves the catalytic β -alkylation of alcohols with high yields (up to 87%) and unprecedented turnovers (ca. 8700) in the presence of only 2.5 mol % of NaO^tBu (Scheme 2.27). They have reported a KIE of 1.61 which indicated involvement of the C-H activation in proposed reaction mechanism. The cobaltous chloride forms an *in-situ* generated octahedral species in the presence of **2.1** or **2.2** which then participates in the hydrogen-borrowing mechanism (similar to Scheme 2.19) to give rise to the desired product.³⁰ In 2021, Balaraman demonstrated the β -alkylation of alcohols (Scheme 2.28) using $\text{NiBr}_2/\text{TMEDA}$ (1:1) in the presence of 1 equivalent of KOH at 130°C using *n*-octane as solvent. The $\text{NiBr}_2/\text{TMEDA}$ (1:1) tolerated a broad range of substrates including aromatic, cyclic, acyclic, aliphatic alcohols and the scope was extended towards the double alkylation of cyclopentanol with various alcohols (Scheme 2.28).³¹

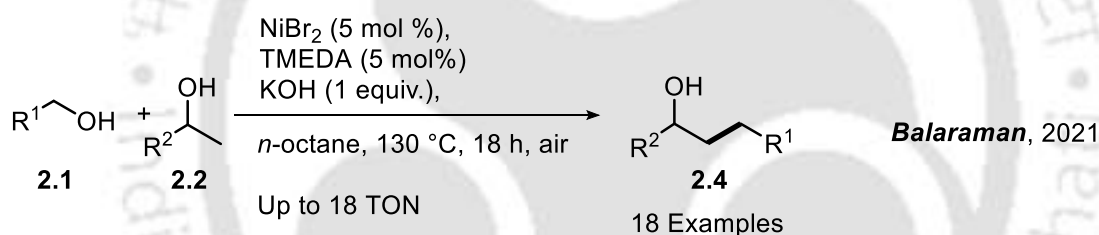
In 2012, Xu and co-workers investigated the β -alkylation of secondary alcohols and α -alkylation of ketones using a ligand-free copper catalyst. They could achieve up to 99% yield of the alkylated product when they have treated benzyl alcohol and 1-phenyl ethanol with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1 mol%) and KOH (30 mol%) at 120°C (Scheme 2.29).³² The first step of the

proposed mechanism initiates either via aerobic oxidation of **2.1** or **2.2** in presence of Cu in air or the oxidation of **2.1** or **2.2** catalysed by Cu(II) under an atmosphere of N₂ (step i). The next step is the aldol condensation of **2.1'** and **2.2'** to **2.3'** in the presence of base (step ii). This is followed by transfer hydrogenation which generates both the intermediates (**2.1'** and **2.2'**) as well as the β -alkylated alcohol (step iii and iv). The **2.1'** and **2.2'** undergoes condensation as soon as formed in the step iv to give rise to **2.3** (step v) (Scheme 2.30).



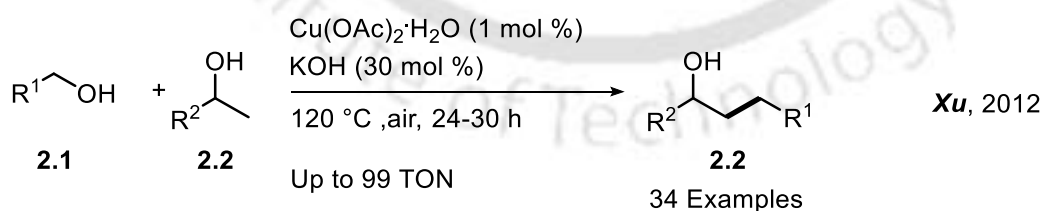
R¹ = C₆H₅, R² = C₆H₅; Yield = 87%; R¹ = C₆H₅, R² = *p*-Cl-C₆H₄; Yield = 88%;
 R¹ = *p*-OMe-C₆H₄, R² = C₆H₅; Yield = 84%; R¹ = C₆H₅, R² = *p*-CF₃-C₆H₄; Yield = 81%

Scheme 2.27: The CoCl₂ catalysed β -alkylation of alcohols reported by Kumar.³⁰



R¹ = C₆H₅, R² = C₆H₅; Yield = 91%; R¹ = *p*-OMe-C₆H₄, R² = C₆H₅; Yield = 82%;
 R¹ = *p*-Me-C₆H₄, R² = C₆H₅; Yield = 84%; R¹ = *o*-OMe-C₆H₄, R² = C₆H₅; Yield = 86%

Scheme 2.28: The Ni catalysed β -alkylation of alcohols reported by Balaraman.³¹



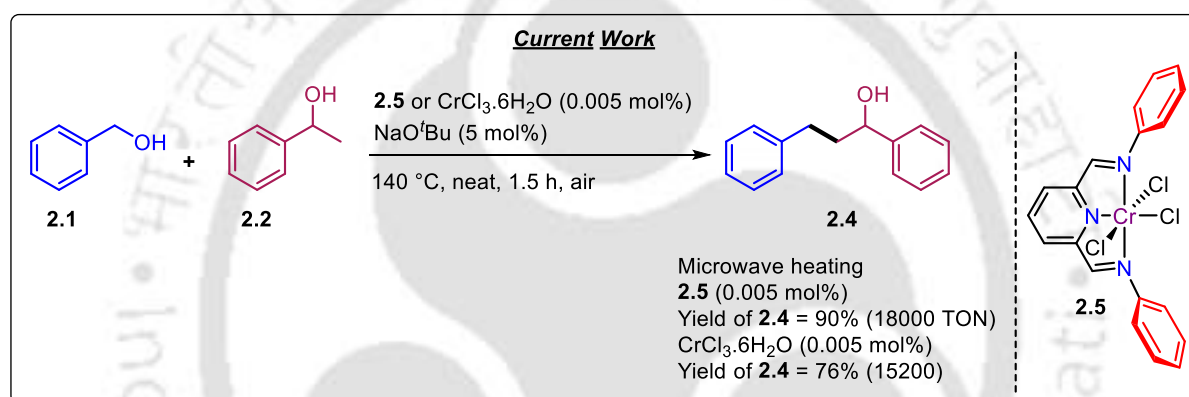
R¹ = C₆H₅, R² = C₆H₅; Yield = 99%; R¹ = C₆H₅, R² = *p*-Cl-C₆H₄; Yield = 88%;
 R¹ = C₆H₅, R² = *p*-OMe-C₆H₄; Yield = 99%; R¹ = *p*-OMe-C₆H₄, R² = *p*-OMe-C₆H₄; Yield = 99%

Scheme 2.29: The Cu catalysed β -alkylation of alcohols reported by Xu.³²

In 2023, Wendt discovered that the β -alkylation of alcohols can be accomplished in the presence of sub-stoichiometric amounts of KOH (25 mol%) at 120 °C after 18 h in air where

β -alkylation of alcohols with very high base loading. It is also seen in the reports by Crabtree,⁵ Gunanathan,³⁴ Jhonson and Wendt³³ that β -alkylation of secondary alcohols with primary alcohols can be mediated only in presence of a base albeit at high loadings (sub-stoichiometric or stoichiometric). On the basis of these facts, the current work attempts to address the following questions:

- Can we develop a strategy to accomplish the β -alkylation of alcohols with catalytic amount of base loading instead of sub-stoichiometric base loading?
- Can we utilise a simple first-row transition metal salt chromium(III) chloride and its corresponding NNN-Cr pincer complex for the β -alkylation of alcohols?
- Can we carry out this transformation under air which will improve the ease of handling?

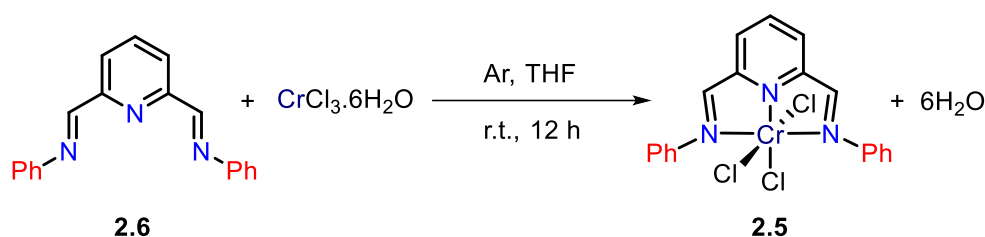


Scheme 2.33. Current work.

2.3. Results and discussion

2.3.1. Synthesis and characterization of (Ph^2NNN) CrCl_3 (2.5).

The NNN pincer-Cr complex **2.5** was synthesized in good yields by treating the Ph^2NNN ligand with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in THF at room temperature for 12 h, followed by washing with diethyl ether and removal of solvent under reduced pressure (Scheme 2.34). The NNN pincer-Cr complex **2.5** was paramagnetic in nature, as indicated by its magnetic susceptibility measurements in the solid-state $\mu_{\text{eff}} = 3.2 \mu_{\text{B}}$ and in solution $\mu_{\text{eff}} = 3.4 \mu_{\text{B}}$. EPR analysis also indicated paramagnetic nature of the complex **2.5** (Figure 2.1). HRMS analysis of **2.5** demonstrated prominent peaks at m/z 406.9962, m/z 429.1622, m/z 461.1829 and m/z 506.2228 that corresponded to $[\mathbf{2.5a}]^+$, $[\mathbf{2.5b} + \text{CH}_3\text{CN}]^+$, $[\mathbf{2.5b} + \text{CH}_3\text{CN} + \text{CH}_3\text{OH}]^+$ and $[\mathbf{2.5b} + \text{CH}_3\text{CN} + 3\text{H}_2\text{O} + \text{Na}]^+$ respectively (Figure 2.2).



Scheme 2.34. Synthesis of $(^{\text{Ph}_2}\text{NNN})\text{CrCl}_3$ (**2.5**).

2.3.2. Optimization of the chromium catalysed β -alkylation of 1-phenyl ethanol with benzyl alcohol.

Considering the fact that use of *bis*(imino)pyridine ligands gave good yield of β -alkylation in the Ni catalysed reactions²⁷ and also on the fact that mere CoCl_2 efficiently accomplished the catalytic β -alkylation of alcohols,³⁰ we set upon to use another 3d-metal salt $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its corresponding pincer complex $(^{\text{Ph}_2}\text{NNN})\text{CrCl}_3$ (**2.5**)³⁵⁻³⁸ for the catalytic β -alkylation of alcohols. Benzyl alcohol and 1-phenylethanol were chosen as the model primary and secondary alcohol respectively for this reaction. To start with, a variety of bases (5 mol%) were screened in the search of the best reaction conditions for the solvent-free β -alkylation of secondary alcohols with primary alcohols in the presence of 0.005 mol% of $(^{\text{Ph}_2}\text{NNN})\text{CrCl}_3$ (**2.5**) in an open vessel under an atmosphere of air at 140 °C (Table 2.1). The reaction did not yield either of the expected products **2.3** and **2.4** when then the reaction was performed in the presence of

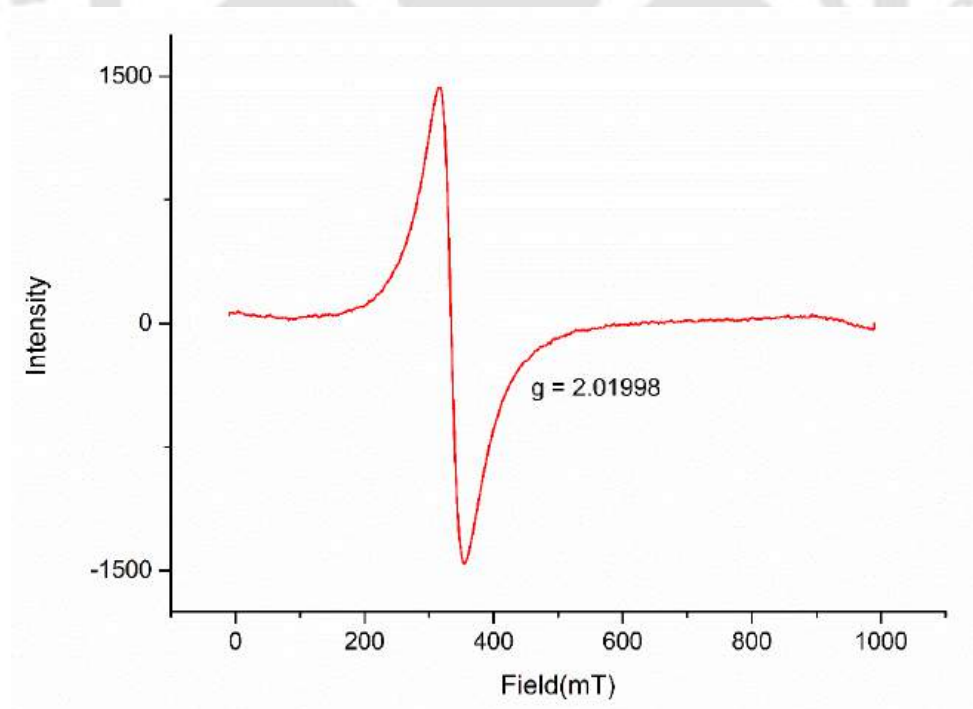


Figure 2.1. The X-band EPR spectra of the complex **2.5** recorded on a JES-FA200 ESR spectrometer at 77K in methanol with microwave power of 0.998 mW and microwave frequency of 9.14 GHz.

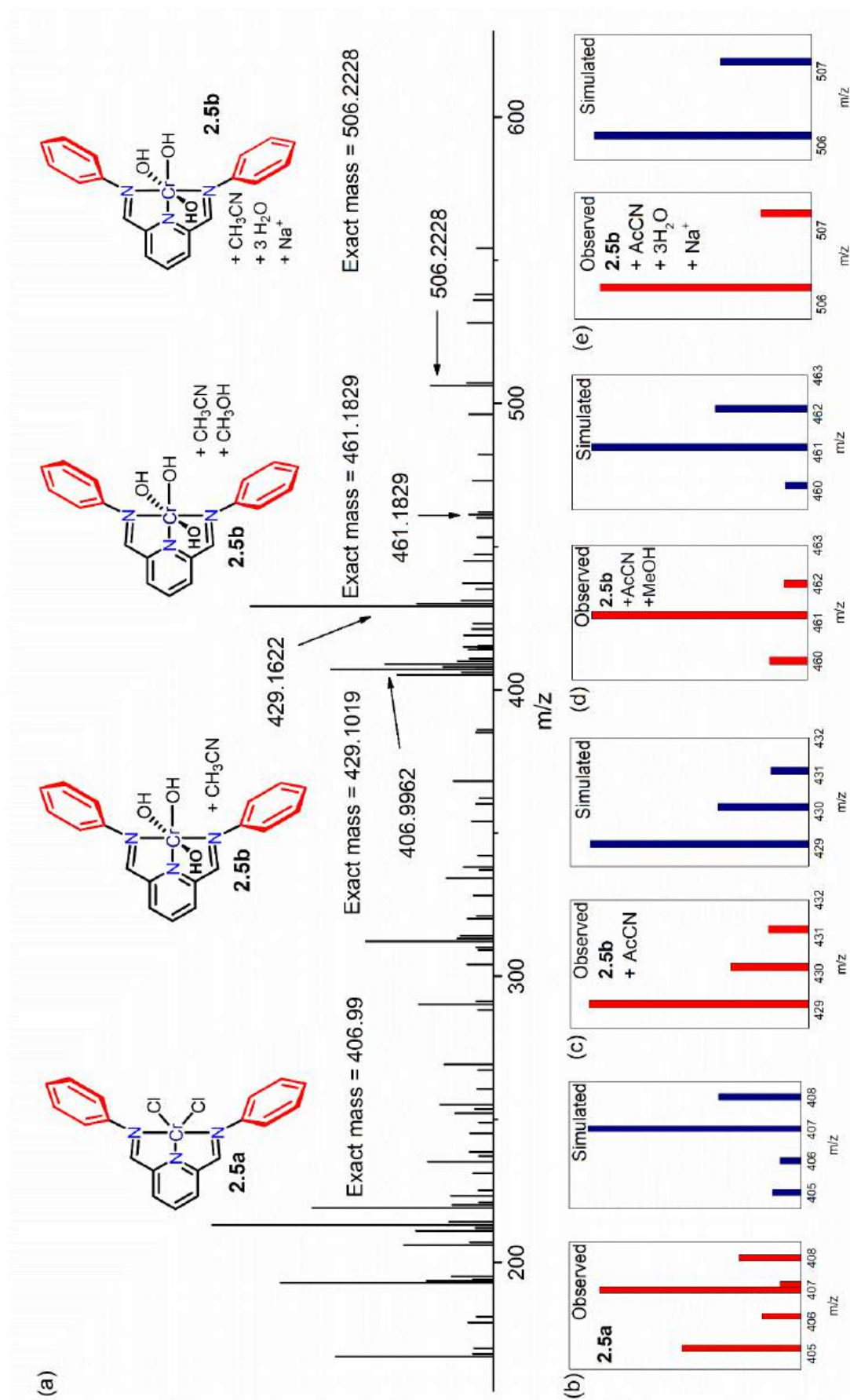


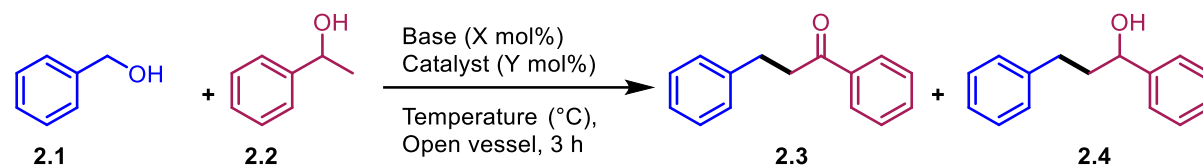
Figure 2.2. (a) HRMS (ESI) plot of complex 2.5. HRMS (ESI) expanded spectra [Observed (red) and Simulated (blue)] of m/z (b) 406.9962 (c) 429.1622 (d) 461.1829 (e) 506.2228.

Na₂CO₃, NaHCO₃, or K₂CO₃ (entries 1, 2 and 3, Table 2.1). In the presence of bases such as KO^tBu, and KOH, only 5% of the β -alkylated product **2.4** was observed (entries 4 and 5, Table 2.1). About 45% of the β -alkylated product **2.4** was obtained when 5 mol% of NaOH was used (entry 6, Table 2.1). A drastic decrease in the yield of **2.4** was noticed when the amount of NaOH was reduced to 2.5 mol% and 1.25 mol% respectively (entries 7 and 8, Table 2.1). In both these reactions, starting material was observed to be present in major amounts after 3 hours of the reaction (entries 7 and 8, Table 2.1). To our delight, when 5 mol% of NaO^tBu was used, the product **2.4** was obtained in major amounts (ca. 84% and 16800 TON) (entry 9, Table 2.1). There was a precipitous decrease in the yield with the decrease in loading of NaO^tBu (entries 10 and 11, Table 2.1). With the best optimized loading of NaO^tBu at 5 mol%, the reaction was attempted with varying loadings of **2.5** (entries 12-15, Table 2.1). The yield of **2.4** decreased to 71% (entry 14, Table 2.1) when the reaction was performed with 0.0025 mol% **2.5** when compared to the yield of 84% obtained in the case of reactions catalysed by 0.005 mol% **2.5** (entry 9, Table 2.1). A further loss in the yield of **2.4** occurred when the reaction was catalysed using only 0.00125 mol% of **2.5** (entry 15, Table 2.1). The **2.5** (0.005 mol%) catalysed reaction at lower temperature resulted in poorer yields (entries 16 and 17, Table 2.1). The activity of 0.005 mol% CrCl₃.6H₂O was lower (79%, entry 18, Table 2.1) than its corresponding pincer complex **2.5** (entry 9, Table 2.1). The reaction gave negligible results either in the absence of catalyst (entry 19, Table 2.1) or in the absence of NaO^tBu (entries 20 and 21, Table 2.1). In addition to the conventional heating method, the reactions were carried out under the influence of microwave heating (140 °C, 75 W and 20 psi) at the optimized reaction conditions. Interestingly, under microwave conditions, better yields of **2.4** (ca. 90% at 18000 TON) after only 1.5 h of the reaction (entry 1, Table 2.2) was observed. Poor reactivity was observed at lower temperatures (entries 2 and 3, Table 2.2) in the **2.5** catalysed reaction under microwave conditions. The yield of β -alkylation with CrCl₃.6H₂O under microwave conditions were similar to those observed under conventional heating however at much reduced reaction times. Similar to the results obtained with conventional heating, the yield of β -alkylation under microwave reactions were lower at lower temperatures (entries 2, 3 and 5, Table 2.2).

2.3.3. The chromium catalysed β -alkylation of various 1-phenyl ethanols with benzyl alcohols.

Alkylation reactions with secondary alcohols are envisaged as more challenging than primary alcohols because of their low susceptibility towards both condensation and hydrogenation steps

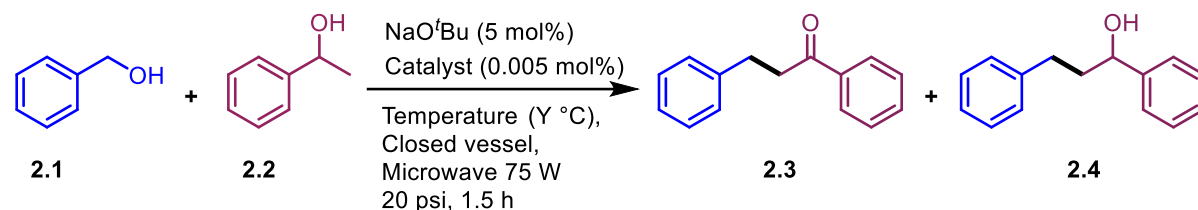
in an alkylation reaction.³⁹ Firstly, the β -alkylation of primary alcohol with a variety of secondary alcohols as an alkylating agent was investigated under the optimized condition (Table 2.3). Secondary alcohols with electron-donating substituents such as methoxy (**2.4a**, **2.4p**), methyl (**2.4k**), *t*-butyl (**2.4c**) groups afforded good yields when both **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ were used as catalysts under conventional heating (ca. 60-75% yield) as well as microwave heating (ca. 55-83% yield). Interestingly, secondary alcohols with electron-withdrawing substituents such as chloro (**2.4f**, **2.4h**), bromo (**2.4i**), trifluoromethyl (**2.4l**) groups gave excellent yields of the corresponding β -alkylated alcohols in the **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed reactions under conventional as well as microwave conditions. But in case of **2.4f**, 50% of product was afforded in presence of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ whereas 81% of product was obtained in presence of **2.5**. Unfortunately, no product was obtained for secondary alcohol containing highly electron-withdrawing nitro-substituent (**2.4j**). Product (**2.4j**) was not detected in the ^1H NMR even on increasing the base loading (10 mol%) and increasing the reaction time for 24 h. The presence of strongly electron-withdrawing nitro substituent reduces the nucleophilicity of the alcohol's α -C making it non-reactive. Thiophene based secondary alcohols (**2.4e**) gave good yields of 61-79% under conventional as well as microwave heating when both **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ were used as catalysts. For other heteroatom (O, N) containing substrates (**2.4b**, **2.4d** and **2.4m**), either there was no trace of product or poor yields were obtained under the optimized conditions. Aliphatic secondary alcohols (**2.4g**, **2.4n**) did not undergo the β -alkylation with benzyl alcohol in presence of both **2.5** as well as $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ under conventional heating conditions. But, under the microwave heating conditions, 23% yield of **2.4g** was observed. Further optimizations under microwave heating might result into higher yields of **2.4g**. Also, the stability of the in-situ generated nucleophile is lower in case of aliphatic alcohols. Interestingly, fused aromatic secondary alcohols such as **2.2o** underwent β -alkylation to afford **2.4o** in 86 % yield. The β -alkylation of various primary alcohols with 1-phenyl ethanol were also tested under the optimized condition (Table 2.4). The primary alcohols bearing electron donating groups like methoxy and methyl gave good to excellent yields (ca. 50-85%) of the corresponding products (**2.4q**, **2.4r**, **2.4v** and **2.4zd**) under the optimized conditions. Poor yield (~19%) of the β -alkylated product (**2.4y**) was obtained for (3-chlorophenyl)methanol under conventional heating. Interestingly, the yield of the product drastically increased to 86% under microwave heating (Table 2.4). Similar result was observed for (4-chlorophenyl)methanol where yield of the product (**2.4za**) increased up to 80% under microwave conditions (Table 2.4). In the case of (4-fluorophenyl)methanol also, the yield of

Table 2.1. Optimization of the chromium catalysed solvent-free β -alkylation of 1-phenylethanol with benzyl alcohol under conventional heating^a

Entry	Base (X mol%) ^b	Catalyst (Y mol%) ^b	Yield(%) ^c and (TON) ^f		Selectivity of 2.4 (%) ^c	C _{balance} (%)
			2.4	2.3		
1	Na ₂ CO ₃ (5)	2.5 (0.005)	0 (0)	0 (0)	0	100
2	NaHCO ₃ (5)	2.5 (0.005)	0 (0)	0 (0)	0	99
3	K ₂ CO ₃ (5)	2.5 (0.005)	0 (0)	0 (0)	0	100
4	KO ^t Bu (5)	2.5 (0.005)	5 (1000)	2 (400)	71	98
5	KOH (5)	2.5 (0.005)	5±2 (1000)	4±0 (800)	56	99
6	NaOH (5)	2.5 (0.005)	45±0.3 (9000)	4 (800)	92	99
7	NaOH (2.5)	2.5 (0.005)	11±2 (2200)	5±1 (1000)	69	99
8	NaOH (1.25)	2.5 (0.005)	3±1 (600)	2±1 (400)	60	99
9	NaO ^t Bu (5)	2.5 (0.005)	84±0.3 (16800)	8±1 (1600)	91	98
10	NaO ^t Bu (2.5)	2.5 (0.005)	9±2 (1800)	3±1 (600)	75	97
11	NaO ^t Bu (1.25)	2.5 (0.005)	2±0.3 (400)	1±1 (200)	67	100
12	NaO ^t Bu (5)	2.5 (0.01)	70	6	92	99
13	NaO ^t Bu (5)	2.5 (0.0075)	70±2	6±1	92	98
14	NaO ^t Bu (5)	2.5 (0.0025)	71±0.1 (14200)	5±1 (1000)	93	97
15	NaO ^t Bu (5)	2.5 (0.00125)	61±2 (12200)	3±1 (600)	95	99
16 ^d	NaO ^t Bu (5)	2.5 (0.005)	12±2 (2400)	3±1 (600)	80	97
17 ^e	NaO ^t Bu (5)	2.5 (0.005)	5±0.5 (1000)	2±1 (400)	71	97
18	NaO ^t Bu (5)	CrCl ₃ .6H ₂ O (0.005)	79±2 (15800)	12±1 (2400)	87	96
19	NaO ^t Bu (5)	—	8	2	80	96
20	—	CrCl ₃ .6H ₂ O (0.005)	0	0	0	99
21	—	2.5 (0.005)	0	0	0	100

^a Reaction conditions: Benzyl alcohol (4 mmol), 1-phenylethanol (4 mmol), base (X mol%), and Cr catalyst (Y mol%) were heated together in air at 140 °C for 3 hours. ^b Mol% of base and catalyst are with respect to total alcohol content (2.1+2.2).

^c Yield determined from ¹H NMR analysis using toluene as standard. Yields reported are the average of two runs. Selectivity = (Yield of 2.4/Total yield (2.4 + 2.3))*100. ^d Reaction performed at 120 °C. ^e Reaction performed at 100 °C. ^f TONs are written in the parenthesis.

Table 2.2. Chromium catalysed solvent-free β -alkylation of 1-phenyl ethanol with benzyl alcohol under microwave conditions^a

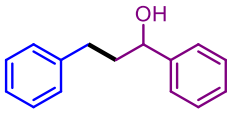
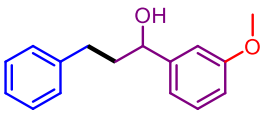
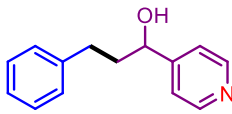
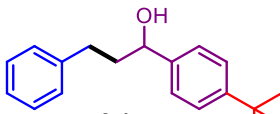
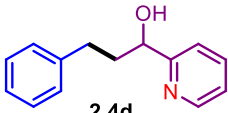
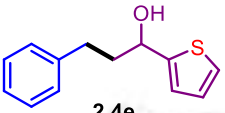
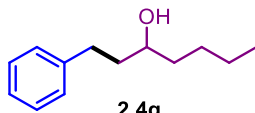
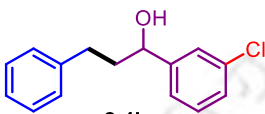
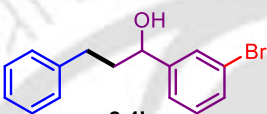
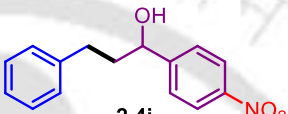
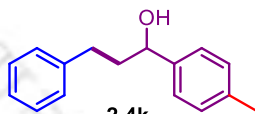
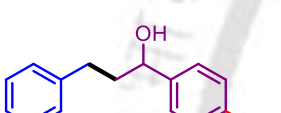
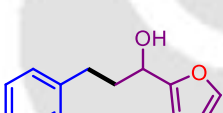
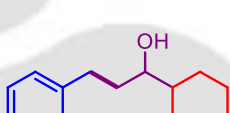
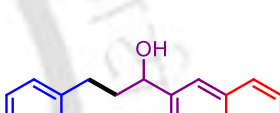
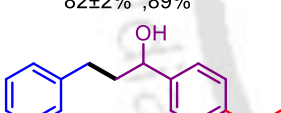
Entry	Temperature (T °C)	Catalyst (0.005 mol%) ^b	Yield (%) ^c and [TON] ^f		Selectivity of 2.4 ^c	C _{balance} (%)
			2.4	2.3		
1	140	2.5	90 (18000)	7 (1400)	93	97
2	120	2.5	26 (5200)	2 (400)	93	97
3	100	2.5	8 (1600)	2 (400)	80	98
4	140	CrCl ₃ ·6H ₂ O	76 (15200)	3 (600)	96	96
5	120	CrCl ₃ ·6H ₂ O	31 (6200)	3 (600)	91	96

^aReaction conditions: Benzyl alcohol (2 mmol), 1-phenylethanol (2 mmol), NaO^tBu (5 mol%), and Cr catalyst (0.005 mol%) were heated together in air at 140 °C for 1.5 hours under 75 W microwave irradiation. ^bMol% of base and catalyst are with respect to total alcohol content (2.1+2.2). ^cYield determined from ¹H NMR analysis using toluene as a standard. Selectivity of 2.4 = ((Yield of 2.4/Total yield (2.3 + 2.4))*100). Yields reported are the average of two runs. ^dTONs are written in the parenthesis.

product (2.4zc) showed an improvement of 3.2 folds (Table 2.4) under microwave conditions. This improvement was also observed for the product (2.4s) where the yield reached 84% under microwave heating. Notably, comparable yield of 82% was obtained upon performing the reaction with higher base loading (10 mol%) under conventional heating. Among the fused-aromatics, naphthalen-1-ylmethanol gave yields up to 71% (2.4t).

On the other hand, anthracen-9-ylmethanol afforded very poor yield of 2.4z (Table 2.4) which could not be improved either by increasing the base loading or the time of the reaction. Unfortunately, products 2.4u and 2.4zb (Table 2.4) arising from aliphatic primary alcohols could not be observed under the optimized conditions. While starting from furan-2-ylmethanol, the yield of product (2.4w) though poor, was more when the reaction was done under microwave condition compared to that observed under conventional heating. Very poor yield was obtained for the product (2.4x) under both conventional and microwave conditions.

Table 2.3. The **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed β -alkylation of a variety of 1-phenyl ethanol derivatives with benzyl alcohol under conventional and microwave heating conditions^a

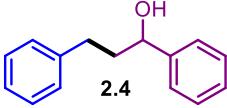
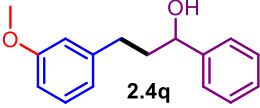
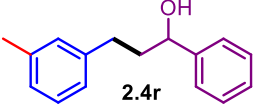
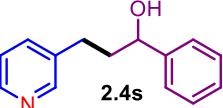
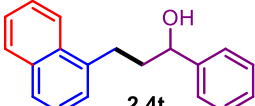
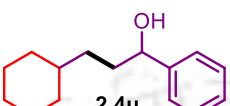
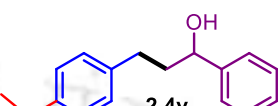
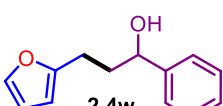
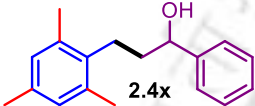
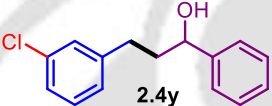
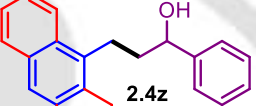
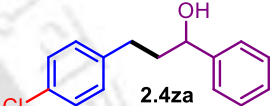
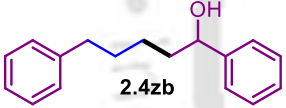
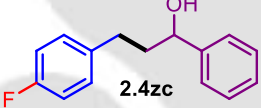
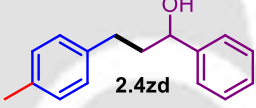
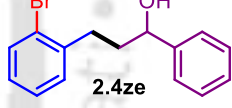
 2.4 84±0.3%^b, 90%^c 79±2%^d, 76%^e	 2.4a 72±2%^b, 75%^c 74.5 ±0.5%^d, 71%^e	 2.4b 0%^b, 18%^c, 28%^f 0%^d, Trace^e, Trace^g	 2.4c 67±2%^b, 83%^c 74±3%^d, 80%^e
 2.4d 30%^b, 6%^c, 25.5±2.5%^d, Trace^e, 45%^g	 2.4e 63.5±2.5%^b, 79%^c 73.5±0.5%^d, 61%^e	 2.4f 81±1%^b, 91%^c, 50±3%^d, 90%^e	 2.4g 0%^b, 23%^c 0%^d, 0%^e
 2.4h 69±3%^b, 91%^c 66.5±3.5%^d, 87%^e	 2.4i 79±2%^b, 88%^c 82.5 ±3.5%^d, 87%^e	 2.4j 0%^b, 0%^c, 0%^d, 0%^e,	 2.4k 64.5±2.5%^b, 82%^c 71.5±0.5%^d, 80%^e
 2.4l 84.5±3%^b, 88%^c 82±2%^d, 89%^e	 2.4m 21±3%^b, 31%^c, 21±3%^d, 17%^e,	 2.4n 0%^b, 0%^c, 0%^d, 0%^d	 2.4o 60±1%^a, 86%^c 70±2%^d, 75%^e
 2.4p 74.5 ±0.5%^b, 58%^c 59.50 ±0.5%^d, 55%^e			

^aReaction conditions: Benzyl alcohol (2 mmol), 1-phenylethanol derivatives (2 mmol), NaO^tBu (0.2 mmol), and Cr catalyst (0.005 mol%) at 140 °C. Yield determined from ^1H NMR analysis using toluene as a standard. Yields reported are the average of two runs. ^bConventional heating conditions with **2.5** as catalyst after 3 h. ^cMicrowave conditions with **2.5** as catalyst after 1.5 h. ^dConventional heating conditions with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst after 3 h. ^eMicrowave conditions with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst after 1.5 h. ^fConventional heating conditions, 10 mol% NaO^tBu with **2.5** as catalyst after 24 h. ^gConventional heating conditions, 10 mol% NaO^tBu , with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst after 24 h.

2.3.4. Mechanistic studies on the chromium catalysed β -alkylation of 1-phenyl ethanol with benzyl alcohol.

With an intention to probe the reaction mechanism, the β -alkylation of 1-phenyl ethanol with benzyl alcohol catalysed independently by **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ were followed with time using EPR as well as HRMS analysis. At $t = 0$, the HRMS analysis of the reaction mixture containing

Table 2.4. The **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed β -alkylation of 1-phenyl ethanol with a variety of benzyl alcohols under conventional and microwave heating conditions^a

 2.4 84±0.3%^b, 90%^c 79±2%^d, 76%^e	 2.4q 78±2%^b, 76%^c 52±2%^d, 78%^e	 2.4r 74±3%^b, 83%^c 75.5±2.5%^d, 67%^e	 2.4s 35 ±1%^b, 56%^c, 82%^f 26±2 %^d, 84%^e, 74%^g
 2.4t 62.5±3.5%^b, 67%^c 56 ±3%^d, 71%^e	 2.4u 0%^b, 0%^c, 0%^f 0%^d, 0%^e, 0%^g	 2.4v 84.5 ±0.5%^b, 74%^c 82.5±1.5%^d, 75%^e	 2.4w 3±1%^b, trace^c, 31%^f trace^d, trace^e, 26%^g
 2.4x 12.5±3.5%^b, 30%^c 9±2%^d, 36%^e,	 2.4y 19±2%^b, 86%^c 9.5±0.5%^d, 58%^e	 2.4z 0%^b, 14%^c, 0%^d, 8%^e,	 2.4za 69 ±1%^b, 81%^c 36%^d, 80%^e
 2.4zb 0%^b, 0%^c, 0%^f 0%^d, 0%^e, 0%^g	 2.4zc 49±1.5%^b, 66%^c,^f 21.5±1.5%^d, 68%^e,^g	 2.4zd 74 ±1%^b, 81%^c 79.5 ±0.5%^d, 83.5%^e	 2.4ze 47±1%^b, 44%^c 37.5 ±1.5%^d, 35%^e

^aReaction conditions: Benzyl alcohol (2 mmol), 1-phenylethanol derivatives (2 mmol), NaO^tBu (0.2 mmol), and Cr catalyst (0.005 mol%) at 140 °C. Yield determined from ^1H NMR analysis using toluene as a standard. Yields reported are the average of two runs. ^bConventional heating conditions with **2.5** as catalyst after 3 h. ^cMicrowave conditions with **2.5** as catalyst after 1.5 h. ^dConventional heating conditions with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst after 3 h. ^eMicrowave conditions with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst after 1.5 h. ^fConventional heating conditions, 10 mol% NaO^tBu , with **2.5** as catalyst after 24 h. ^gConventional heating conditions, 10 mol% NaO^tBu , with $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst after 24 h.

benzyl alcohol (4 mmol), 1-phenylethanol (4 mmol), 5 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in the presence of **2.5** mol% NaO^tBu (Figure 2.4) shows peak at $m/z = 243.0730$, $m/z = 431.5330$, $m/z = 687.3843$ which corresponds to the *in-situ*³⁰ formed molecular species **2.9a**, **2.9a'** and **2.9a''**. After one hour of heating the reaction mixture at 140 °C, HRMS analysis demonstrates peaks at $m/z = 243.0703$, $m/z = 352.2153$, $m/z = 431.5328$ and $m/z = 766.2749$ which corresponds to the species **2.9a**, **2.13a**, **2.9a'** and **2.13a'** respectively, formed by the complexation³⁰ of the reactants as well as the products with Cr. These results are very similar to our recent report on

CoCl_2 catalysed β -alkylation of 1-phenyl ethanol with benzyl alcohol.³⁰ Similarly, the HRMS analysis of the reaction mixture containing benzyl alcohol (4 mmol), 1-phenyl ethanol (4 mmol), 5 mol% **2.5** and 5 mol% NaO^tBu , at $t = 0$ shows peak at $m/z = 443.1747$ corresponding to the species **2.6b** (Figure 2.5). Then the reaction mixture was heated at 140°C for 1 hour whose HRMS analysis gave peaks at $m/z = 457.1656$, $m/z = 679.2920$ and $m/z = 859.3874$

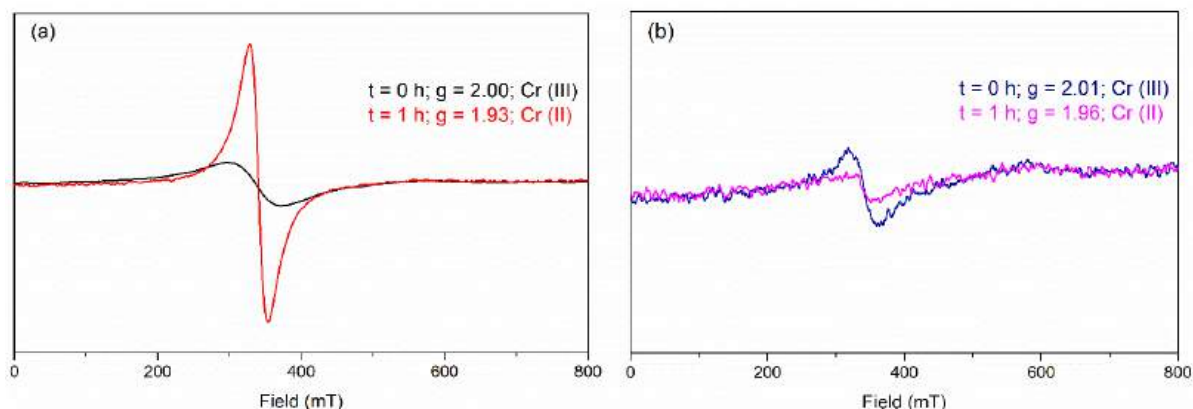


Figure 2.3. EPR analysis of reaction mixture containing benzyl alcohol (4 mmol), 1-phenylethanol (4 mmol), NaO^tBu (0.4 mmol), and Cr catalyst (5 mol%) in air (a) $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ after 0 h (black line) at room temperature and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ after 1 h at 140°C (red line). (b) **2.5** after 0 h (blue line) at room temperature and **2.5** after 1 h at 140°C (magenta line). The X-band EPR spectra was recorded on a JESFA200 ESR spectrometer at 77K with microwave power of 0.998 mW and microwave frequency of 9.14 GHz.

which corresponds to the molecular species **2.6b'**, **2.13b** and **2.13b'** respectively (Figure 2.5). HRMS analysis of the reaction mixture obtained from the β -alkylation of 1-phenyl ethanol with benzyl alcohol catalysed independently by **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ clearly indicate the molecular nature of the catalysts involved. Further the retention of the pincer fragments in reactions catalysed by **2.5** indicate the integrity of the pincer complex under the reaction conditions. The absence of any heterogeneous catalysts and the involvement of well-defined molecular catalysts in the β -alkylation of 1-phenyl ethanol with benzyl alcohol catalysed independently by **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ were fortified by hot filtration tests^{30, 40-41} and mercury-drop experiments (Table 2.5). In the hot-filtration test,⁴¹⁻⁴² the reaction mixtures containing 5 mmol benzyl alcohol, 5 mmol 1-phenyl ethanol, 5 mol% NaO^tBu and either $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.005 mol%) or **2.5** (0.005 mol%) were filtered under hot condition after 30 minutes of heating at 140°C . Heating of the filtrate was then resumed leading to yields of **2.4** that were comparable to the reactions where filtration was not performed (entries 2 and 5 Vs. entries 1 and 4, Table 2.5). On a similar note, there was hardly any drop in the yield upon addition of excess mercury

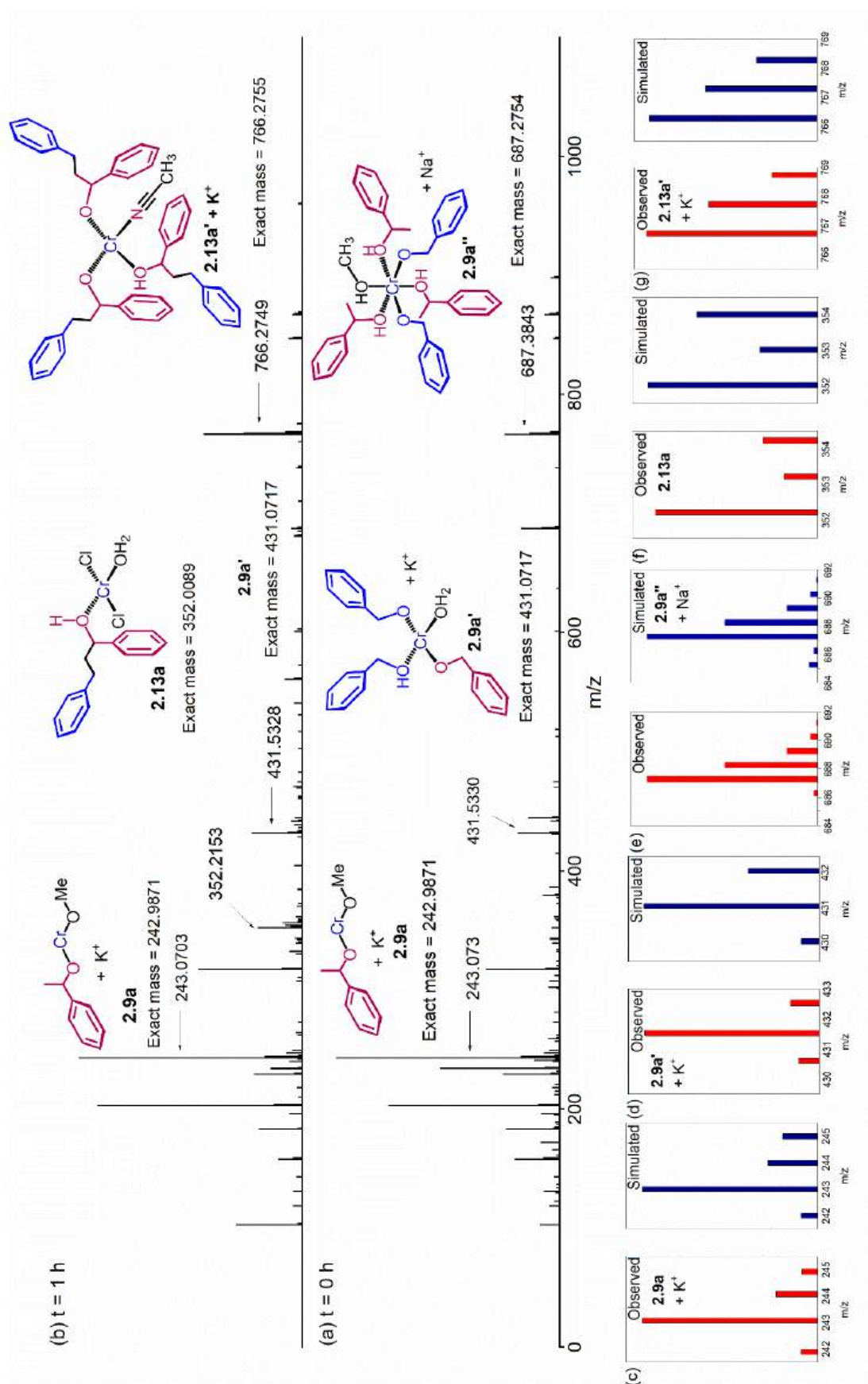
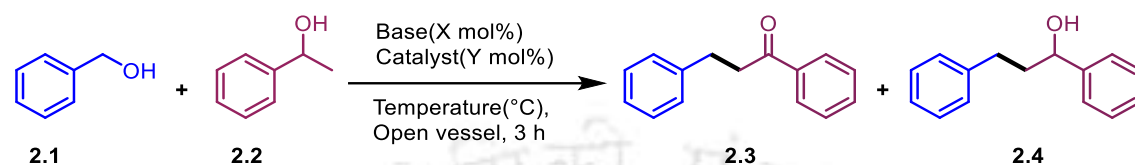


Figure 2.4. HRMS analysis of a mixture of **2.1** (5 mmol) and **2.2** (5 mmol) in the presence of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%) and NaO^tBu (0.5 mmol) after (a) 0 h at room temperature and (b) 1 h at 140 °C. HRMS (ESI) expanded spectra [Observed (red) and Simulated (blue)] of m/z (c) 242.9871 (d) 431.0717 (e) 352.0089 (f) 687.3843 (g) 766.2755.

to the reaction catalysed independently by **2.5** and $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (entries 3 and 6 Vs. entries 1 and 4, Table 2.5).

Table 2.5. Effect of hot filtration and mercury drop test in the chromium catalysed solvent-free β -alkylation of 1-phenyl ethanol with benzyl alcohol under conventional heating ^a



Entry	Base (5 mol%) ^b	Catalyst (0.005 mol %) ^b	Yield(%) ^c and (TON) ^f		Selectivity of 2.4 = ((Yield of 2.4 /Total yield 2.3 + 2.4)*100)
			2.4	2.3	
1	NaO ^t Bu	2.5	84±0.3 (16800)	8±1 (1600)	91
2 ^d	NaO ^t Bu	2.5	82 (16400)	11 (2200)	88
3 ^e	NaO ^t Bu	2.5	81 (16200)	6 (1200)	93
4	NaO ^t Bu	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$	79±2 (15800)	12±1 (2400)	86
5 ^d	NaO ^t Bu	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$	83 (16600)	9 (1800)	90
6 ^e	NaO ^t Bu	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$	80 (16000)	6 (1200)	93

^aReaction Conditions: Benzyl alcohol (2 mmol), 1-phenyl ethanol (2 mmol), base (5 mol%), and Cr catalyst (0.005 mol%) were heated together in air at 140 °C for 3 hours. ^bMol% of base and catalyst are with respect to total alcohol content (**2.1**+**2.2**). ^cYield determined from ¹H NMR analysis using toluene as a standard. Yields reported are the average of two runs. ^dResult obtained from heating the filtrate for 2.5 h post hot-filtration after 30 minutes of reaction. ^eReaction performed in the presence of excess mercury. ^fTON are written in the parenthesis.

EPR analysis of the reaction catalysed by $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ at $t = 0$ h and $t = 1$ h points to the involvement of Cr(III) ($g = 2.0098$)⁴² and Cr(II) ($g = 1.98056$)⁴³⁻⁴⁶ species respectively (Figure 2.3a and 2.3b). Similarly, EPR analysis of the **2.5** catalysed reactions provides evidence for the presence of Cr (III) ($g = 2.01434$)⁴² and Cr (II) ($g = 1.98591$)⁴³⁻⁴⁶ species at $t = 0$ h and $t = 1$ h respectively (Figure 2.3c and 2.3d). In addition, independent magnetic moment measurements of a solution containing **2.5** and **2.5** + NaOH in $\text{CD}_3\text{OH}/t$ -butanol (98:2) mixture determined by Evan's method. Magnetic moment was found to be $3.4 \mu\text{B}$ (that corresponds to an octahedral Cr (III) complex) at room temperature and $4.8 \mu\text{B}$ ⁴² (that corresponds to a high-spin octahedral Cr (II) complex) after heating at 140 °C respectively.

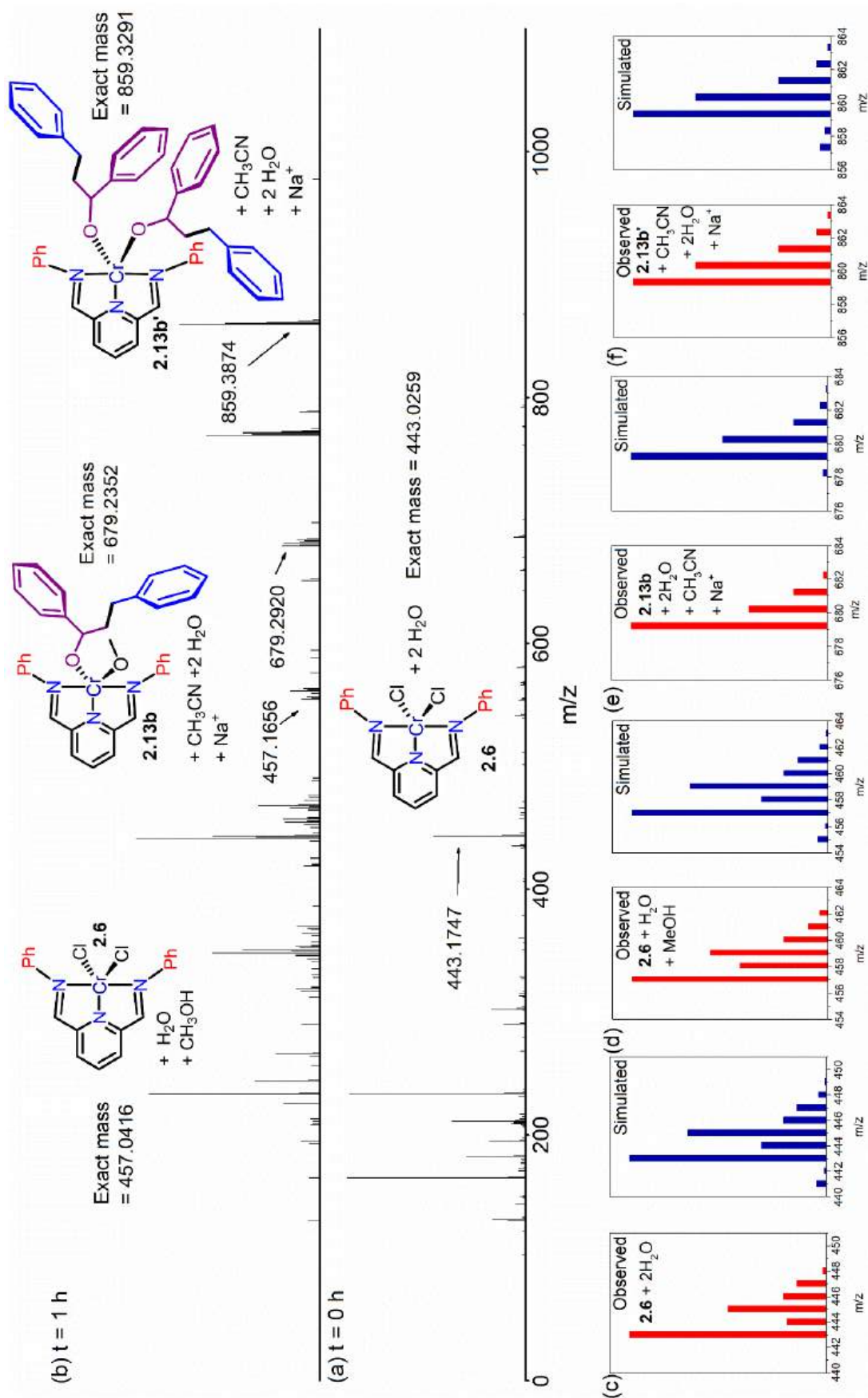


Figure 2.5. HRMS analysis of a mixture of **2.1** (5 mmol) and **2.2** (5 mmol) in the presence of **2.5** (5 mol%) and NaO'Bu (0.5 mmol) after (a) 0 h at room temperature and (b) 1 h at 140 °C. HRMS (ESI) expanded spectra [Observed (red) and Simulated (blue)] of m/z (c) 443.0259 (d) 457.0416 (e) 679.2352 (f) 859.3291.

This is indicative of the reduction of Cr (III) precursor to an active Cr (II) species during the course of the reaction that bears a stark similarity to a recent report with ruthenium-based catalysts.⁴⁷ Interestingly, all the intermediates observed in the HRMS analysis (Figure 2.4 and 2.5) correspond to Cr (II) species. Further information on the reaction mechanism was obtained from the reaction of benzyl alcohol (**2.1**) with acetophenone (**2.2'**) catalysed independently by **2.5** (equation 1, Scheme 2.34) and CrCl₃.6H₂O (equation 2, Scheme 2.34).

In both these reactions **2.4** was observed as the major product, **2.3** being the minor product with trace amounts of 1-phenyl ethanol (**2.2**). Hydrogen was detected along with the dehydrogenated form of the alcohol, when only benzyl alcohol (**2.1**) or 1-phenyl ethanol (**2.2**) was allowed to react independently under the standard conditions either with **2.5** (equations 3 and 5, Scheme 2.34) or with CrCl₃.6H₂O (equations 4 and 6, Scheme 2.34). Deuterium labelling experiments were performed to attain further insight into the reaction mechanism (equation 7, Scheme 2.34). Upon heating a reaction mixture containing **2.1** (2 mmol), **2.1a** (2 mmol), **2.2** (4 mmol) and **2.5** (0.005 mol%) in the presence of 5 mol% NaO^tBu at 140 °C for 3h, the product **2.4a** was obtained in 75% isolated yield.

The ¹H NMR analysis of **2.4a** indicated a KIE of 7.33 which clearly points to the involvement of a C-H making or a breaking process in the rate-determining step (RDS). Thus, from HRMS, EPR, hot-filtration and mercury-drop studies, one can infer that both **2.5** and its precursor CrCl₃.6H₂O generates respective homogeneous molecular Cr (II) species which are active for the β -alkylation reaction. This forms the basis of the proposed mechanism. In the presence of **2.1** and **2.2**, CrCl₃.6H₂O would readily form several derivatives of **2.7** (Scheme 2.35) as inferred from HRMS analysis (Figure 2.3, t = 0 h) which is in line with our previous studies with CoCl₂.¹⁶ In the presence of NaO^tBu, both the Cr (III) precursors **2.5** and **2.7**, have shown to lead to a Cr (II) active species **2.6** and **2.8** respectively (Figure 2.4 and 2.5 and Scheme 2.35). Salt metathesis of **2.6** and **2.8** with NaO^tBu in the presence of **2.1** and **2.2** would lead to the corresponding alkoxides **2.9** and **2.10** (Scheme 2.35). For the sake of simplicity, only the sites where reaction occurs are shown in intermediates **2.9-2.13** and neither the pincer backbone of the derivatives of **2.6** nor the three ligands of the derivatives of **2.8** have been shown.

A β -hydride elimination from **2.9/2.10** gives the Cr-H species **2.11** along with the extrusion of corresponding benzaldehyde (**2.1'**) or acetophenone (**2.2'**). Alcoholysis of **2.11** with **2.1/2.2** would result in evolution of hydrogen along with the regeneration of **2.9/2.10**. Notably the hydrogen gas was detected by GC in the independent dehydrogenation reactions of **2.1** and **2.2** catalysed by both **2.5** (equation 3 and 5, Scheme 2.34) and CrCl₃.6H₂O (equation 4 and 6,

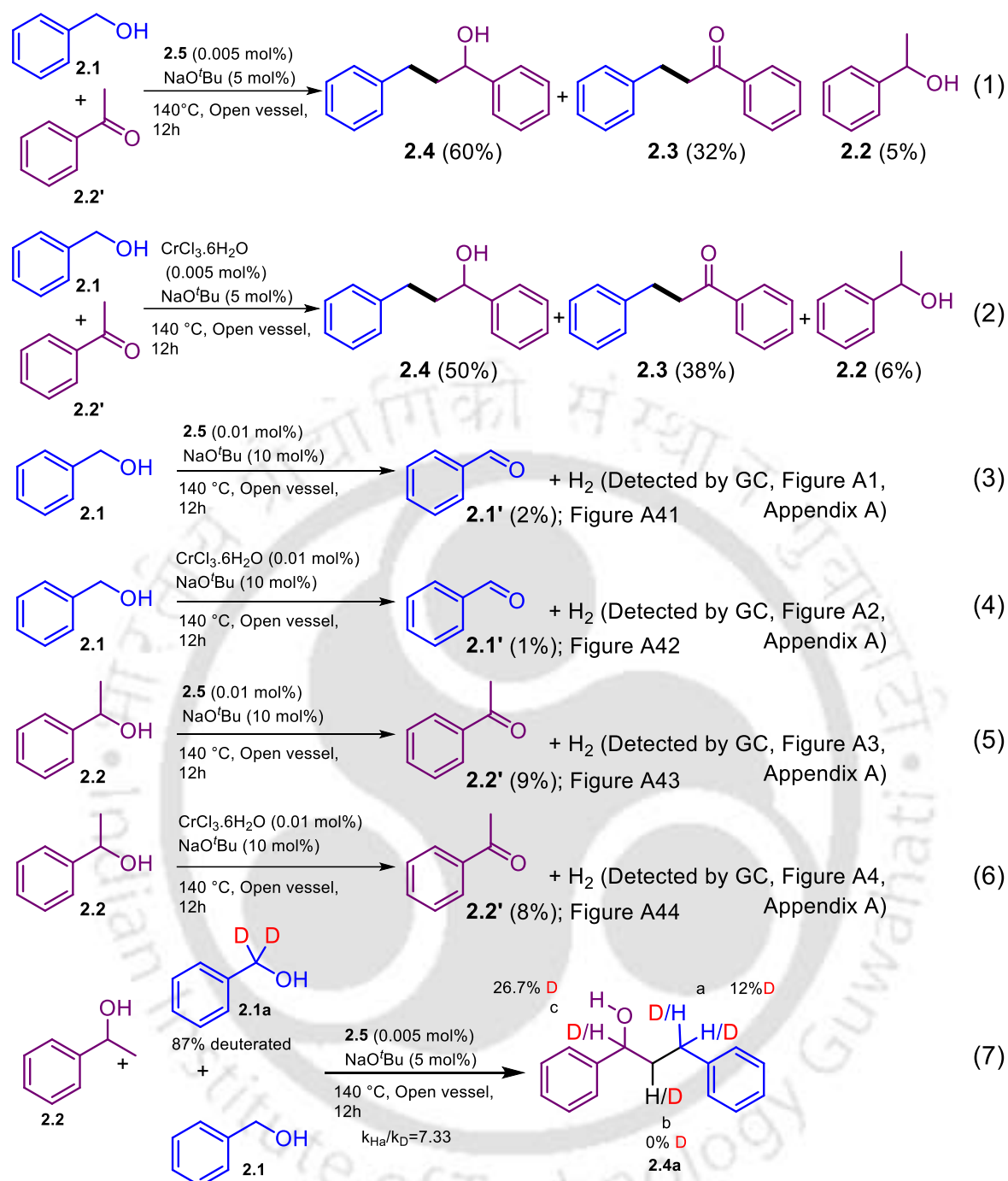
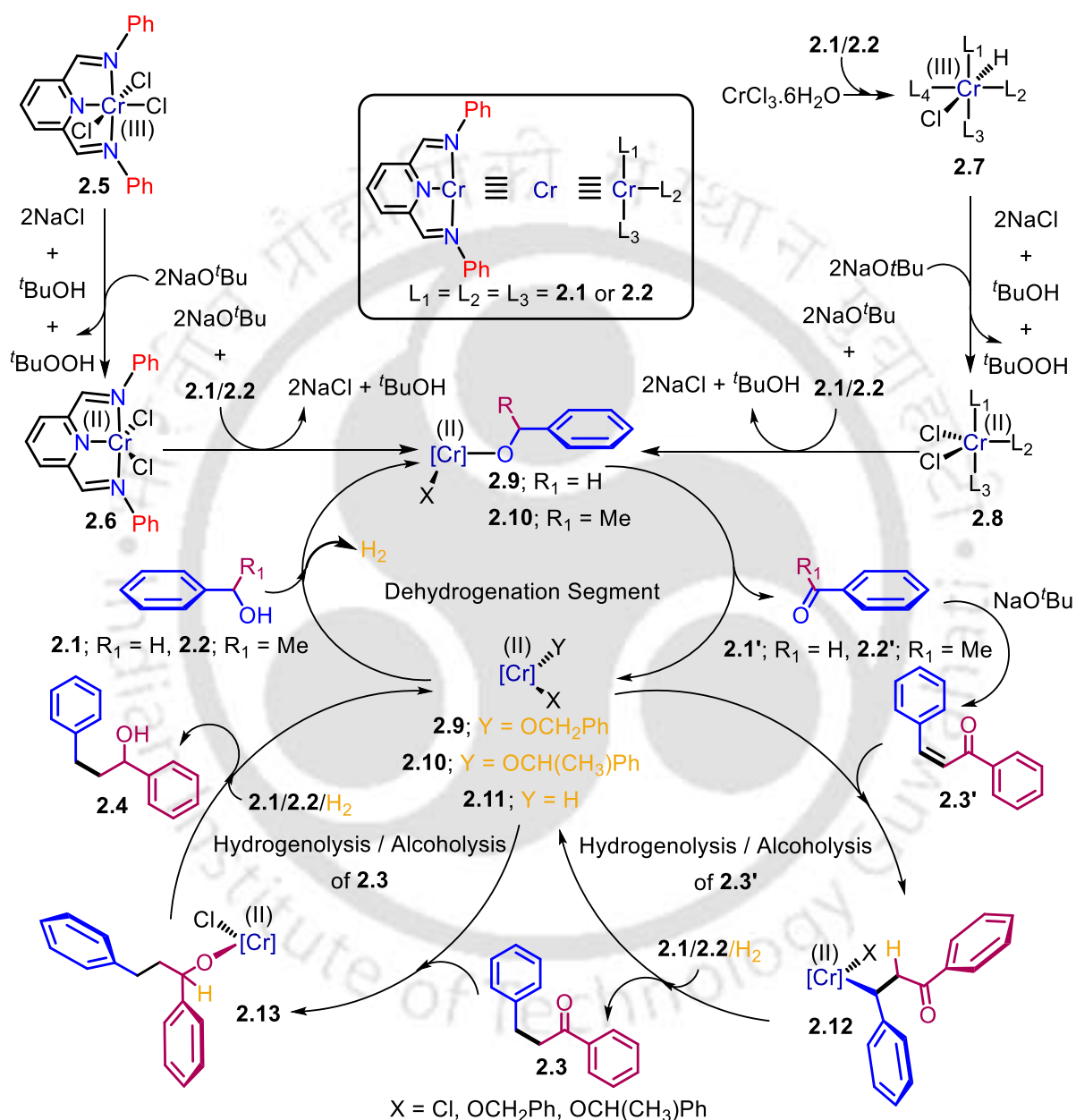


Figure A45 and Section A3, Appendix A

Scheme 2.34. Control Experiments.

Scheme 2.34). An uncatalysed condensation of **2.1'** with **2.2'** in the presence of base results in the formation of **2.3'**. Insertion of **2.3'** into the Cr-H bond in **2.11** would lead to species **2.12** which upon σ -bond metathesis with H₂/**2.1**/**2.2** results in formation of **2.3** along with the regeneration of **2.11**/**2.9**/**2.10**. A similar insertion of **2.3** into **2.11** followed by

alcoholysis/hydrogenolysis sequence can account for the formation of **2.4**. While open-vessel reaction conditions suggest the involvement of alcoholysis step as a major contributor to product formation, the KIE of 7.33 coupled with observation of several derivatives of **2.13** in the HRMS analysis are indicative of the insertion of **2.3** into the Cr-H bond in **2.11** as the RDS.



Scheme 2.35. Plausible mechanism involved in the chromium catalysed β -alkylation of 1-phenylethanol with benzyl alcohol.

2.3.5. Conclusions

This is the first report on a chromium catalysed β -alkylation of secondary alcohols with primary alcohols. High yields (ca. 90%) of the β -alkylated product was obtained with a selectivity of 91% at very low loadings (0.005 mol%) of the pincer-chromium catalyst based on *bis*(imino-pyridine) under microwave conditions in the presence of 5 mol% NaO^tBu. In comparison, the precursor CrCl₃.6H₂O showed a lower activity (0.84 folds). Nevertheless, the reaction catalysed by both the pincer chromium complex and its precursor are based on well-defined molecular Cr(II) complexes as indicated by HRMS, EPR, hot filtration and mercury-drop studies. Open-vessel reaction conditions suggest that alcoholysis appears to be the most preferred pathway. Deuterium labelling experiments suggest the involvement of the C-H bond activation in the rate determining step with a KIE of 7.33. Analysis of the resting-state species as detected by HRMS analysis suggest that the insertion of the β -alkylated ketone into the Cr-H bond is likely to be the RDS. The fact that CrCl₃.6H₂O itself is active and that it is based on a readily available, abundant and inexpensive 3d-metal offers immense promise and exciting possibilities in accomplishing related reactions.

2.4. Experimental

2.4.1. Materials and methods.

All manipulations were carried out in air. All the chemicals were purchased from MERCK or Sigma-Aldrich and used as such. The solvent such as tetrahydrofuran (THF) was purchased from MERCK and was dried via double distillation over Na/Benzophenone prior to experiment.

2.4.2. Physical Measurements.

¹H, ¹³C were recorded either on a Bruker ASCEND 600 operating at 600 MHz for ¹H and 151 MHz for ¹³C or on a Bruker AVANCE 400 operating at 400 MHz for ¹H and 100 MHz for ¹³C. Chemical shifts (δ) are reported in ppm, spin-spin coupling constants (J) are expressed in Hz, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet and q = quartet. HRMS measurements were recorded using an Agilent Accurate-Mass Q-TOF ESI-MS 6520. The X-band EPR spectra was recorded on a JES-FA200 ESR spectrometer. Solidstate magnetic susceptibility was recorded using a Sherwood Scientific magnetic balance MSB-1 at room temperature. GC analysis (TCD detection) was performed on an Agilent 7820-GC instrument fitted with Agilent Front SSZ Inlet N2 using a HPPLLOT Q column (30 m length x 530 μ m x 40 μ m). Agilent 7820-GC back detector TCD Oven temperature: 50 °C Time at starting temp: 0 min, Hold time = 10 min, Inlet temperature: 100 °C, Detector temperature

(TCD): 250 °C, Detector temperature (FID): 300 °C, Flow rate (carrier): 5 mL/min (N₂) and Split ratio: 10.

2.4.3. Synthetic procedures.

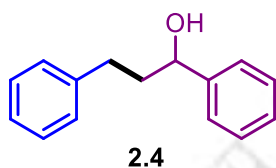
Synthesis of (*Ph*²NNN)CrCl₃] (2.5). To a solution of *Ph*²NNN ligand³⁷⁻³⁸ (0.15 g, 0.5256 mmol) in 5 mL of anhydrous THF was added CrCl₃.6H₂O (0.142 g, 0.5256 mmol) in a pear-shaped flask under argon atmosphere. The resultant mixture was stirred at room temperature for 12 h. After stirring for overnight, the solvent was evaporated under reduced pressure. The olive green solid obtained was washed with diethyl ether (3 x 2 mL) to remove the excess ligand, if any followed by evacuation. An olive green solid (0.1945 g, yield = 84%) was obtained. EPR analysis revealed a single peak with a g value of 2.01998 (Figure 2.1). HRMS (ESI) m/z calculated for [2.5a]⁺: 407.0048, found 406.9962; calculated for [2.5b + CH₃CN]⁺: 429.1019, found m/z = 429.1622; calculated for [2.5b + CH₃CN + CH₃OH]⁺: 461.1280, found m/z = 461.1829; calculated for [2.5b + CH₃CN + 3H₂O + Na]⁺: 506.2228, found m/z = 506.2228. Magnetic susceptibility μ_{eff} = 3.2 μ B (Solid-State magnetic balance), 3.4 μ B (Evan's method)

2.4.4. General procedure for the chromium catalysed β -alkylation of alcohols under conventional heating. In a 25 mL two-necked round bottom flask containing required amount of the catalyst 2.5 (0.0002 g, 0.0004 mmol) or CrCl₃.6H₂O (0.0001 g, 0.0004 mmol) withdrawn from their respective stock solution in benzyl alcohol, 5 mol% NaO^tBu (0.0384 g, 0.4 mmol) was added followed by the addition of benzyl alcohol (0.413 mL, 4 mmol) and 1-phenyl ethanol (0.482 mL, 4 mmol). The reaction was then allowed to stir at 140 °C for 3 h in air. After 3 h, the reaction mixture was brought to room temperature and a small aliquot was withdrawn from the mixture for NMR analysis. The yield of 2.4 was determined from ¹H NMR analysis by adding 0.01 mL of toluene in the NMR tube as a standard and CDCl₃ as the NMR solvent. Then the β -alkylated alcohols were purified by silica gel column chromatography using 0-5% ethyl acetate in *n*-hexane as eluent.

2.4.5. General procedure for the chromium catalysed β -alkylation of alcohols under microwave heating. In a 10 mL microwave vial containing the required amount of the catalyst 2.5 (0.00008 g, 0.0002 mmol) or CrCl₃.6H₂O (0.000053 g, 0.0002 mmol) withdrawn from their respective stock solution in benzyl alcohol, 5 mol% NaO^tBu (0.0192 g, 0.2 mmol) was added followed by the addition of benzyl alcohol (0.207 mL, 2 mmol) and 1-phenyl ethanol (0.241

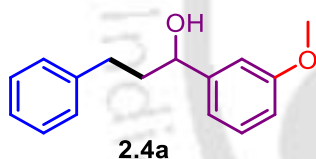
mL, 2 mmol). The reaction was then allowed to stir at 140 °C for 1.5 h under microwave conditions (75 W, 20 psi) in air. After 1.5 h, the reaction mixture was brought to room temperature and a small aliquot was drawn from the mixture for NMR analysis. The yield of **2.4** was determined from ^1H NMR analysis by adding 0.01 mL of toluene in the NMR tube as an internal standard and CDCl_3 as the NMR solvent. Then the β -alkylated alcohols were purified by silica gel column chromatography using 0-5% ethyl acetate in *n*-hexane as eluent.

1,3-diphenylpropan-1-ol (**2.4**):²⁷



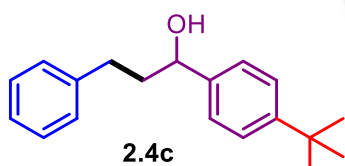
^1H NMR (500 MHz, CDCl_3): δ 7.26 (d, J = 4.3 Hz, 4H), 7.18 (q, J = 6.0 Hz, 3H), 7.10 (d, J = 7.5 Hz, 3H), 4.60 (t, J = 6.4 Hz, 1H), 2.62-2.55 (m, 2H), 2.10 – 1.89 (m, 2H), 1.80 (s, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ [144.7, 141.9, 128.7, 127.8, 126.0] (Ar), 74.0 (CH(OH)), 40.6 (CH₂), 32.2 (CH₂).

1-(3-methoxyphenyl)-3-phenylpropan-1-ol (**2.4a**):²⁷



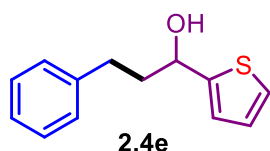
^1H NMR (500 MHz, CDCl_3): δ 7.33 – 7.18 (m, 6H), 6.94 (d, J = 6.5 Hz, 2H), 6.84 (d, J = 8.0 Hz, 1H), 4.69 (s, 1H), 3.83 (s, 3H), 2.80-2.66 (m, 2H), 2.19 – 2.00 (m, 2H), 1.92 (s, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [146.4, 141.9, 129.7, 128.5, 126.0, 118.4, 113.2, 111.5] (Ar), 73.9 (CH(OH)), 55.4 (OCH₃), 40.5 (CH₂), 32.2 (CH₂).

1-(4-(tert-butyl)phenyl)-3-phenylpropan-1-ol (**2.4c**):²⁷



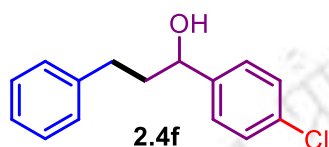
^1H NMR (500 MHz, CDCl_3): δ 7.37 (d, J = 8.2 Hz, 2H), 7.26 (dd, J = 15.2, 7.2 Hz, 4H), 7.18 (dd, J = 13.2, 7.2 Hz, 3H), 4.66 (t, J = 7.8 Hz, 1H), 2.80 – 2.63 (m, 2H), 2.18 – 1.99 (m, 2H), 1.85 (d, J = 2.9 Hz, 1H), 1.32 (s, 9H). $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ [150.8, 142.0, 141.7, 128.6, 128.5, 125.9, 125.8, 125.6] (Ar), 73.8 (CH(OH)), 40.4 (CH₂), 34.7 (C(CH₃)₃), 32.3 (CH₃), 31.5 (CH₂).

3-phenyl-1-(thiophen-2-yl)propan-1-ol (**2.4e**):²⁰



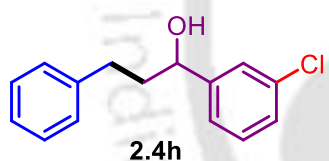
^1H NMR (600 MHz, CDCl_3): δ 7.34 – 7.30 (m, 2H), 7.30 – 7.28 (m, 1H), 7.24 (d, J = 7.9 Hz, 3H), 7.02 – 6.99 (m, 2H), 4.99 – 4.93 (m, 1H), 2.84 – 2.71 (m, 2H), 2.30 – 2.15 (m, 2H), 2.05 (d, J = 4.2 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [148.6, 141.6, 128.6, 126.1, 124.8, 124.1] (Ar), 69.7 (CH(OH)), 40.8 (CH_2), 32.1 (CH_2).

1-(4-chlorophenyl)-3-phenylpropan-1-ol (2.4f):²⁷



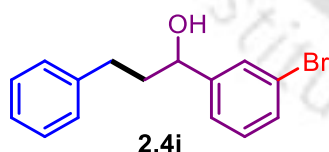
^1H NMR (500 MHz, CDCl_3): δ 7.32 (d, J = 8.6 Hz, 2H), 7.30 – 7.25 (m, 4H), 7.21 – 7.17 (m, 3H), 4.67 (ddd, J = 8.3, 5.1, 3.3 Hz, 1H), 2.76–2.63 (m, 2H), 2.14 – 1.95 (m, 2H), 1.88 (d, J = 3.5 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (126 MHz, CDCl_3): δ [143.2, 141.6, 133.4, 128.8, 128.6, 128.5, 127.4, 126.1] (Ar), 73.3 (CH(OH)), 40.6 (CH_2), 32.1 (CH_2).

1-(3-chlorophenyl)-3-phenylpropan-1-ol (2.4h):²⁰



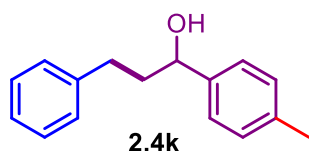
^1H NMR (600 MHz, CDCl_3): δ 7.38 (s, 1H), 7.34 – 7.26 (m, 4H), 7.23 (dd, J = 13.4, 8.0 Hz, 4H), 4.69 (dt, J = 8.0, 4.1 Hz, 1H), 2.80–2.68 (m, 2H), 2.16 – 2.00 (m, 2H), 1.98 (d, J = 3.3 Hz, 1H).

1-(3-bromophenyl)-3-phenylpropan-1-ol (2.4i):²⁷



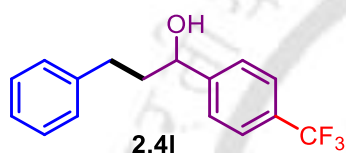
^1H NMR (600 MHz, CDCl_3): δ 7.54 (s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.26 – 7.20 (m, 4H), 4.68 (dt, J = 8.2, 4.4 Hz, 1H), 2.81 – 2.67 (m, 2H), 2.16 – 1.97 (m, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [147.1, 141.6, 130.8, 130.2, 129.2, 128.6, 128.5, 126.1, 124.6, 122.8] (Ar), 73.3 (CH(OH)), 40.6 (CH_2), 32.0 (CH_2).

3-phenyl-1-(p-tolyl)propan-1-ol (2.4k):²⁰



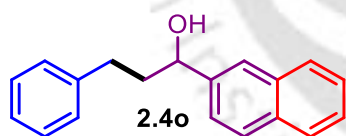
^1H NMR (600 MHz, CDCl_3): δ 7.31 (t, $J = 7.6$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.21 (dd, $J = 16.2, 7.7$ Hz, 5H), 4.68 (t, $J = 5.2$ Hz, 1H), 2.80 – 2.66 (m, 2H), 2.39 (s, 3H), 2.20 – 2.02 (m, 2H), 1.91 (s, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [142.0, 141.7, 137.4, 129.3, 128.6, 128.5, 126.0, 125.9] (Ar), 73.8 (CH(OH)), 40.5 (CH_2), 32.2 (CH_2), 21.2 (CH_3).

3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (2.4l):²⁰



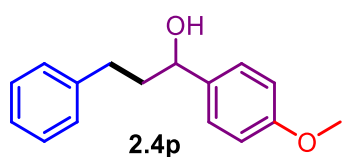
^1H NMR (600 MHz, CDCl_3): δ 7.61 (d, $J = 8.1$ Hz, 2H), 7.46 (d, $J = 8.2$ Hz, 2H), 7.30 (t, $J = 7.6$ Hz, 2H), 7.20 (t, $J = 8.1$ Hz, 3H), 4.76 (dt, $J = 8.1, 4.3$ Hz, 1H), 2.79 – 2.67 (m, 2H), 2.15 – 2.00 (m, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [148.6, 141.4, 128.6, 128.5, 126.3, 126.2, 125.6, 125.6, 125.56, 125.53] (Ar), 73.3 (CH(OH)), 40.7 (CH_2), 32.0 (CH_2).

1-(naphthalen-2-yl)-3-phenylpropan-1-ol (2.4o):²⁰



^1H NMR (600 MHz, CDCl_3): δ 7.88 – 7.77 (m, 4H), 7.59 – 7.48 (m, 3H), 7.39 – 7.21 (m, 5H), 4.89 (dt, $J = 7.9, 3.1$ Hz, 1H), 2.82 – 2.70 (m, 2H), 2.30 – 2.15 (m, 2H), 2.03 (s, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [142.0, 141.9, 133.4, 133.2, 128.6, 128.54, 128.52, 128.1, 127.8, 126.3, 126.0, 124.8, 124.2] (Ar), 74.1 (CH(OH)), 40.5 (CH_2), 32.2 (CH_2).

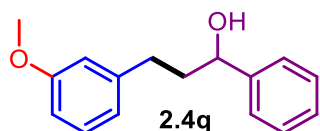
1-(4-methoxyphenyl)-3-phenylpropan-1-ol (2.4p):²⁷



^1H NMR (600 MHz, CDCl_3): δ 7.32 – 7.28 (m, 4H), 7.21 (d, $J = 7.1$ Hz, 3H), 6.92 (d, $J = 8.7$ Hz, 2H), 4.66 (t, $J = 6.6$ Hz, 1H), 3.83 (s, 3H), 2.76 – 2.64 (m, 2H), 2.20 – 2.00 (m, 2H), 1.86 (s, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [159.2,

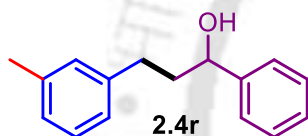
142.0, 136.8, 128.6, 127.3, 126.0, 114.0] (Ar), 73.6 (CH(OH)),
55.4 (OCH₃), 40.5 (CH₂), 32.2 (CH₂).

3-(3-methoxyphenyl)-1-phenylpropan-1-ol (2.4q):²⁷



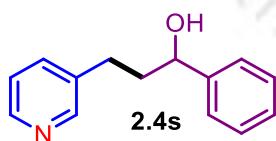
¹H NMR (500 MHz, CDCl₃): δ 7.25 – 7.06 (m, 6H), 6.70 – 6.61 (m, 3H), 4.57 – 4.51 (m, 1H), 3.66 (s, 3H), 2.65 – 2.48 (m, 2H), 2.14 (s, 1H), 1.95 (dtd, J = 49.6, 14.1, 7.3 Hz, 2H).
¹³C{H} NMR (126 MHz, CDCl₃): δ [159.7, 143.5, 129.4, 128.5, 127.6, 126.0, 120.9, 114.3, 111.2] (Ar), 73.8 (CH(OH)), 55.2 (OCH₃), 40.4 (CH₂), 32.1 (CH₂).

1-phenyl-3-(m-tolyl)propan-1-ol (2.4r):²⁰



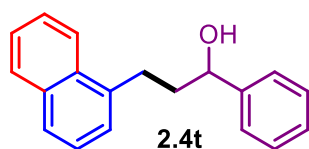
¹H NMR (600 MHz, CDCl₃): δ 7.36 (d, J = 4.3 Hz, 4H), 7.32 – 7.27 (m, 1H), 7.17 (t, J = 7.4 Hz, 1H), 7.03 – 6.98 (m, 3H), 4.72 – 4.68 (m, 1H), 2.75-2.61 (m, 2H), 2.32 (s, 3H), 2.16 – 2.00 (m, 3H), 1.85 (s, 1H).
¹³C{H} NMR (151 MHz, CDCl₃): δ [144.7, 141.8, 138.1, 129.4, 128.6, 128.4, 127.8, 126.7, 126.1, 125.6] (Ar), 74.1 (CH(OH)), 40.6 (CH₂), 32.1 (CH₂), 21.5 (CH₃).

1-phenyl-3-(pyridin-3-yl)propan-1-ol (2.4s):²⁷



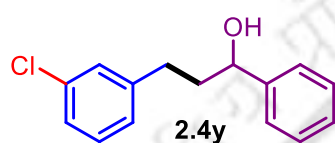
¹H NMR (600 MHz, CDCl₃): δ 8.43 – 8.38 (m, 2H), 7.52 (dt, J = 7.9, 2.0 Hz, 1H), 7.37 (d, J = 4.5 Hz, 4H), 7.32 – 7.28 (m, 1H), 7.21 (dd, J = 7.8, 4.8 Hz, 1H), 4.70 (dd, J = 8.0, 5.2 Hz, 1H), 2.80-2.68 (m, 3H), 2.17-1.99 (m, 3H).
¹³C{H} NMR (151 MHz, CDCl₃): δ [147.4, 144.7, 137.4, 136.2, 128.8, 127.9, 126.1] (Ar), 73.6 (CH(OH)), 40.3 (CH₂), 29.4 (CH₂).

3-(naphthalen-1-yl)-1-phenylpropan-1-ol (2.4t):²⁰



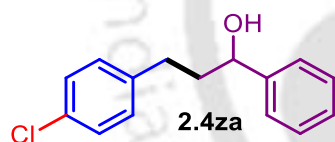
^1H NMR (600 MHz, CDCl_3): δ 8.02 – 7.99 (m, 1H), 7.89 – 7.85 (m, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.53 – 7.47 (m, 3H), 7.43 – 7.35 (m, 6H), 7.34 – 7.30 (m, 1H), 4.83 (dt, J = 8.0, 4.2 Hz, 1H), 3.31 – 3.10 (m, 2H), 2.32 – 2.15 (m, 2H), 1.96 (d, J = 3.3 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [144.6, 138.1, 134.0, 132.0, 128.9, 128.7, 127.8, 126.8, 126.1, 125.9, 125.7, 125.6, 123.9] (Ar), 74.4 (CH(OH)), 40.0 (CH_2), 29.3 (CH_2).

3-(3-chlorophenyl)-1-phenylpropan-1-ol (2.4y):²⁰



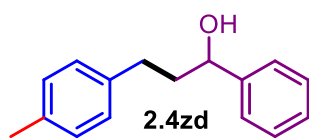
^1H NMR (600 MHz, CDCl_3): δ 7.36 (d, J = 6.5 Hz, 4H), 7.29 (ddd, J = 8.5, 5.8, 2.1 Hz, 1H), 7.22 – 7.15 (m, 3H), 7.07 (dt, J = 7.4, 1.5 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 2.77 – 2.62 (m, 2H), 2.15 – 1.97 (m, 2H), 1.89 (s, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [144.5, 144.0, 134.2, 129.8, 128.7, 127.9, 126.2, 126.0] (Ar), 73.8 (CH(OH)), 40.3 (CH_2), 31.8 (CH_2).

3-(4-chlorophenyl)-1-phenylpropan-1-ol (2.4za):²⁷



^1H NMR (600 MHz, CDCl_3): δ 7.41 – 7.35 (m, 4H), 7.32 (t, J = 7.6 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.70 (ddd, J = 8.2, 5.2, 3.4 Hz, 1H), 2.78 – 2.63 (m, 2H), 2.17 – 1.98 (m, 2H), 1.90 (d, J = 3.3 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [144.5, 140.3, 131.7, 129.9, 128.7, 128.6, 127.9, 126.0] (Ar), 73.8 (CH(OH)), 40.4 (CH_2), 31.5 (CH_2).

1-phenyl-3-(p-tolyl)propan-1-ol (2.4zd):²⁷



^1H NMR (600 MHz, CDCl_3): δ 7.40 – 7.35 (m, 4H), 7.30 (tt, J = 6.5, 3.0 Hz, 1H), 7.12 (s, 4H), 4.71 – 4.67 (m, 1H), 2.76 – 2.62 (m, 2H), 2.35 (s, 3H), 2.17 – 2.00 (m, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, CDCl_3): δ [144.7, 135.4, 129.2, 128.6, 128.4, 127.7, 126.0] (Ar), 73.9 (CH(OH)), 40.6 (CH_2), 31.6 (CH_2), 21.1 (CH_3).

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Appendix A

A1. Gas Chromatography Analysis:

GC analysis (TCD detection) was performed on an Agilent 7820-GC instrument fitted with Agilent Front SSZ Inlet N2 HP-PLOT Q column (30 m length x 530 μm x 40 μm) using the following method:

Agilent 7820-GC back detector TCD

Oven temperature: 50 $^{\circ}\text{C}$

Time at starting temp: 0 min

Hold time = 10 min

Inlet temperature: 100 $^{\circ}\text{C}$

Detector temperature (TCD): 250 $^{\circ}\text{C}$

Detector temperature (FID): 300 $^{\circ}\text{C}$

Flow rate (carrier): 5 mL/min (N₂)

Split ratio: 10

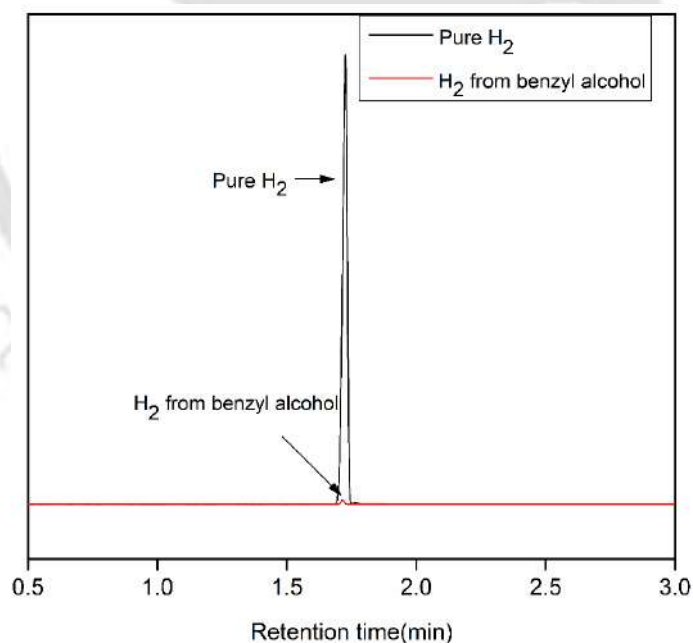


Figure A1: Evidence for H₂ evolution in the dehydrogenation of benzyl alcohol (**2.1**) catalysed by **2.5** (0.01 mol %) and NaO^tBu (10 mol%) at 140 $^{\circ}\text{C}$ via GC analysis.

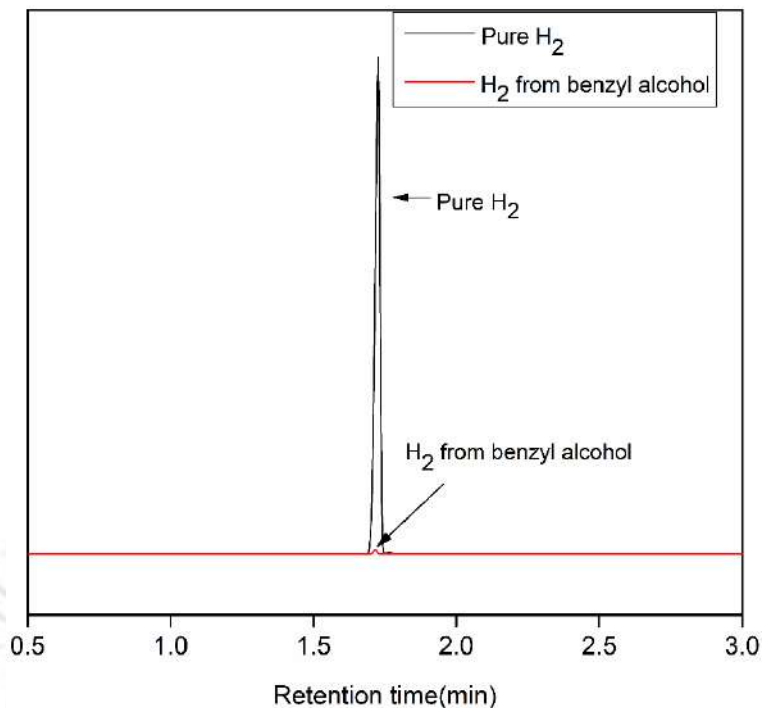


Figure A2: Evidence for H₂ evolution in the dehydrogenation of benzyl alcohol (2.1) catalysed by CrCl₃.6H₂O (0.01 mol %) and NaO^tBu (10 mol%) at 140 °C via GC analysis.

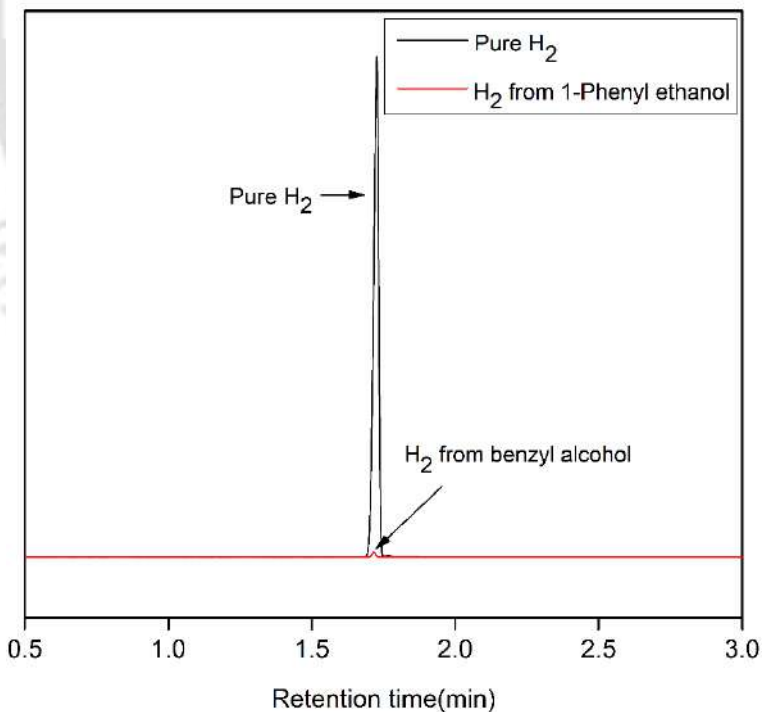


Figure A3: Evidence for H₂ evolution in the dehydrogenation of 1-Phenyl ethanol (2.2) catalysed by 2.5 (0.01 mol %) and NaO^tBu (10 mol%) at 140 °C via GC analysis.

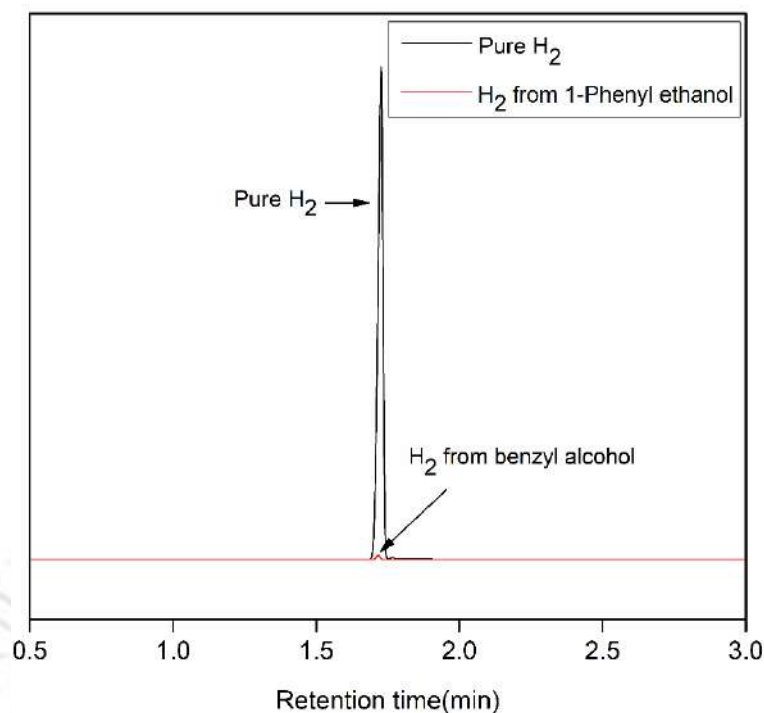


Figure A4: Evidence for H₂ evolution in the dehydrogenation of 1-Phenyl ethanol (**2.2**) catalysed by CrCl₃·6H₂O (0.01 mol %) and NaO^tBu (10 mol%) at 140 °C via GC analysis.

A2. NMR Spectra:

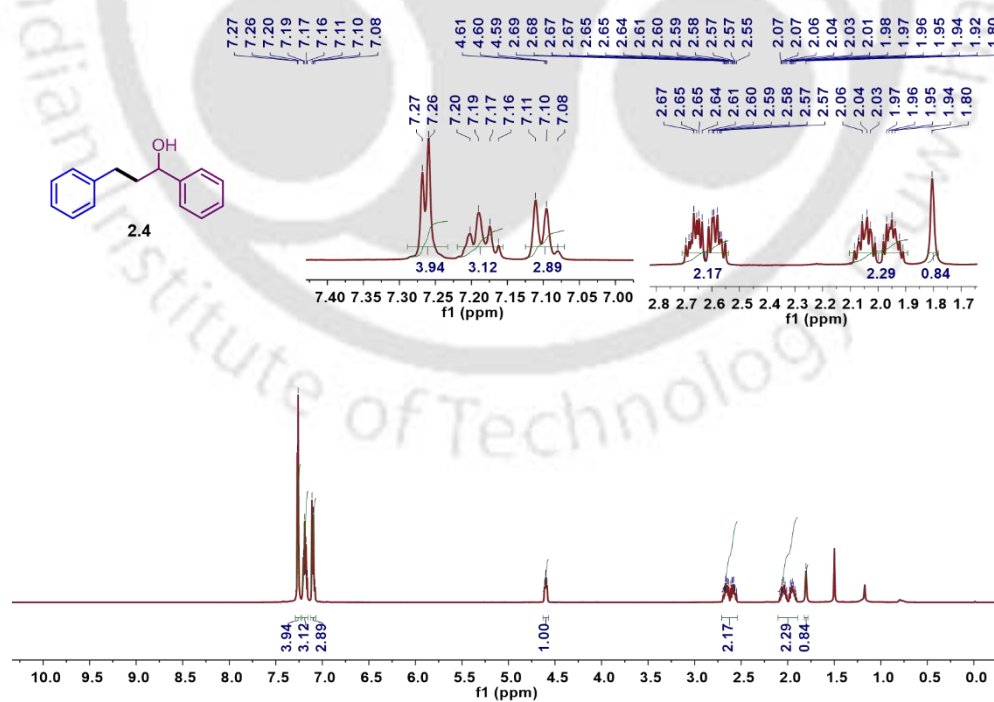


Figure A5. ¹H NMR spectra of 1,3-diphenylpropan-1-ol (**2.4**) recorded in CDCl₃.

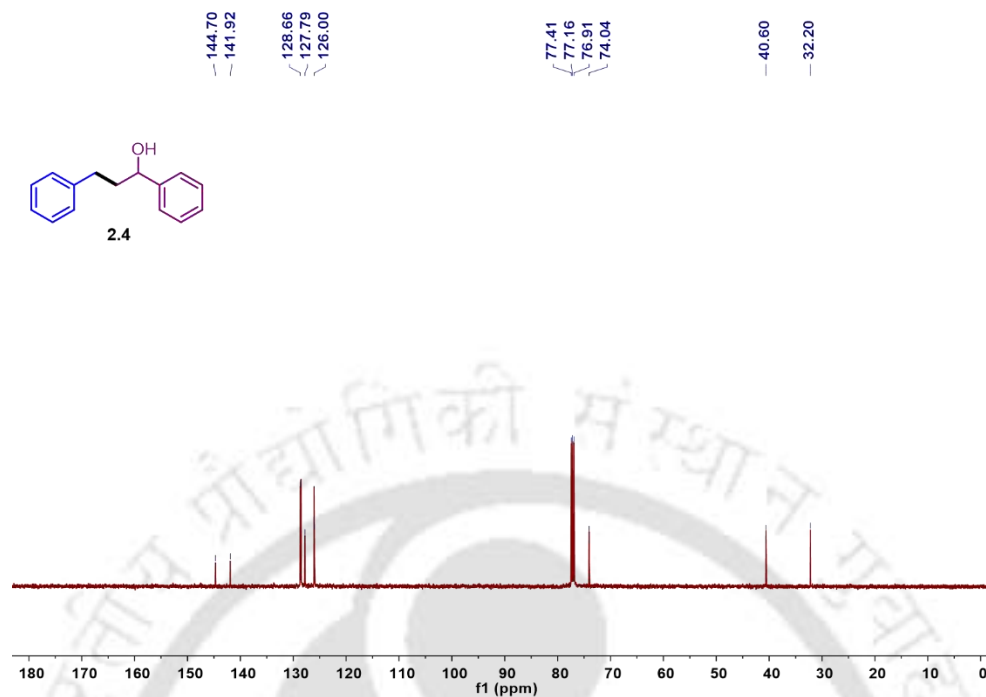


Figure A6. $^{13}\text{C}\{\text{H}\}$ NMR spectra of 1,3-diphenylpropan-1-ol (2.4) recorded in CDCl₃.

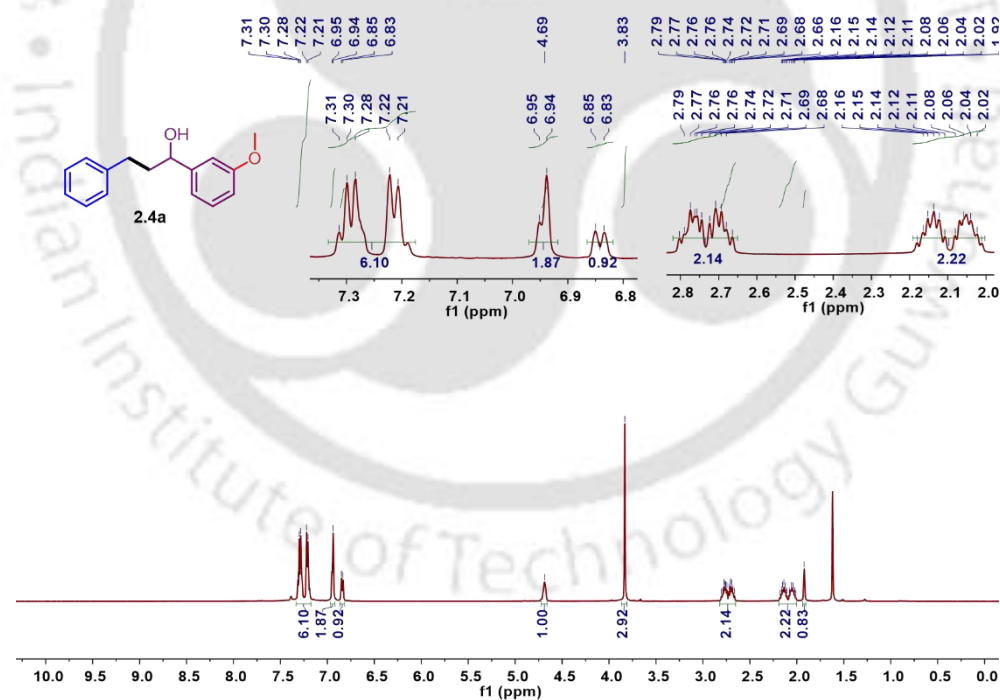


Figure A7: ^1H NMR spectra of 1-(3-methoxyphenyl)-3-phenylpropan-1-ol (2.4a) recorded in CDCl₃.

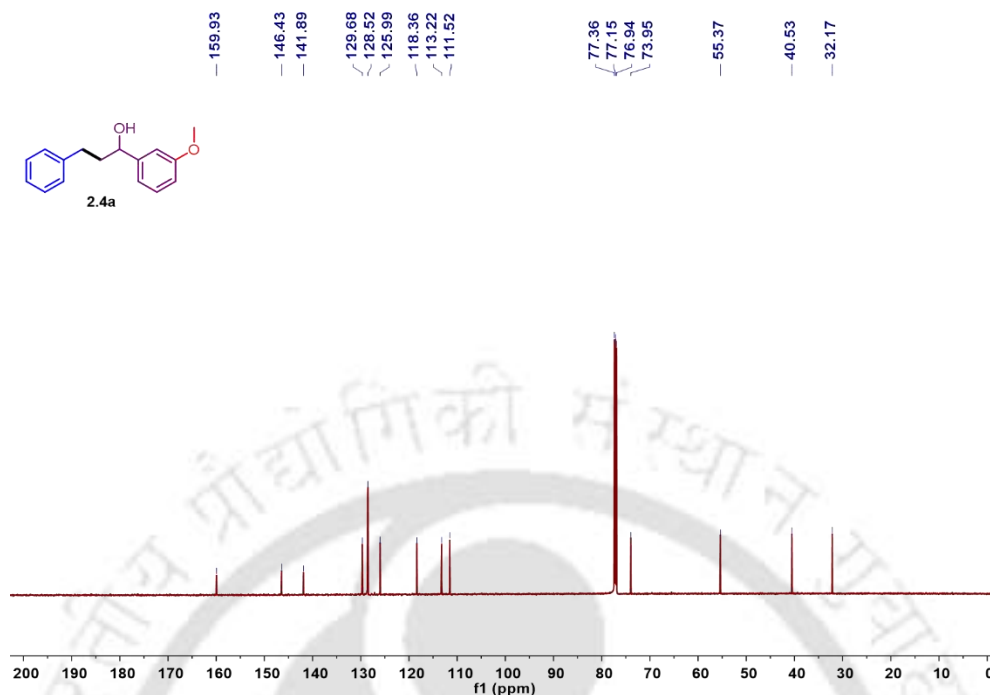


Figure A8: $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of 1-(3-methoxyphenyl)-3-phenylpropan-1-ol (**2.4a**) recorded in CDCl₃.

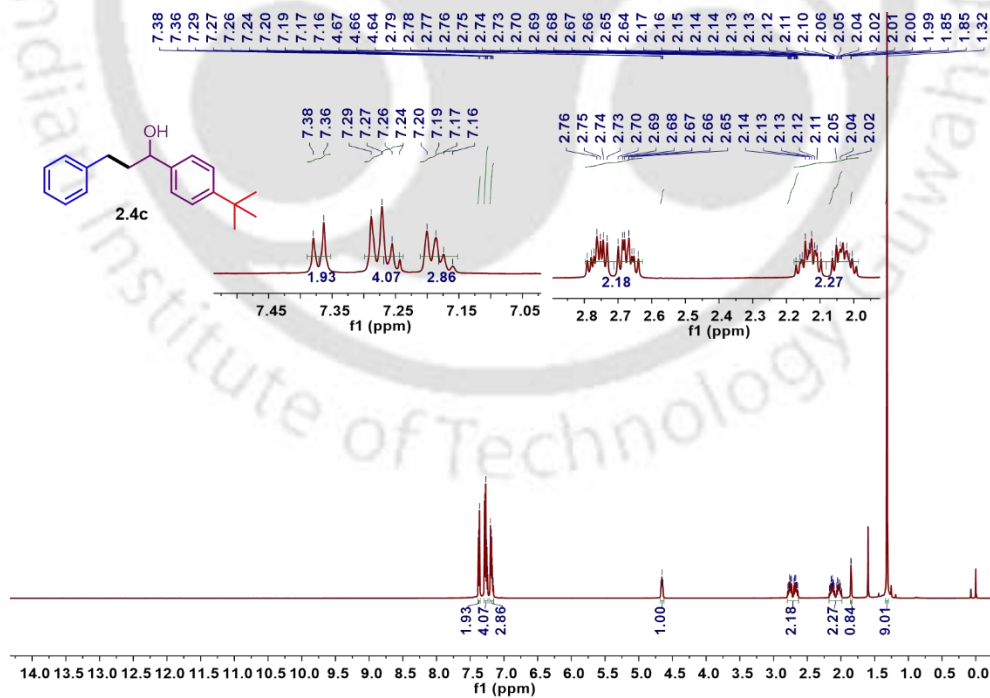


Figure A9: ^1H NMR spectra of 1-(4-(tert-butyl)phenyl)-3-phenylpropan-1-ol (**2.4c**) recorded in CDCl₃.

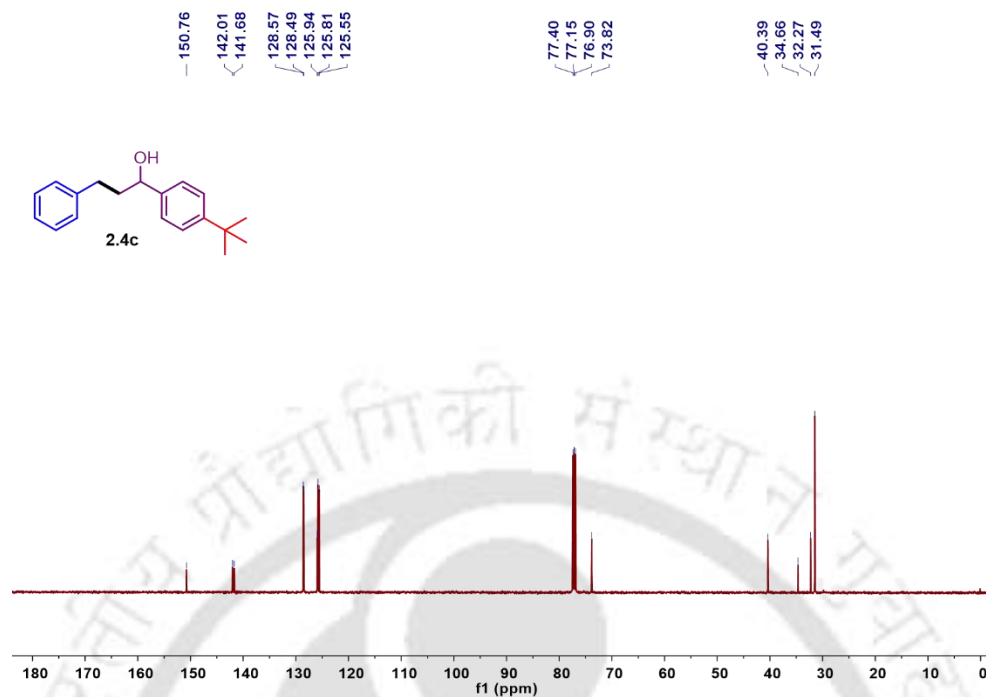


Figure A10: ¹³C{H} NMR spectra of 1-(4-(tert-butyl)phenyl)-3-phenylpropan-1-ol (2.4c) recorded in CDCl₃.

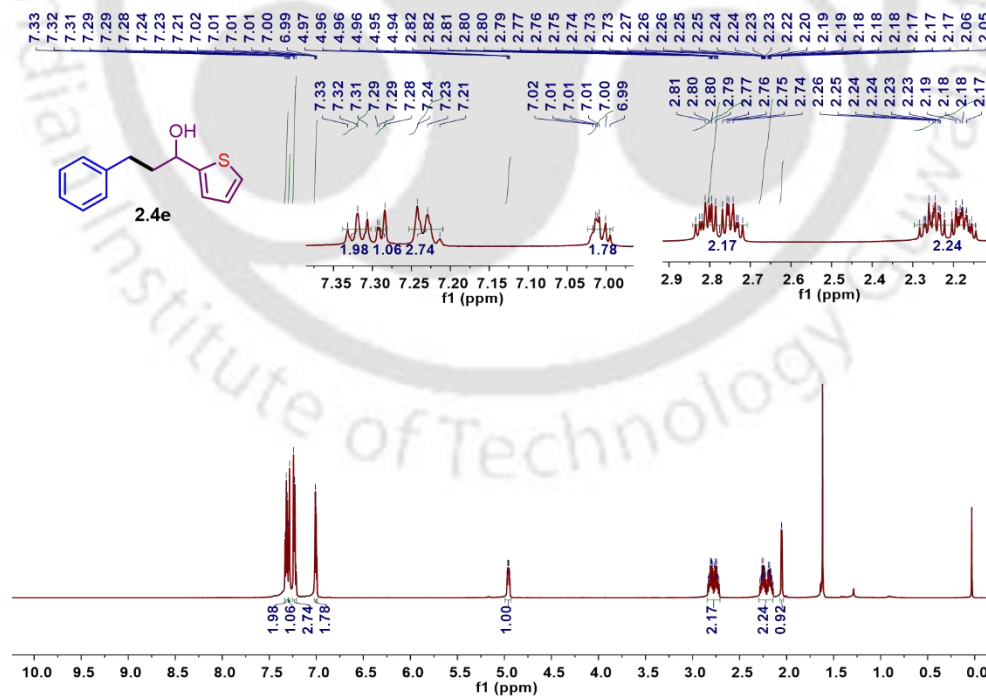


Figure A11: ¹H NMR spectra of 3-phenyl-1-(thiophen-2-yl)propan-1-ol (2.4e) recorded in CDCl₃.

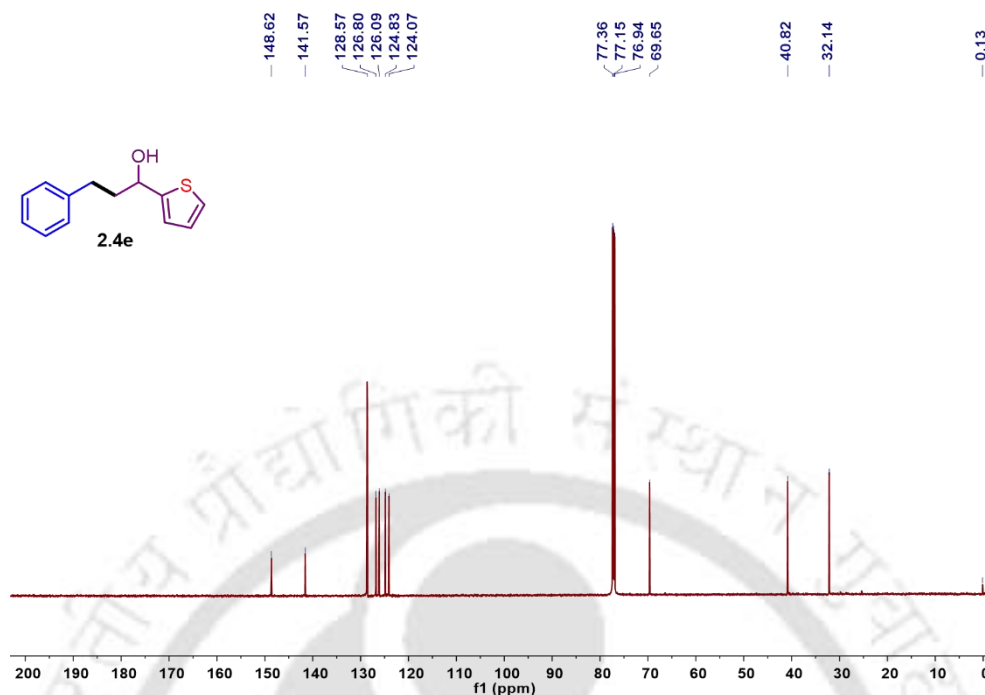


Figure A12: ¹³C{H} NMR spectra of 3-phenyl-1-(thiophen-2-yl)propan-1-ol (2.4e) recorded in CDCl₃.

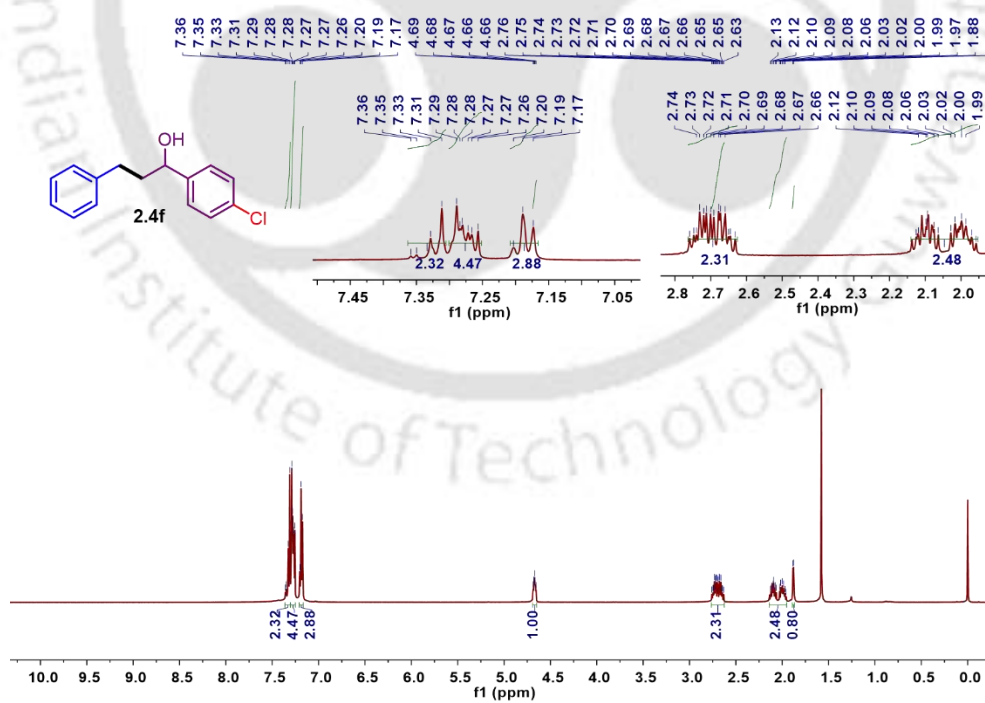


Figure A13: ¹H NMR spectra of 1-(4-chlorophenyl)-3-phenylpropan-1-ol (2.4f) recorded in CDCl₃.

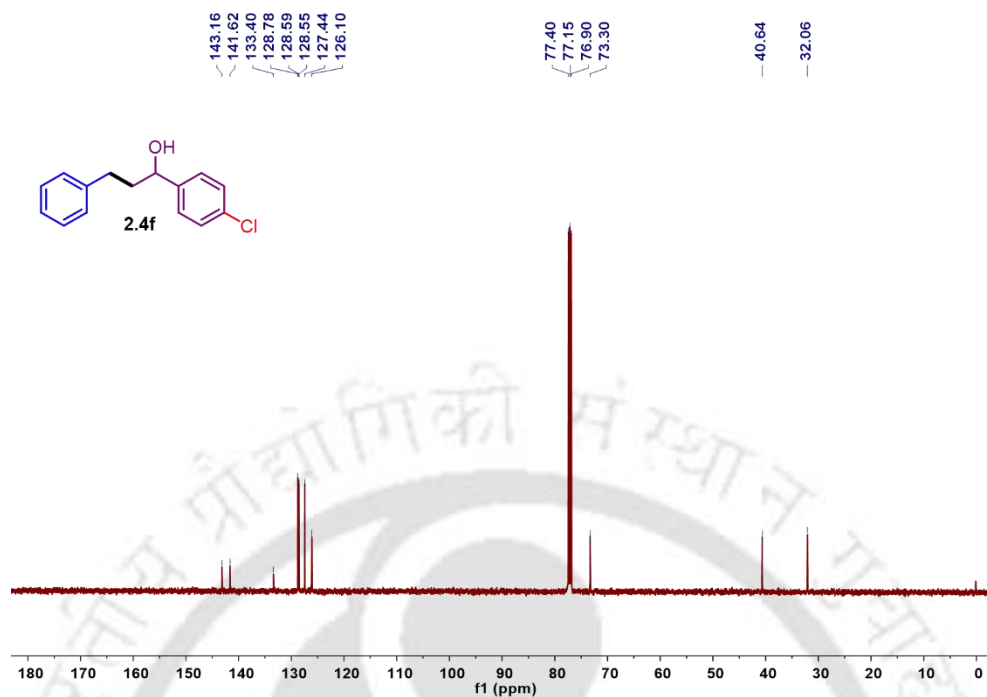


Figure A14: ¹³C {¹H} NMR spectra of 1-(4-chlorophenyl)-3-phenylpropan-1-ol (2.4f) recorded in CDCl₃.

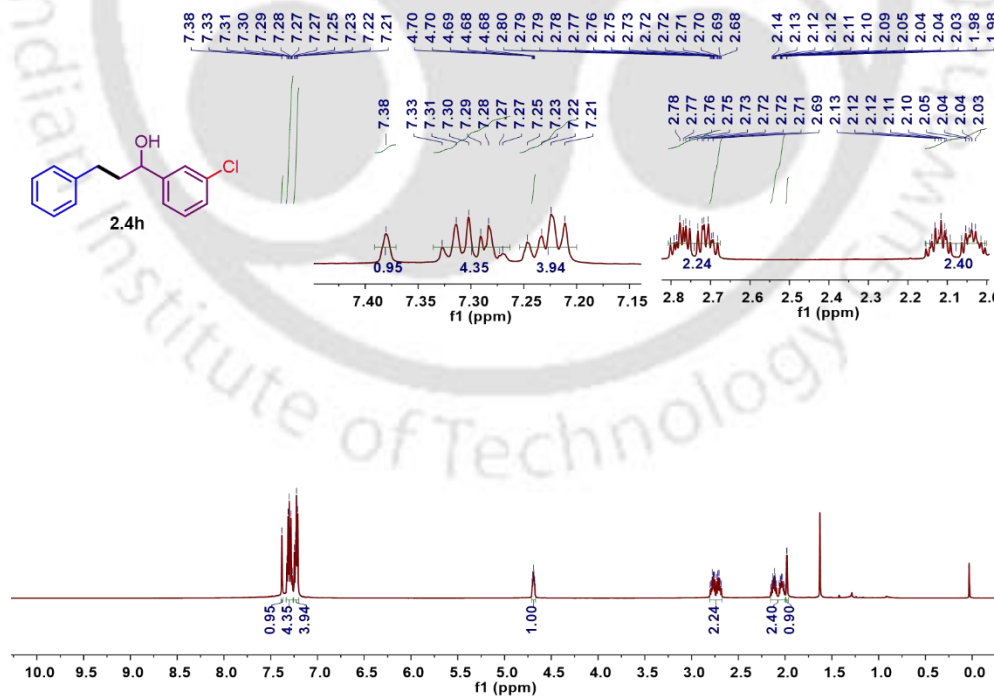


Figure A15: ¹H NMR spectra of 1-(3-chlorophenyl)-3-phenylpropan-1-ol (2.4h) recorded in CDCl₃.

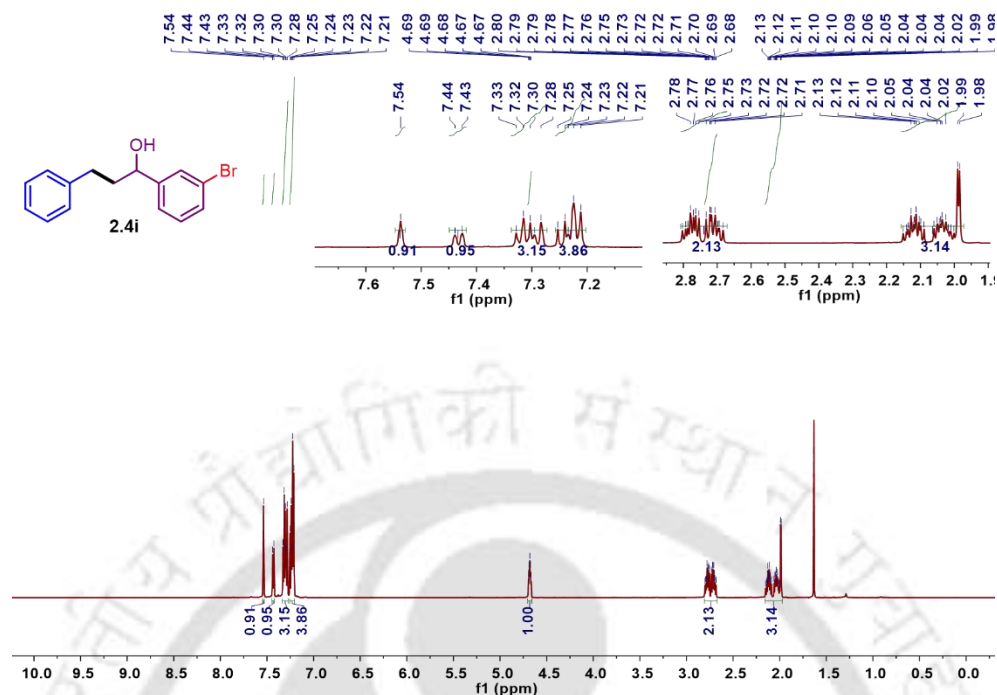


Figure A16: ^1H NMR spectra of 1-(3-bromophenyl)-3-phenylpropan-1-ol (2.4i) recorded in CDCl_3 .

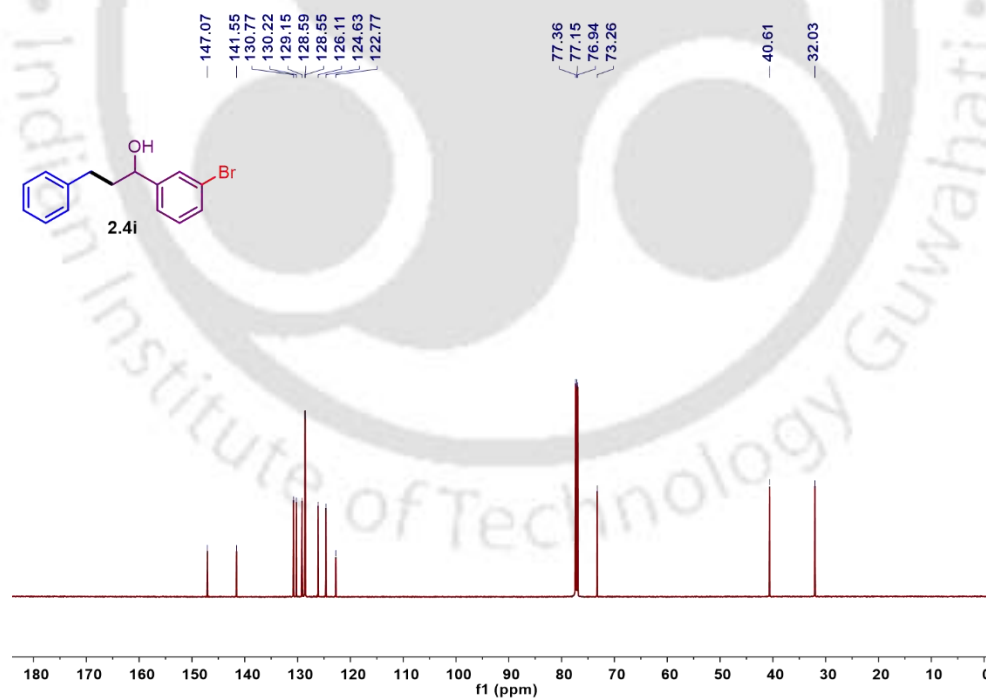


Figure A17: $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of 1-(3-bromophenyl)-3-phenylpropan-1-ol (2.4i) recorded in CDCl_3 .

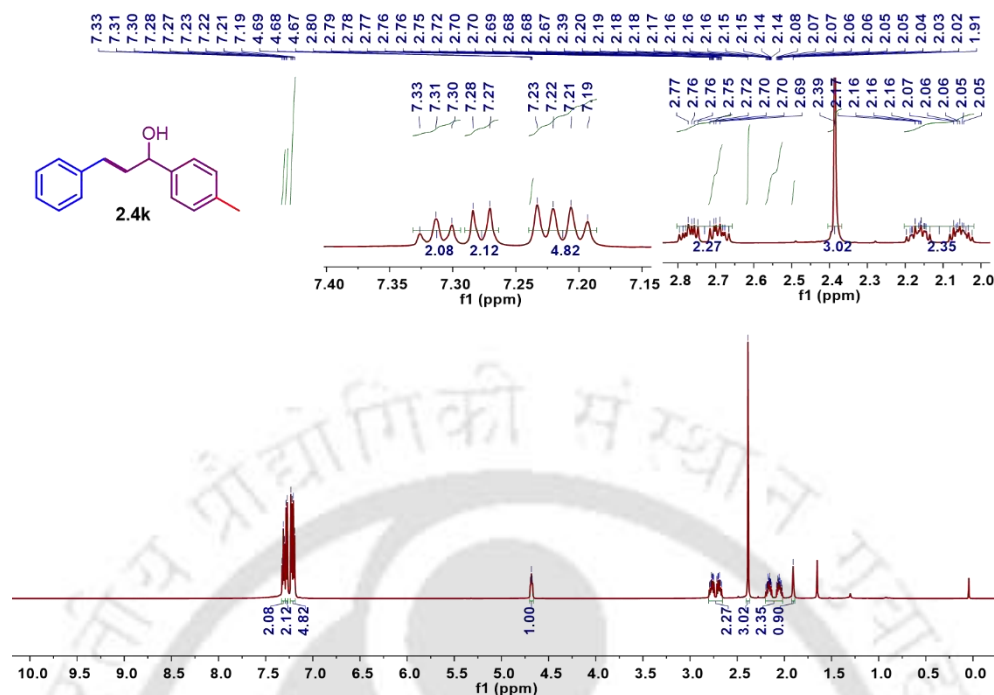


Figure A18: ¹H NMR spectra of 3-phenyl-1-(p-tolyl)propan-1-ol (2.4k) recorded in CDCl₃.

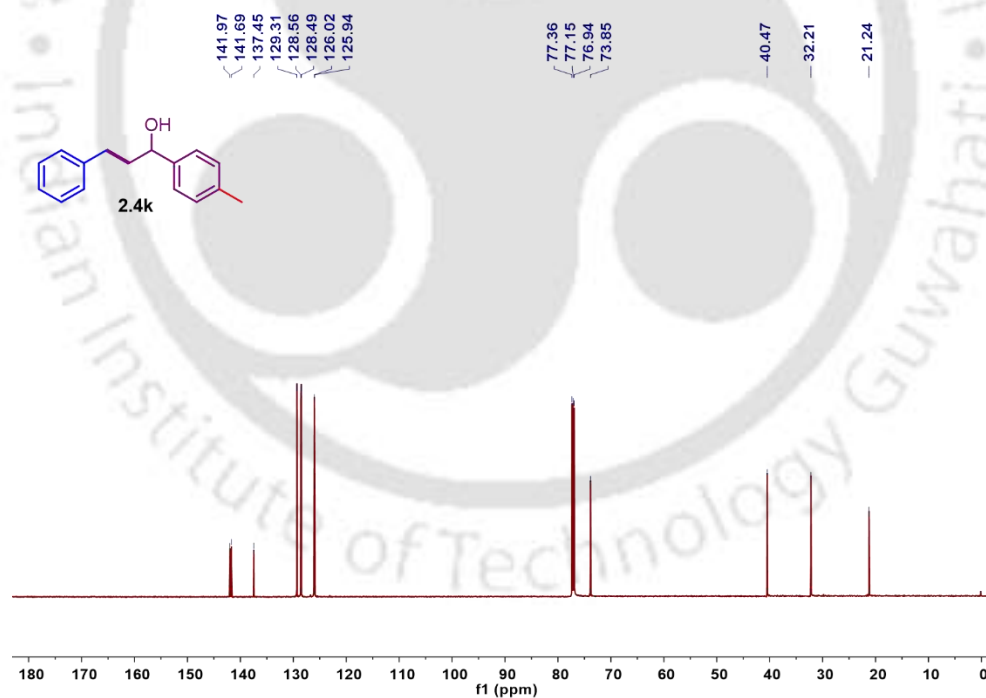


Figure A19: ¹³C{H} NMR spectra of 3-phenyl-1-(p-tolyl)propan-1-ol (2.4k) recorded in CDCl₃.

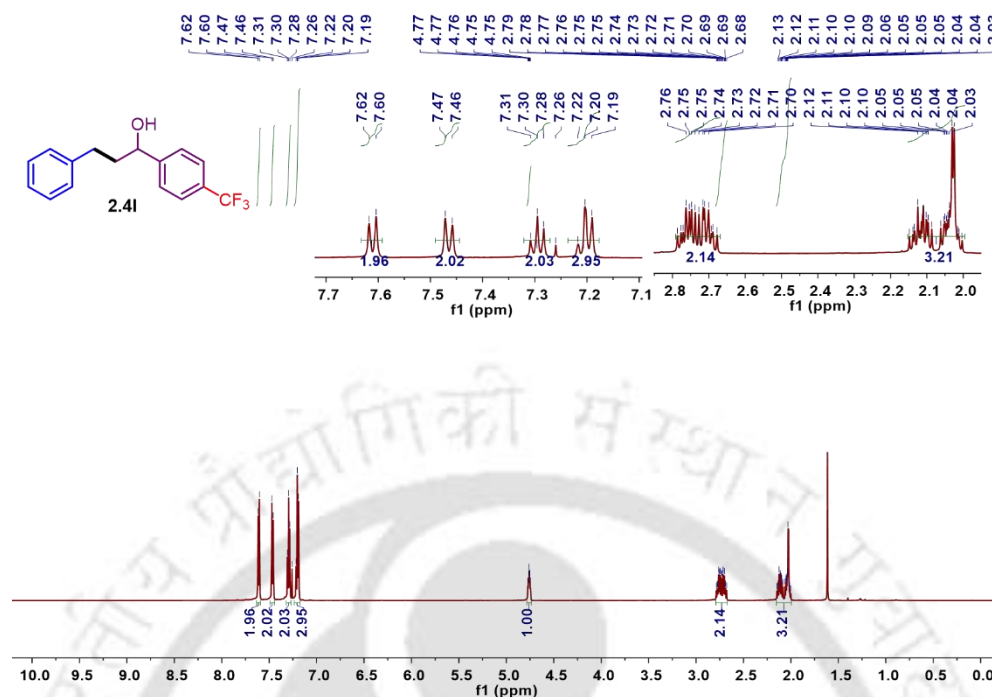


Figure A20: ^1H NMR spectra of 3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (2.4I) recorded in CDCl_3 .

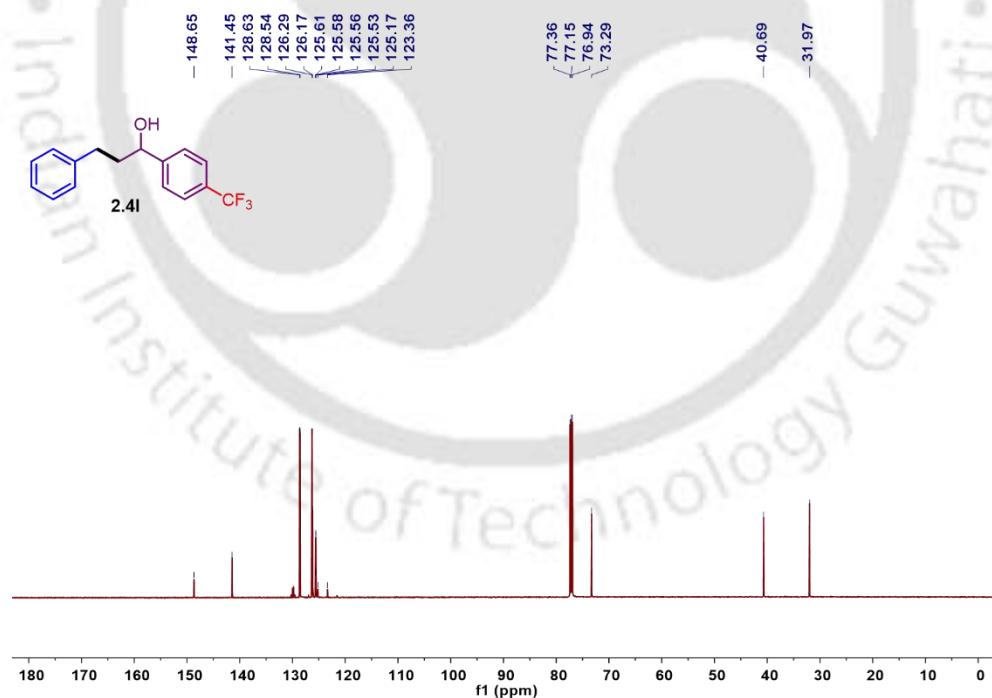


Figure A21: $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of 3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (2.4I) recorded in CDCl_3 .

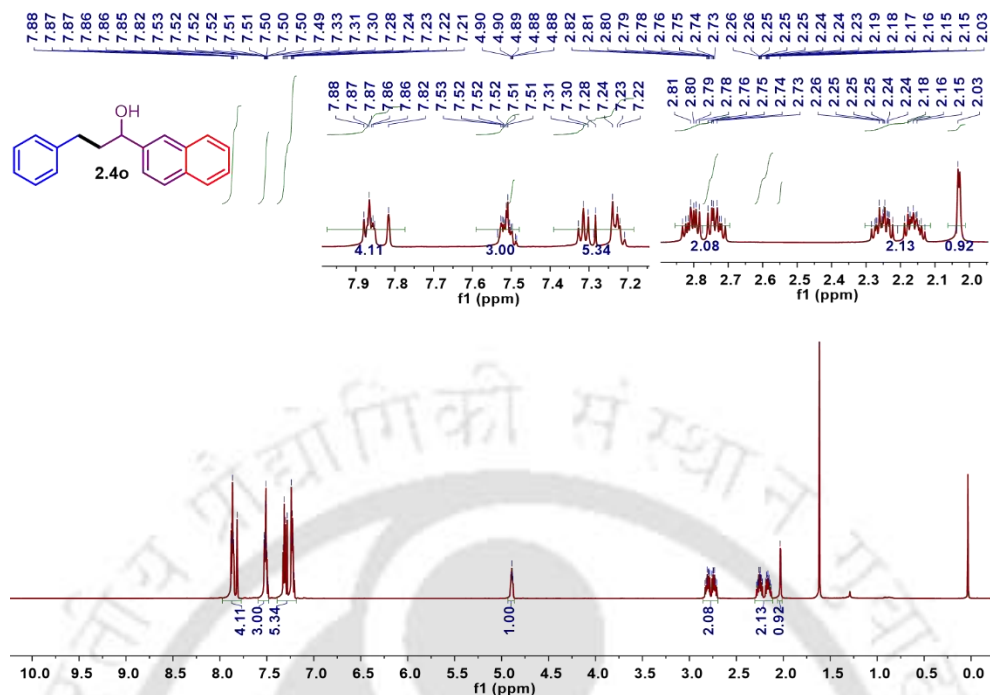


Figure A22: ^1H NMR spectra of 1-(naphthalen-2-yl)-3-phenylpropan-1-ol (**2.4o**) recorded in CDCl_3 .

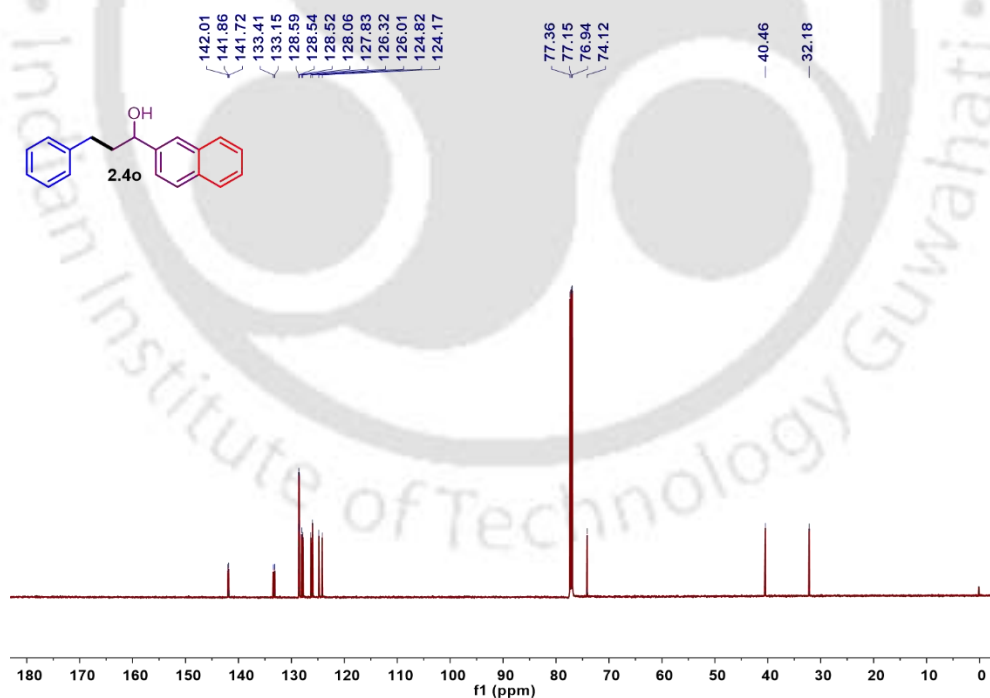


Figure A23: ^{13}C NMR spectra of 1-(naphthalen-2-yl)-3-phenylpropan-1-ol (**2.4o**) recorded in CDCl_3 .

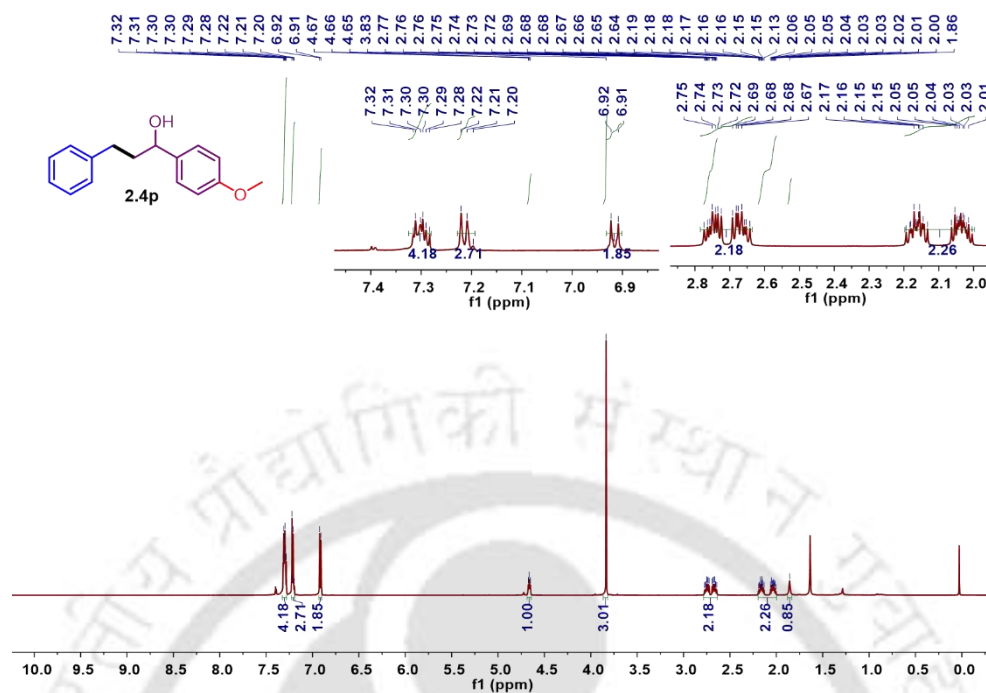


Figure A24: ¹H NMR spectra of 1-(4-methoxyphenyl)-3-phenylpropan-1-ol (**2.4p**) recorded in CDCl₃.

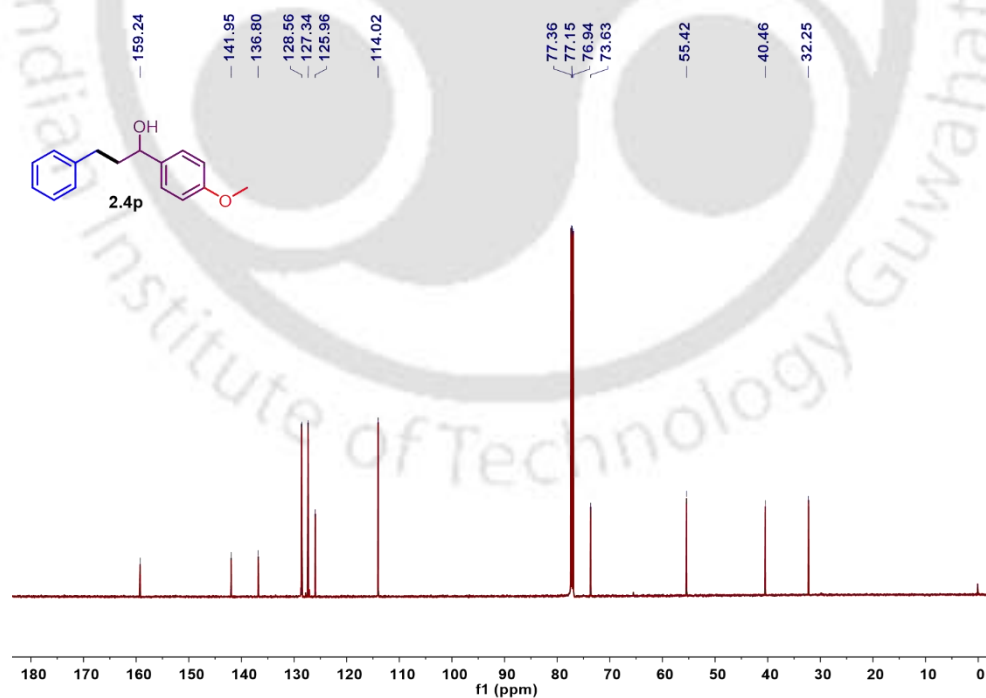


Figure A25: ¹³C{¹H} NMR spectra of 1-(4-methoxyphenyl)-3-phenylpropan-1-ol (**2.4p**) recorded in CDCl₃.

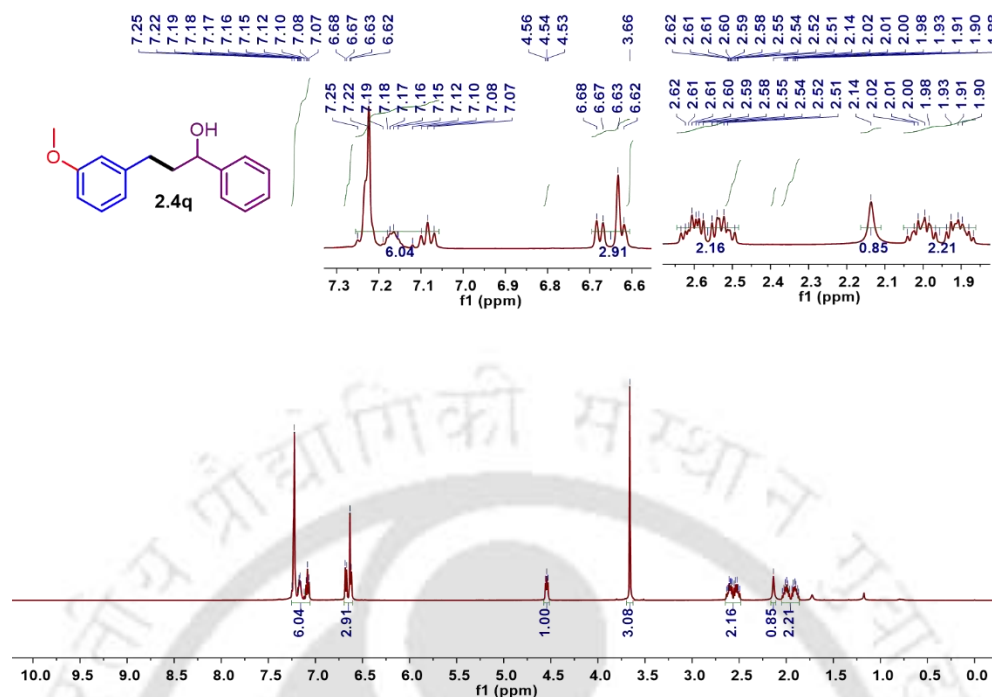


Figure A26: ^1H NMR spectra of 3-(3-methoxyphenyl)-1-phenylpropan-1-ol (**2.4q**) recorded in CDCl_3 .

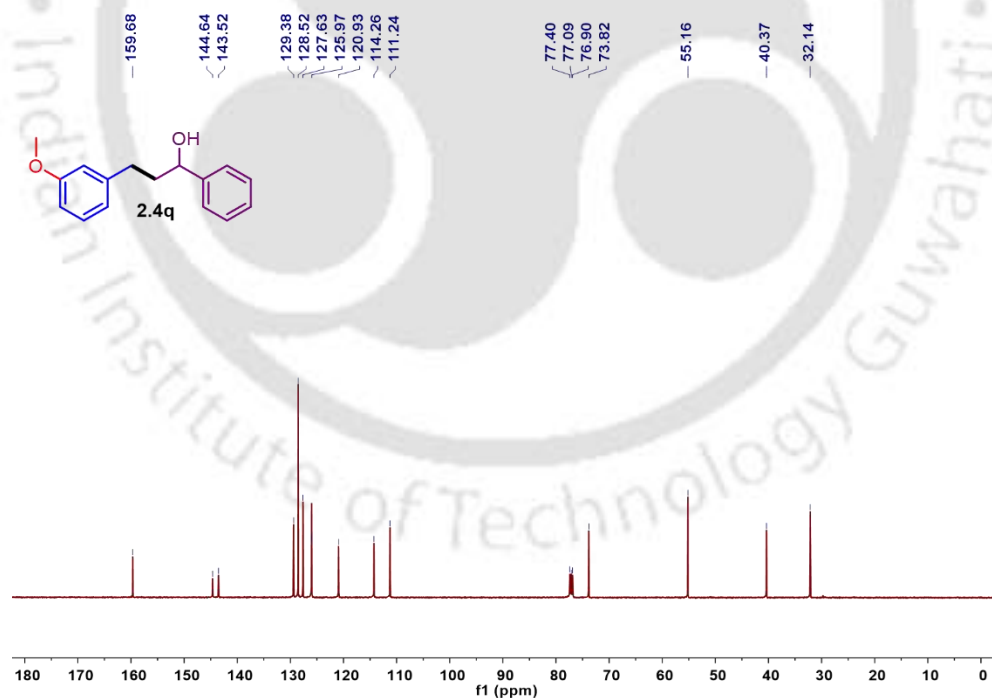


Figure A27: $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of 3-(3-methoxyphenyl)-1-phenylpropan-1-ol (**2.4q**) recorded in CDCl_3 .

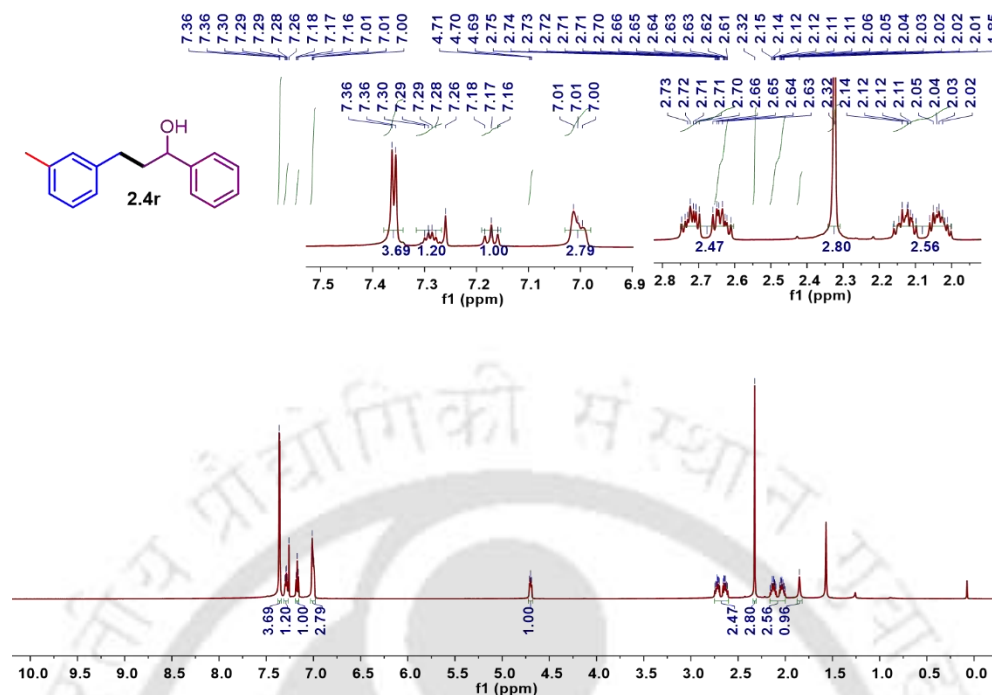


Figure A28: ¹H NMR spectra of 1-phenyl-3-(m-tolyl)propan-1-ol (**2.4r**) recorded in CDCl₃.

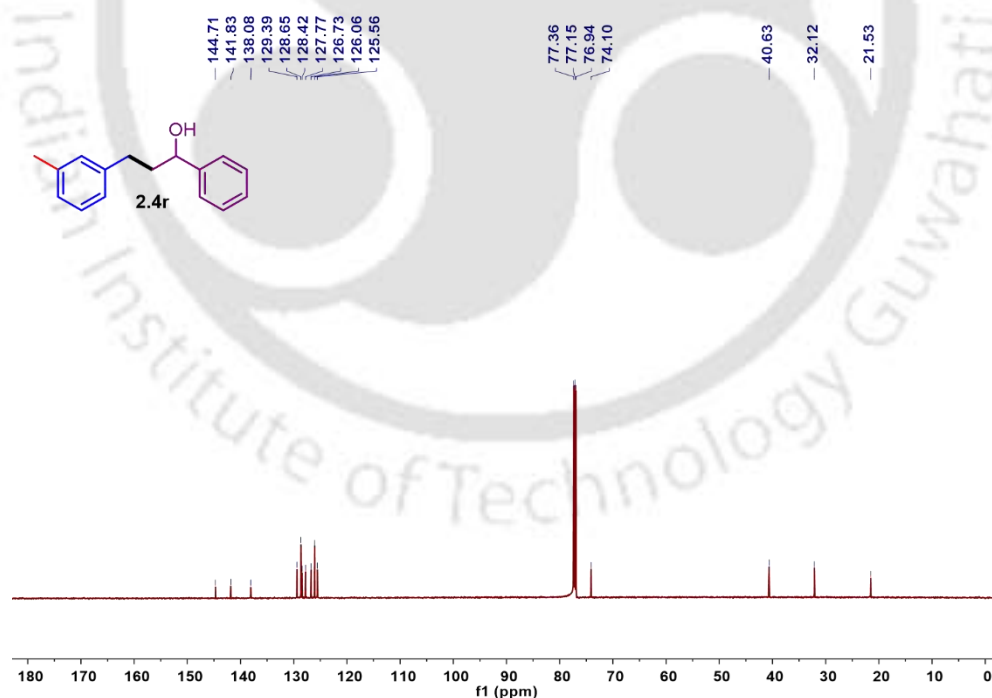


Figure A29: ¹³C{¹H} NMR spectra of 1-phenyl-3-(m-tolyl)propan-1-ol (**2.4r**) recorded in CDCl₃.

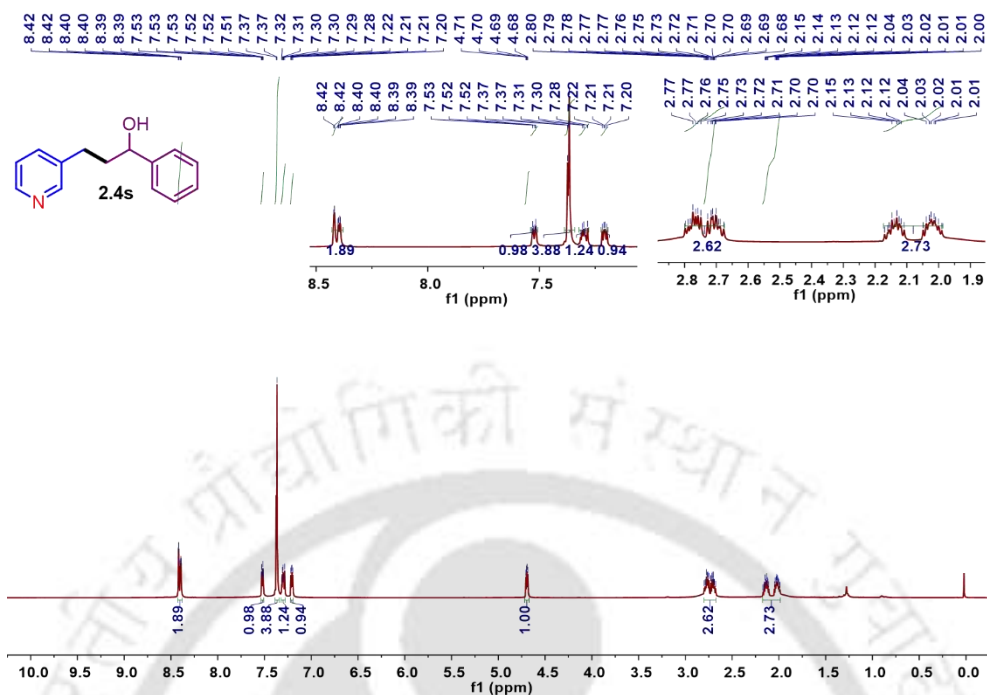


Figure A30: ¹H NMR spectra of 1-phenyl-3-(pyridin-3-yl)propan-1-ol (2.4s) recorded in CDCl₃.

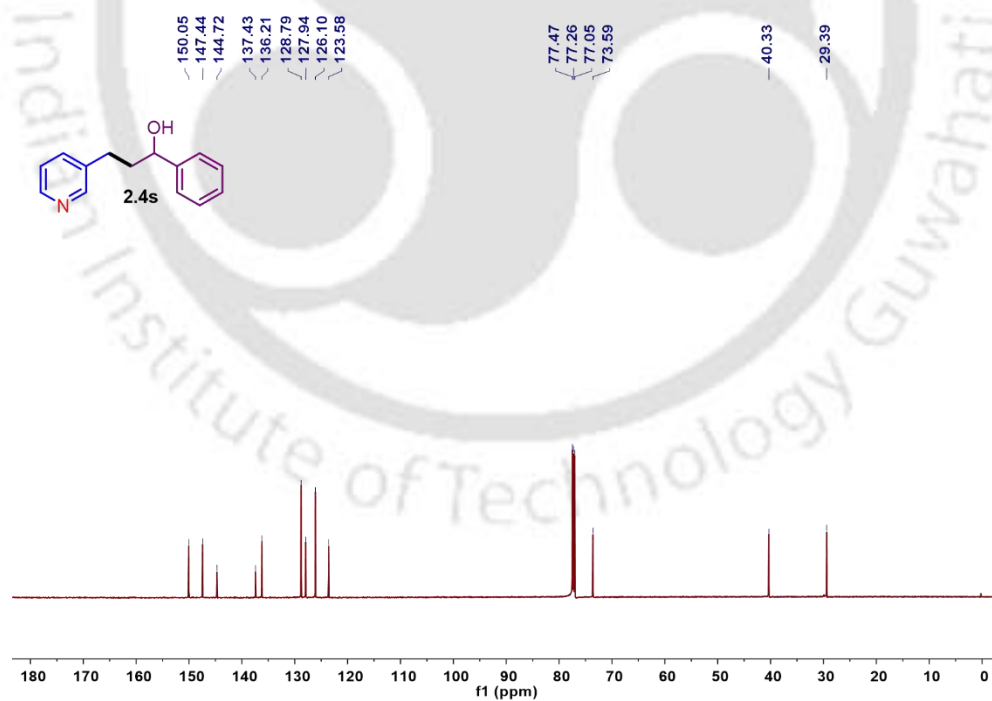


Figure A31: ¹³C{¹H} NMR of 1-phenyl-3-(pyridin-3-yl)propan-1-ol (2.4s) recorded in CDCl₃.

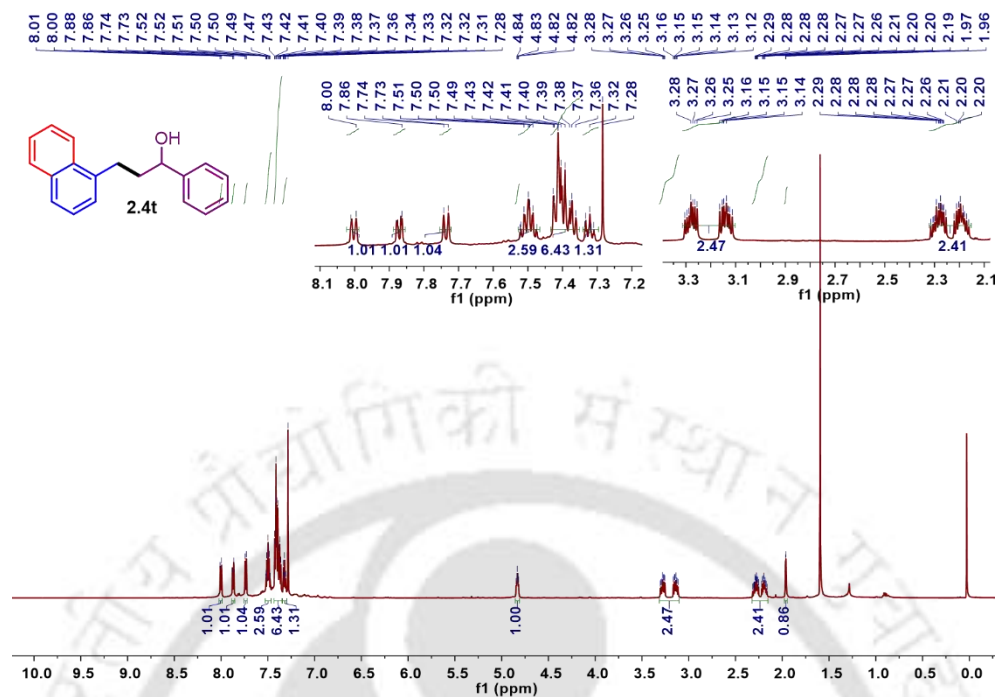


Figure A32: ^1H NMR spectra of 3-(naphthalen-1-yl)-1-phenylpropan-1-ol (2.4t) recorded in CDCl_3 .

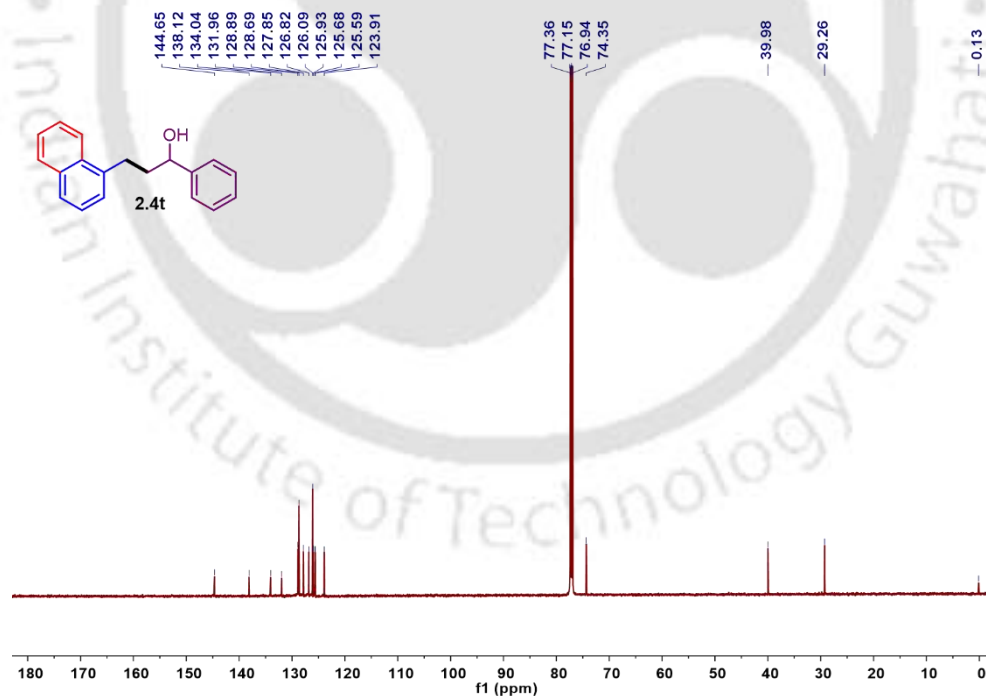


Figure A33: $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of 3-(naphthalen-1-yl)-1-phenylpropan-1-ol (2.4t) recorded in CDCl_3 .

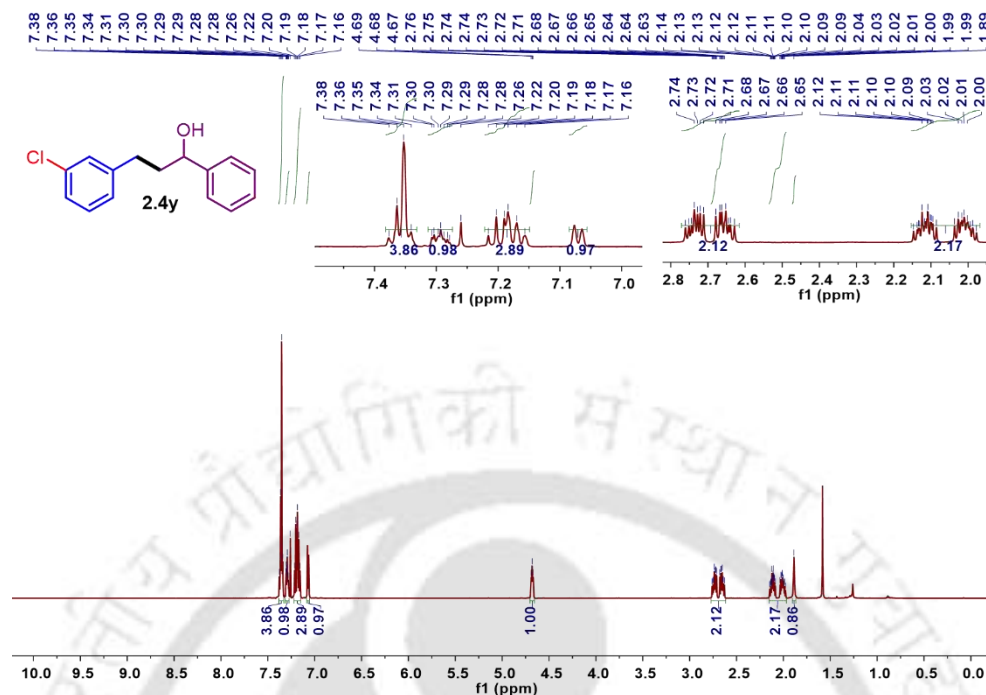


Figure A34: ^1H NMR spectra of 3-(3-chlorophenyl)-1-phenylpropan-1-ol (**2.4y**) recorded in CDCl_3 .

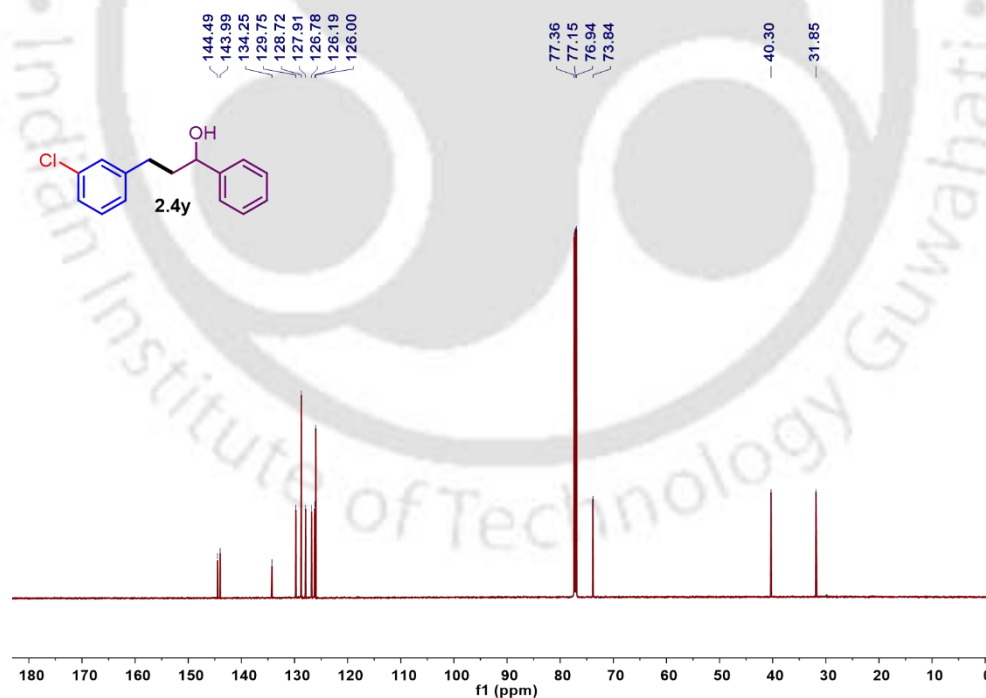


Figure A35: ^{13}C NMR spectra of 3-(3-chlorophenyl)-1-phenylpropan-1-ol (**2.4y**) recorded in CDCl_3 .

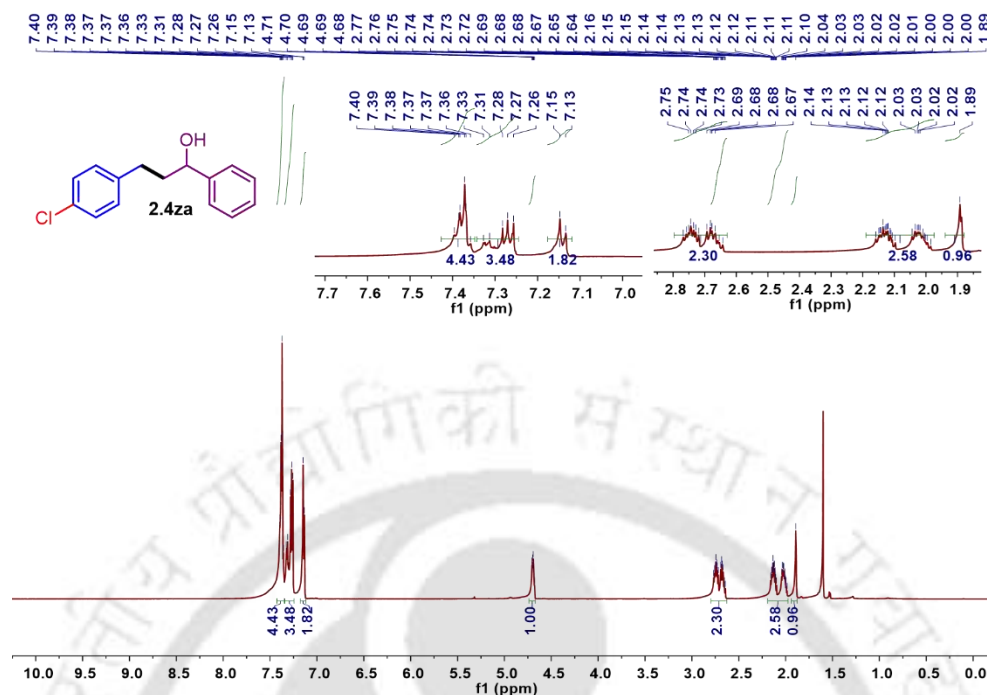


Figure A36: ¹H NMR spectra of 3-(4-chlorophenyl)-1-phenylpropan-1-ol (**2.4za**) recorded in CDCl₃.

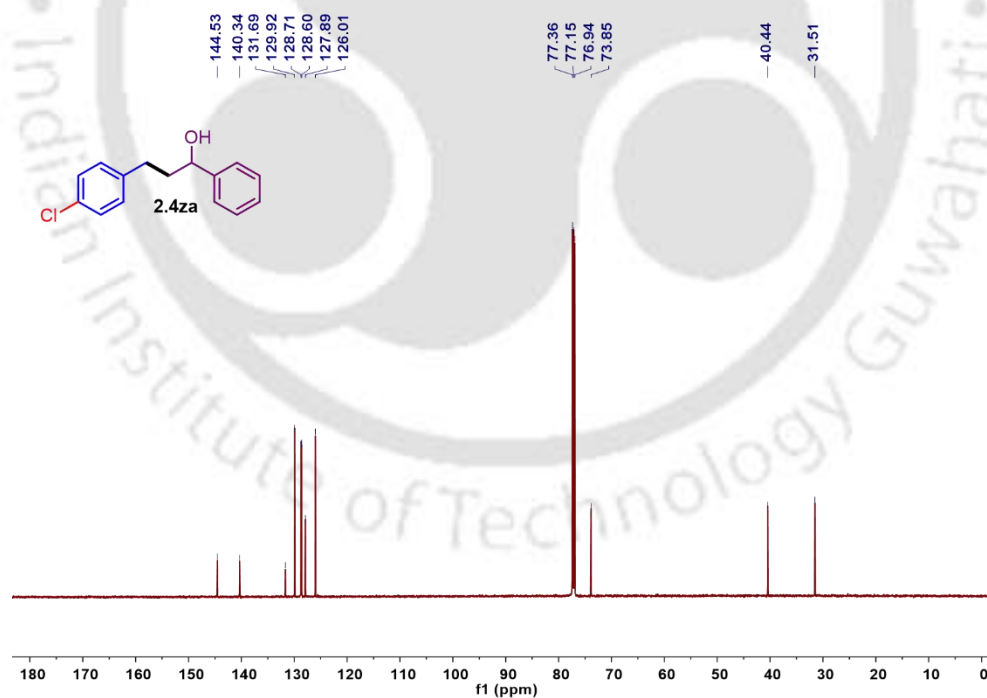


Figure A36: ¹³C{¹H} NMR spectra of 3-(4-chlorophenyl)-1-phenylpropan-1-ol (**2.4za**) recorded in CDCl₃.

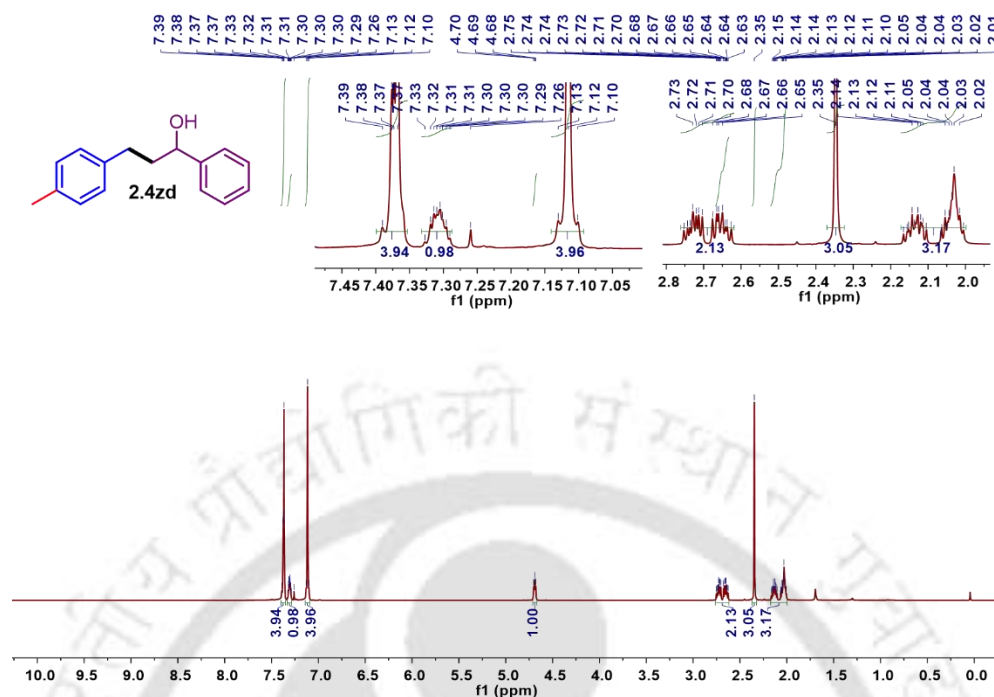


Figure A38: ¹H NMR spectra of 1-phenyl-3-(p-tolyl)propan-1-ol (2.4zd) recorded in CDCl₃.

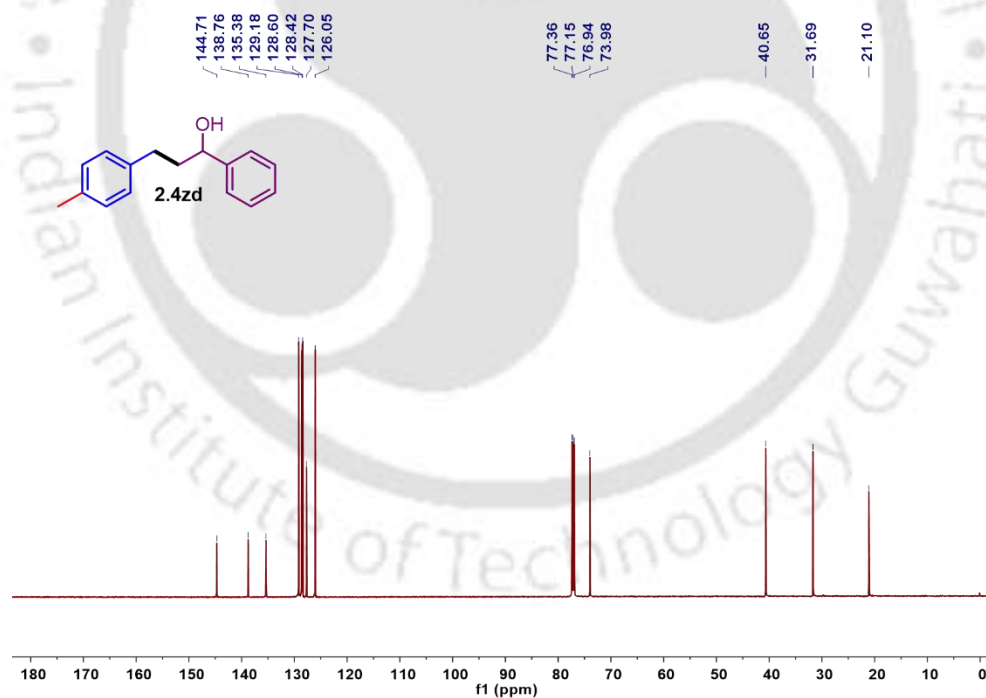


Figure A39: ¹³C{¹H} NMR spectra of 1-phenyl-3-(p-tolyl)propan-1-ol (2.4zd) recorded in CDCl₃.

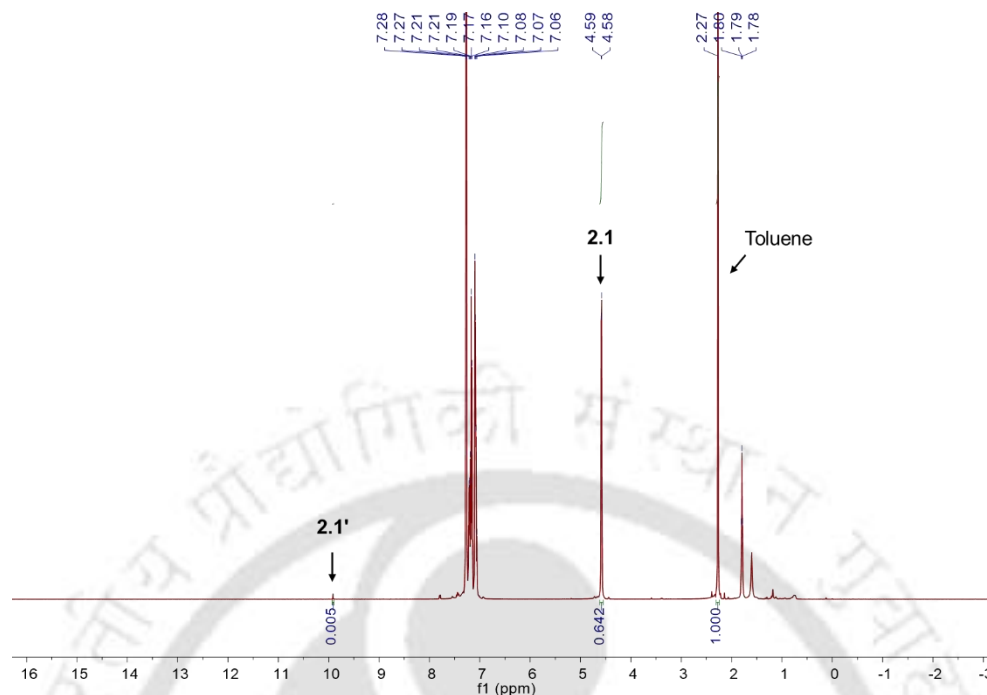


Figure A40: ¹H NMR spectra of the reaction mixture of benzyl alcohol (4 mmol), 2.5 (0.01 mol%), NaO'Bu (10 mol%) heated at 140 °C for 12 h, recorded in CDCl₃. (equation 3, Scheme 2.34).

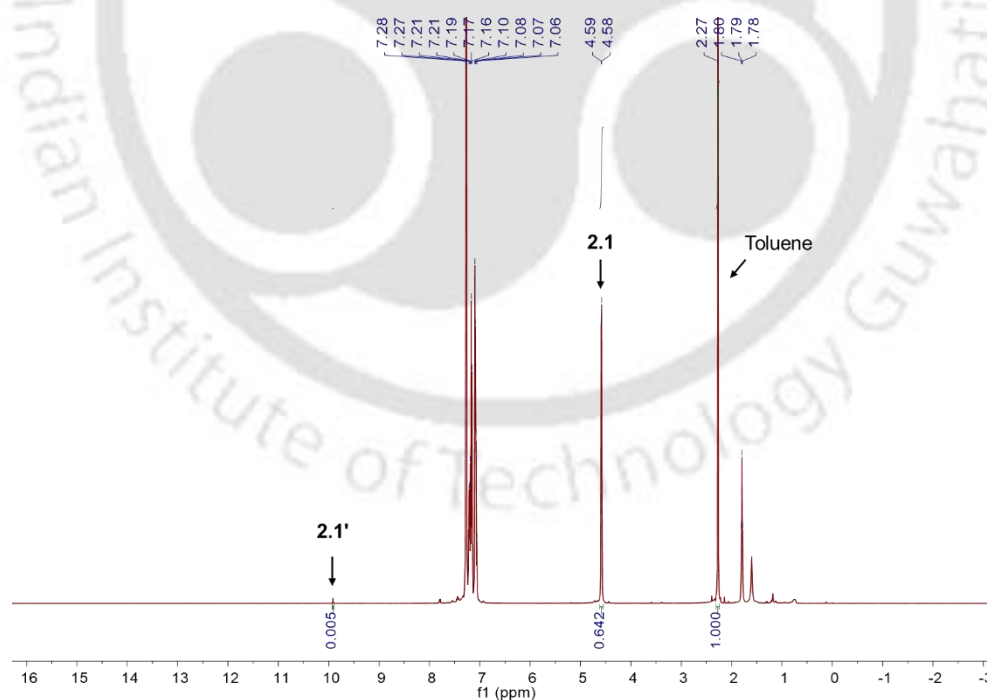


Figure A41. ¹H NMR spectra of the reaction mixture of benzyl alcohol (4 mmol), CrCl₃.6H₂O (0.01 mol%), NaO'Bu (10 mol%) heated at 140 °C for 12 h, recorded in CDCl₃ (equation 4, Scheme 2.34).

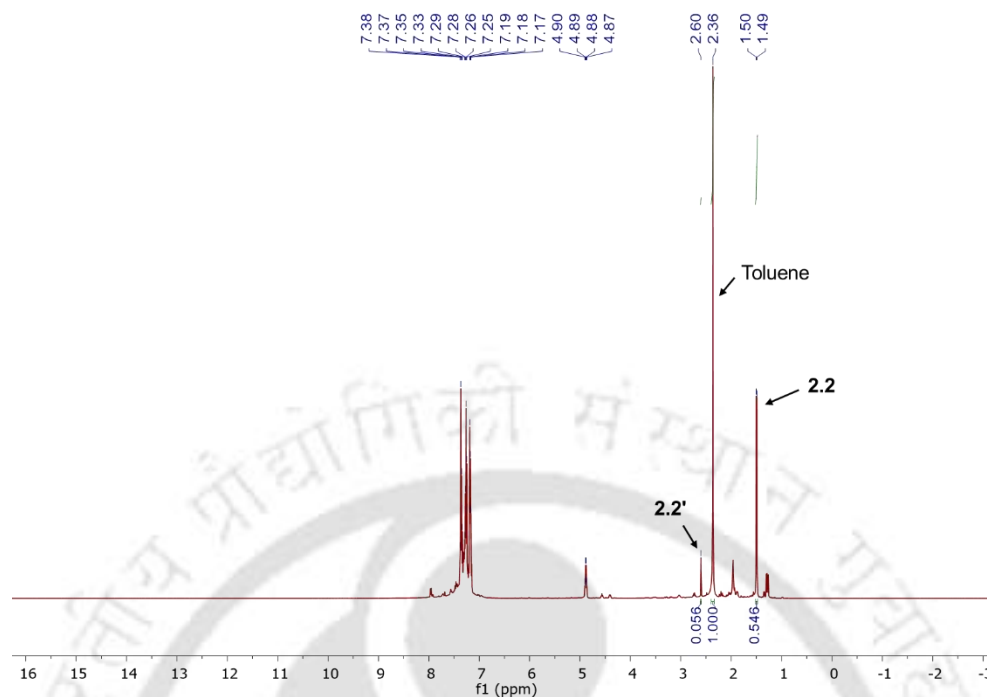


Figure A42. ¹H NMR spectra of the reaction mixture of 1-phenyl ethanol (4 mmol), 2.5 (0.01 mol%), NaO'Bu (10 mol%) heated at 140 °C for 12 h, recorded in CDCl₃. (equation 5, Scheme 2.34).

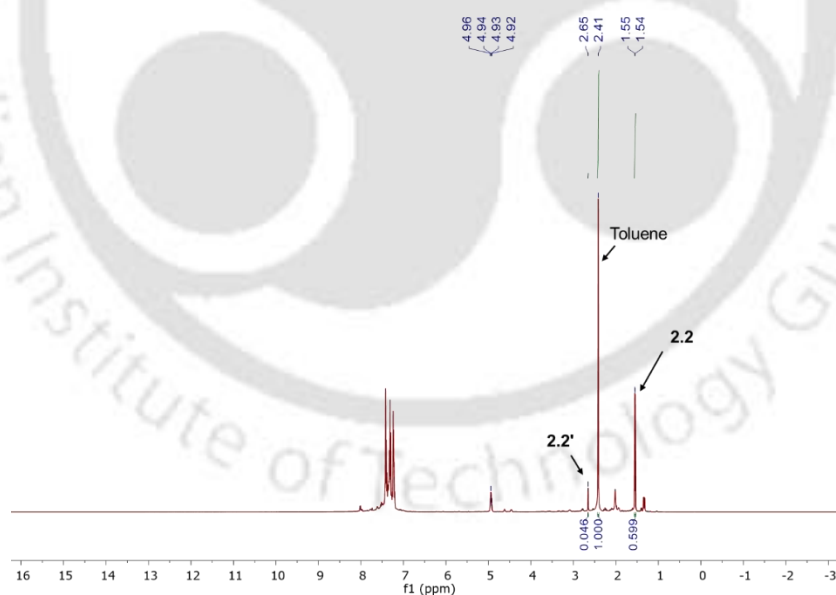


Figure A43. ¹H NMR spectra of the reaction mixture of 1-phenyl ethanol (4 mmol), CrCl₃.6H₂O (0.01 mol%), NaO'Bu (10 mol%) heated at 140 °C for 12 h, recorded in CDCl₃. (equation 6, Scheme 2.34).

A3. Calculation of Kinetic Isotopic Effect (KIE):

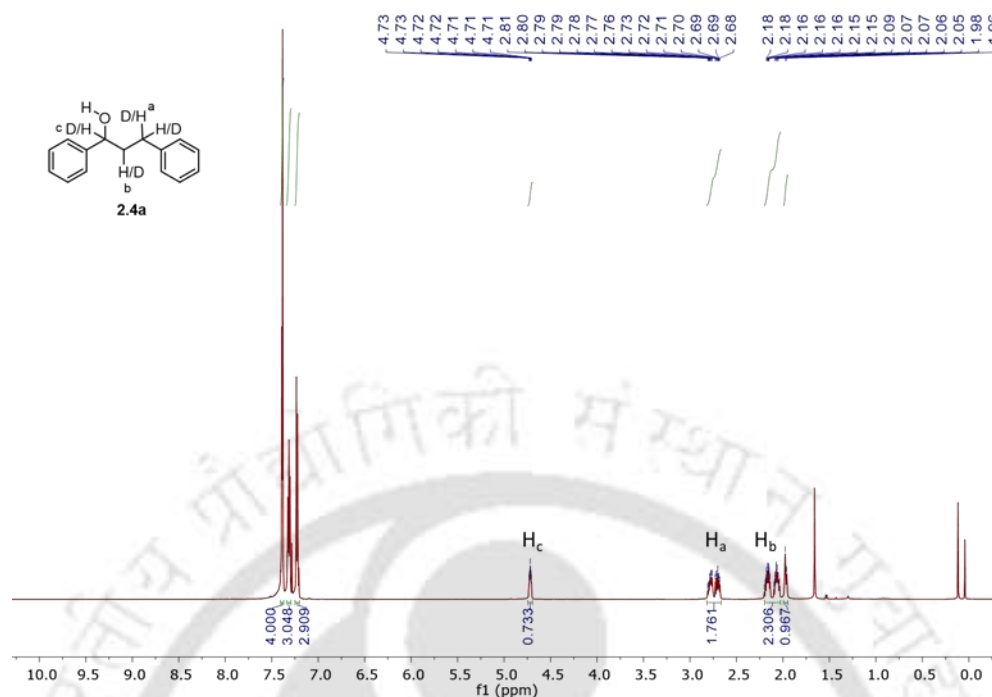


Figure A44. ^1H NMR spectra of the reaction mixture of benzyl alcohol (2 mmol), deuterated benzyl alcohol (2 mmol), 1-phenyl ethanol (4 mmol), **2.5** (0.005 mol%), NaO^tBu (10 mol%) heated at 140°C for 12 h, recorded in CDCl_3 . (equation 7, Scheme 2.34).

$$\frac{K_{\text{Ha}}}{K_{\text{D}}} = \text{KIE}$$

Where, the conversion to deuterated product was calculated by ^1H -NMR integration value

$$K_{\text{H}} = \frac{\text{Integral value}}{\text{Number of protons}} * 100 = A * 100$$

$$K_{\text{D}} = (1-A)*100$$

$$A = \frac{\text{Integral value}}{\text{Number of protons}}$$

A4. Magnetic moment of **2.5** in solution (Evan's method):

Magnetic moment in solution was measured by following the Evan's NMR method.¹⁻³ A mixture of $\text{MeOH-d}_4/t\text{-BuOH}$ (98:2) was prepared. An aliquot of 2% $t\text{-BuOH}$ in MeOH-d_4 solution was transferred to two melting point capillary tubes. A stock solution of $(^{\text{Ph}_2}\text{NNN})\text{CrCl}_3$ (0.0011 g, 0.0025 mmol) in a 1 mL 2% $t\text{-BuOH}$ (2%) in MeOH-d_4 was prepared. 0.5 mL stock solution was drawn and transferred to one NMR tube. To the same NMR tube a capillary containing the 2% $t\text{-BuOH}$ in MeOH-d_4 solution was inserted. NMR spectrum was recorded on a Bruker ASCEND

600 operating at 600 MHz. A chemical shift difference of 30 Hz was observed for the *t*-BuOH peak between the inner and outer tubes. Based on the equation $\mu_B = 798(\Delta_M T)^{0.5}$ [T= temperature of measurement and $\Delta_M = 3\Delta f/1000fc$, where Δf is the paramagnetic shift of the solvent in Hz, f is the frequency of the NMR instrument in Hz, and c is the molar concentration of the metal complex], we have observed the magnetic moment $\mu_{\text{eff}} = 3.37 \mu_B$ which is in convenience with a Cr(III) species.

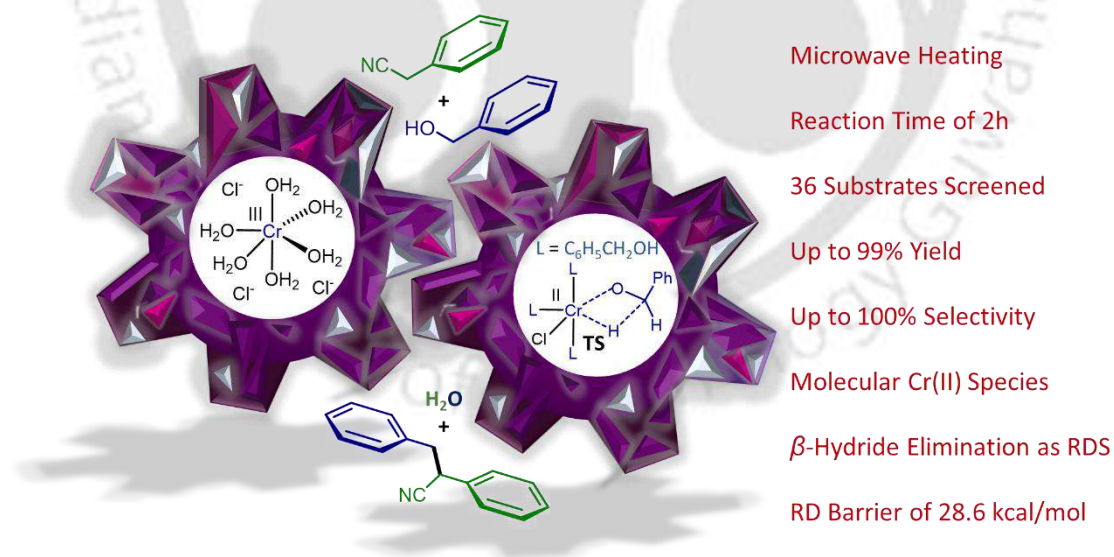
Then NaOH (0.044g, 1.1 mmol) was added to 0.5 mL of the remaining stock solution of (^{Ph}₂NNN)CrCl₃ (0.0011 g, 0.0025 mmol) which was prepared in 1 mL 2% *t*-BuOH (2%) in MeOH-d₄. To the same NMR tube a capillary containing the 2% *t*-BuOH in MeOH-d₄ solution was inserted. NMR spectrum was recorded on a Bruker ASCEND 600 operating at 600 MHz. For better assurance of the value the experiment was repeated twice. On an average of two runs a chemical shift difference of 72 Hz was observed for the *t*-BuOH peak between the inner and outer tubes which gave an average magnetic moment of 5.04 μ_B which is in convenience with a Cr(II) species.

8. References:

1. D. F. Evans, *J Chem Soc.*, 1959, DOI: 10.1039/JR9590002003, 2003-2005.
2. T. Inagaki, A. Ito, J.-i. Ito and H. Nishiyama, *Angew. Chem. Int. Ed.*, 2010, **49**, 9384-9387.
3. G. J. P. Britovsek, V. C. Gibson, S. K. Spitzmesser, K. P. Tellmann, A. J. P. White and D. J. Williams, *J. Chem. Soc., Dalton Trans.*, 2002, DOI: 10.1039/B106614P, 1159-1171.

Chapter- III

The α -Alkylation of Nitriles with Primary Alcohols Catalysed by Chromium(III) Chloride

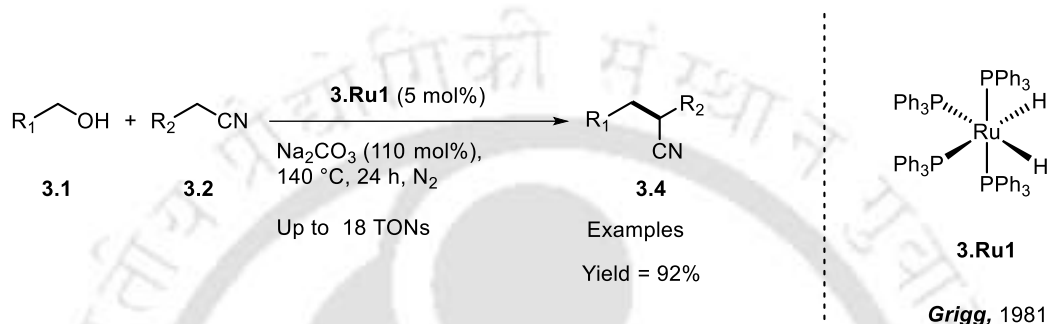


Narjinari, H.; Kumar, A.* α -Alkylation of Nitriles with Alcohols in Air Catalyzed by Chromium Chloride under Microwave Irradiation and Ligand-Free Conditions *J. Org. Chem.* **2026**, <https://doi.org/10.1021/acs.joc.5c03097>.



3.1. Introduction

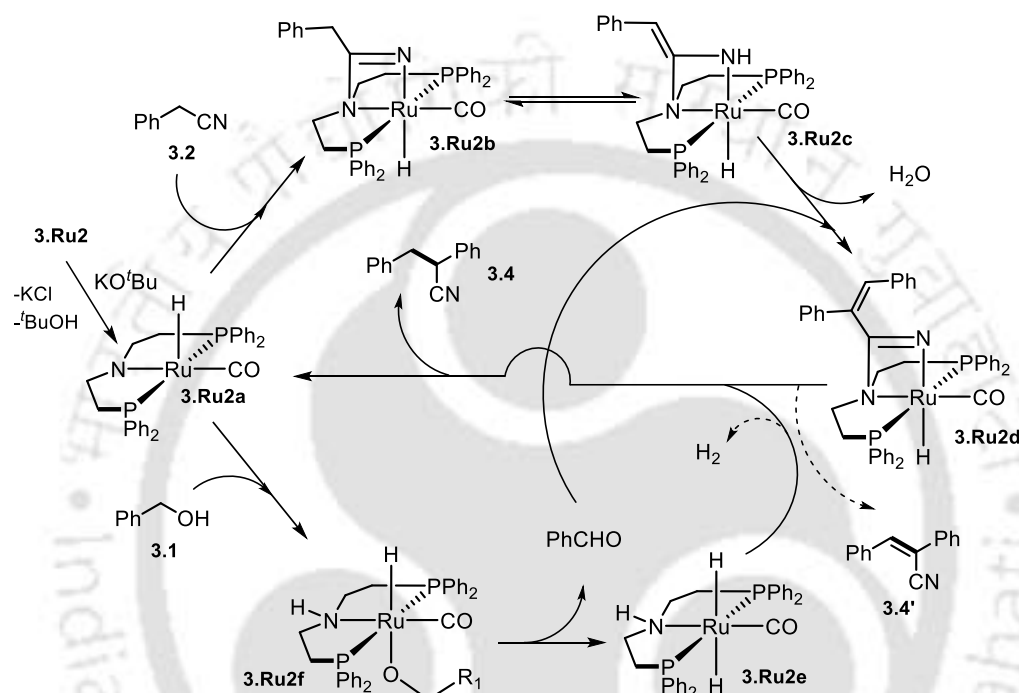
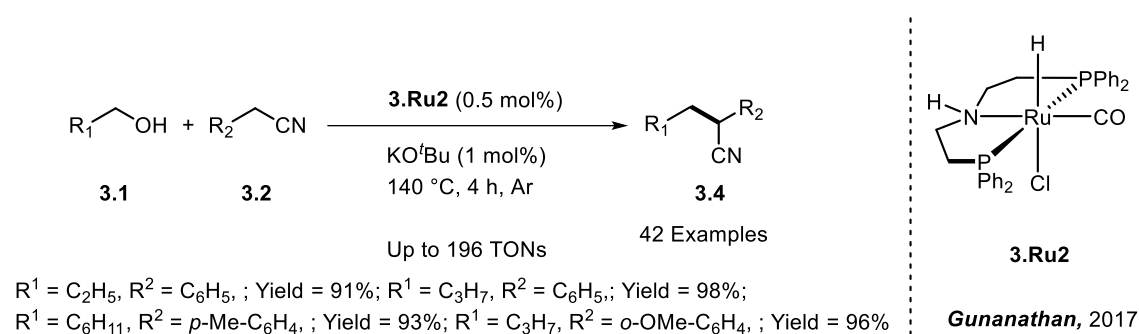
Stitching two carbon atoms to form new C-C bonds has been an evergreen focal point in organic chemistry.¹ Traditionally, C-C bond formation is accomplished via C-H or C-X (X = halide) activation catalysed by transition metals which follows either radical² or organometallic mechanism.⁴⁻⁵ Recent years have witnessed a surge in the use of alcohols⁶⁻⁸ readily available from renewable biomass sources as alkylating agents to accomplish various C-C bond formation reactions.⁴⁻⁵



Scheme 3.1. The $\text{RuH}_2(\text{PPh}_3)_4$ catalysed α -alkylation of nitriles reported by Grigg.³

Synthesis of α -alkylated nitrile is one of the versatile applications of C-C bond formation, since nitrile functionality can act as a potential candidate in organic transformations, which can be transformed into carboxylic acids,^{12,13} amides,^{12,13} amines^{12,13} and oxazolines^{12,13} among many others.¹²⁻¹⁴ There are several reports on the transformation of benzyl alcohol **3.1** and benzyl nitrile **3.2** to α -alkylated nitrile **3.4** catalysed by noble and precious transition metals like Ru,^{3, 9-11, 15} Ir,¹⁶⁻¹⁹ Rh²⁰ and Os.²¹

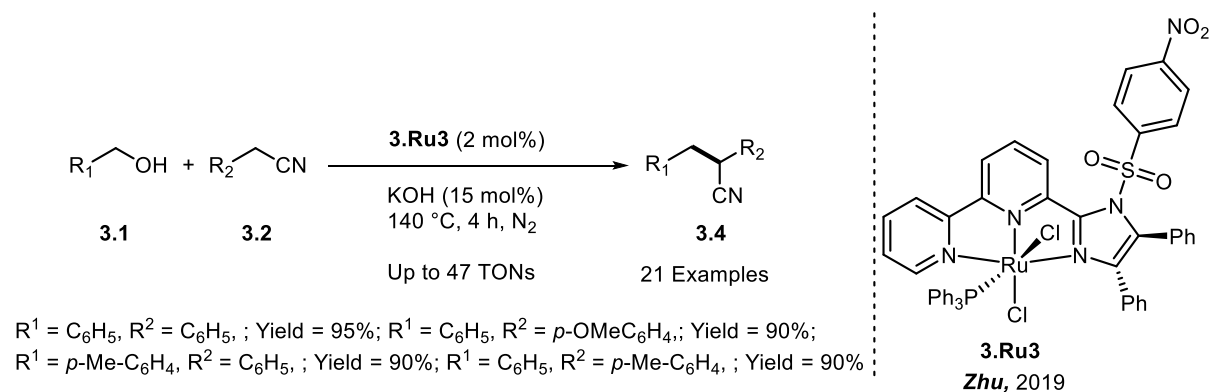
Grigg was the first to report on the $\text{RuH}_2(\text{PPh}_3)_4$ **3.Ru1** (5 mol%) catalysed α -alkylation of nitriles where 92% yield of the α -alkylated nitrile was obtained in presence of 110 mol% sodium carbonate under an atmosphere of N_2 (Scheme 3.1).³ The next report on the ruthenium catalysed α -alkylation of nitriles came from Gunanathan where 98% yield of the α -alkylated nitrile was obtained in the presence of 0.5 mol% PNP-Ru pincer complex **3.Ru2** and KO^tBu (1 mol%) at 135 °C under an argon atmosphere (Scheme 3.2). The active species **3.Ru2a** resulted from deprotonation of **3.Ru2** in the presence of base, is seen to react independently with both benzyl alcohol and benzyl nitrile and form a Ru-alkoxide species **3.Ru2f** and a Ru-metallacyclic species **3.Ru2b** respectively (Scheme 3.2). The species **3.Ru2b** tautomerizes to an enamine species **3.Ru2c**. The Ru-alkoxide **3.Ru2f** then undergoes β -hydride elimination to form a dihydride species **3.Ru2f** along with a molecule of benzaldehyde. The benzaldehyde



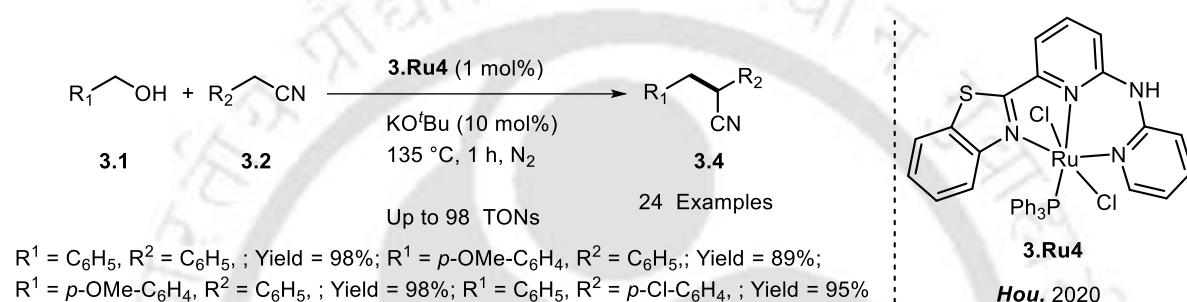
Scheme 3.2. The PNP pincer-ruthenium catalysed α -alkylation of nitriles reported by Gunanathan.⁹

and the Ru-enamine adduct **3.Ru2c** undergoes [2+2] Michael addition and this Michael addition adduct **3.Ru2d** reacts with the Ru-dihydride species **3.Ru2e** to give the final product **3.4** (Scheme 3.2). This whole process represents metal-ligand cooperation.⁹ Later, Li has provided the computational insight of the mechanism reported by Gunanathan,⁹ and revealed that hydrogen-transfer step is the rate determining step with a barrier of 23.9 kcal/mol.²²

Zhu reported the NNN pincer-Ru **3.Ru3** catalysed α -alkylation of nitriles which afforded the alkylated product in up to 98% yield under N_2 atmosphere (Scheme 3.3). The reaction proceeds via an inner-sphere mechanism which involved processes such as dehydrogenation of alcohols, condensation of the resulting carbonyls with nitrile followed by hydrogenation of the unsaturated nitrile.¹⁰

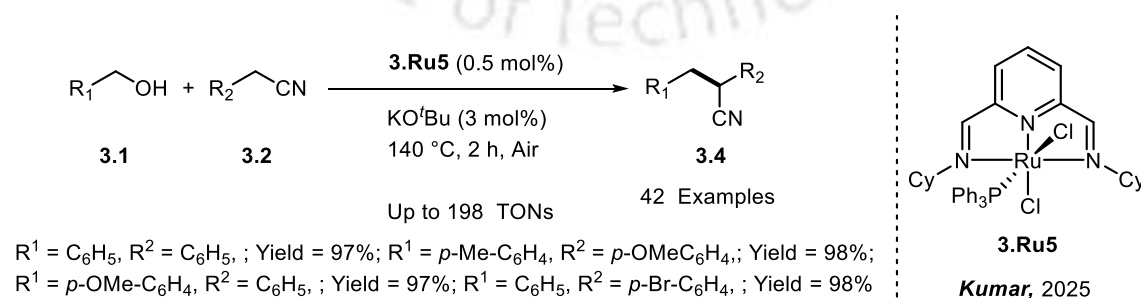


Scheme 3.3. The NNN pincer-ruthenium catalysed α -alkylation of nitriles reported by Zhu.¹⁰



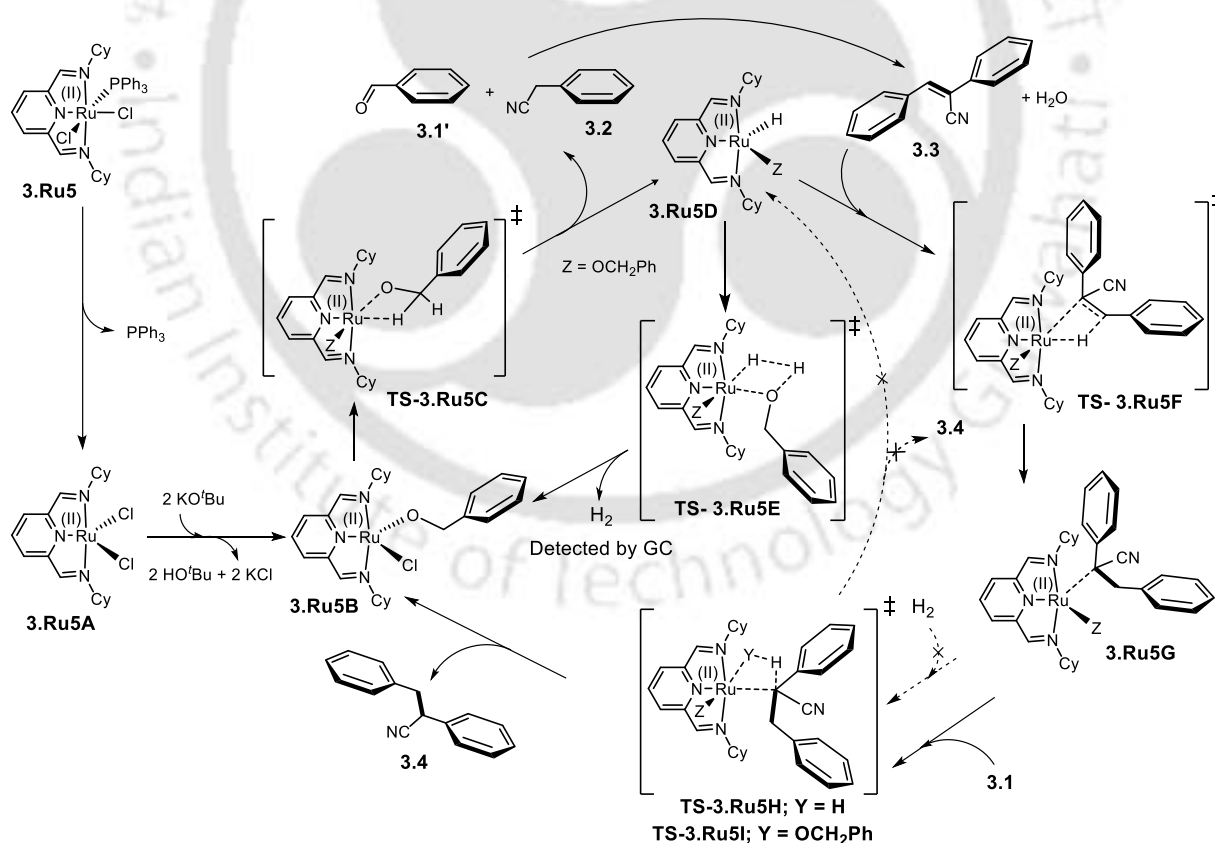
Scheme 3.4. The NNN pincer-ruthenium catalysed α -alkylation of nitriles reported by Hou.¹¹

Hou designed NNN pincer-Ru complexes based on $^{PBT}NN^XN$ ligands containing linker atoms such as O, S, NCH₃ and NH. The complex **3.Ru4** with NH linking functionality has shown the best activity and has afforded up to 98% yield of the desired product at a catalyst loading of 1 mol% within 1 hour at 135 °C under N₂ atmosphere (Scheme 3.4). A variety of substrates have been investigated. Based on control experiments, they have proposed an inner-sphere mechanism and further details about the inhibition of the formation of the product **3.4** in the presence of oxygen, was obtained from the kinetic studies.¹¹



Scheme 3.5a. The NNN pincer-ruthenium catalysed α -alkylation of nitriles reported by Kumar.¹⁵

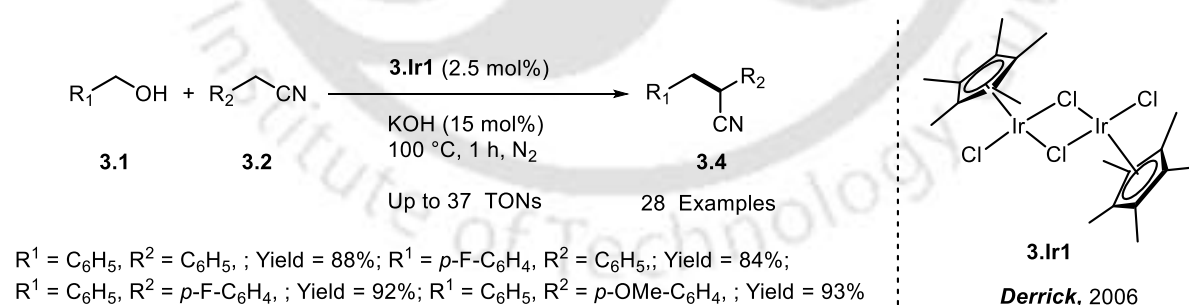
Recently, Kumar demonstrated the α -alkylation of nitriles catalysed by 0.5 mol% [(Cy²NNN)RuCl₂(PPh₃)] **3.Ru5** in the presence of only 3 mol% KO^tBu and observed 99% yield of the desired product at 140 °C, within 2 hours under air (Scheme 3.5a). The reaction proceeds via the dissociation of PPh₃ from **3.Ru5** and generates the species **3.Ru5A**. In the presence of KO^tBu and **3.1**, the species **3.Ru5A** undergoes salt metathesis and generates an alkoxide species **3.Ru5B** (Scheme 3.5b). A β -hydride elimination from **3.Ru5B** leads to the generation of the Ru-hydride **3.Ru5D** species along with the extrusion of **3.1'**. A subsequent σ -bond metathesis of **3.Ru5D** in the presence of **3.1** regenerates the alkoxide species **3.Ru5B**. The intermediates **3.1** and **3.2** undergoes base mediated condensation to give rise to **3.3** (Scheme 3.5b). The species **3.3** undergoes insertion into the Ru-hydride species **3.Ru5D** to give **3.Ru5G** which then undergoes alcoholysis in the presence of **3.1** to regenerate the alkoxide species **3.Ru5B** and releases the desired product **3.4** (Scheme 3.5b). They have reported a KIE of 2.50 which gave indication of the involvement of C-H bond breaking/making process in the catalytic cycle. Further a detailed DFT studies showed that it follows inner-sphere mechanism where the alcoholysis step was found to be the RDS with an energy barrier of 28.7 kcal/mol.¹⁵



Scheme 3.5b. Plausible mechanism of the α -alkylation of nitriles catalysed by **3.Ru5** reported by Kumar.¹⁵

Derrick reported an iridium catalysed α -alkylation of nitriles where **3.Ir1** (2.5 mol%) in presence of KOH (15 mol%) afforded up to 93% of the α -alkylated product at 100 °C, after 1 hour under N₂ atmosphere (Scheme 3.6). They have shown the application of the developed protocol to a wide range of substrates including aliphatic alcohols, aromatic and heteroaromatic alcohols. The reaction proceeds via dehydrogenation of alcohol to aldehyde along with the generation of a hydride species. The catalyst, acts as a Lewis acid and activates the nitrile which is further deprotonated in the presence of base to form a nucleophilic species. A Knoevenagel condensation between the aldehyde and the nucleophilic species formed *in-situ* gives rise to the unsaturated nitrile, which then gets hydrogenated by the hydride species and forms the final product.¹⁶ Recently, the same catalyst **3.Ir1** was employed by Xu, where the α -alkylated arylacetonitrile or arylacetamide was obtained selectively only by tuning the base. Arylacetonitrile was obtained in presence of K₂CO₃ whereas arylacetamide was obtained in presence of KO^tBu.¹⁸

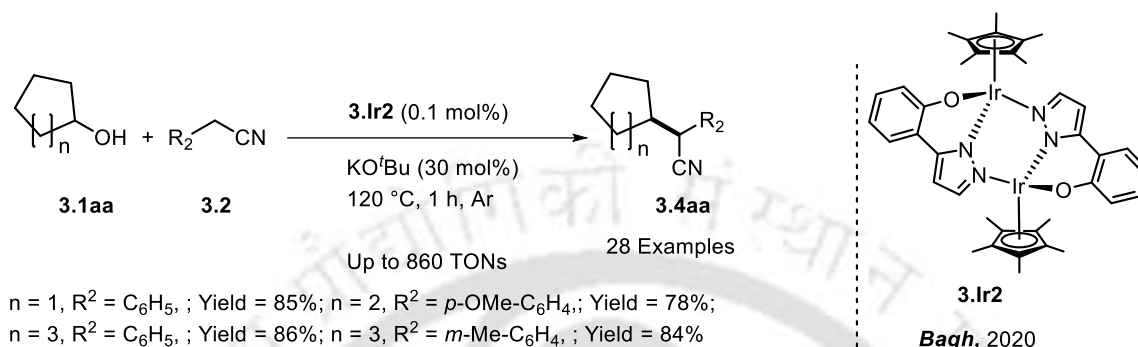
Bagh developed an iridium catalyst **3.Ir2** (0.1 mol%) which could catalyse the α -alkylation of nitriles with cyclic and aliphatic alcohols in up to 86% yields of the desired product under an atmosphere of Ar (Scheme 3.7). Thorough mechanistic investigation revealed that this transformation follows the hydrogen-borrowing strategy, where the alcohol is first oxidised to ketone by **3.Ir2**, which then undergoes base mediated aldol-type condensation in the presence of a nitrile to generate vinyl nitrile. Further reduction of vinyl nitrile in presence of the Ir-hydride species generates the final product.¹⁹



Scheme 3.6. Iridium catalysed α -alkylation of nitriles reported by Derrick.¹⁶

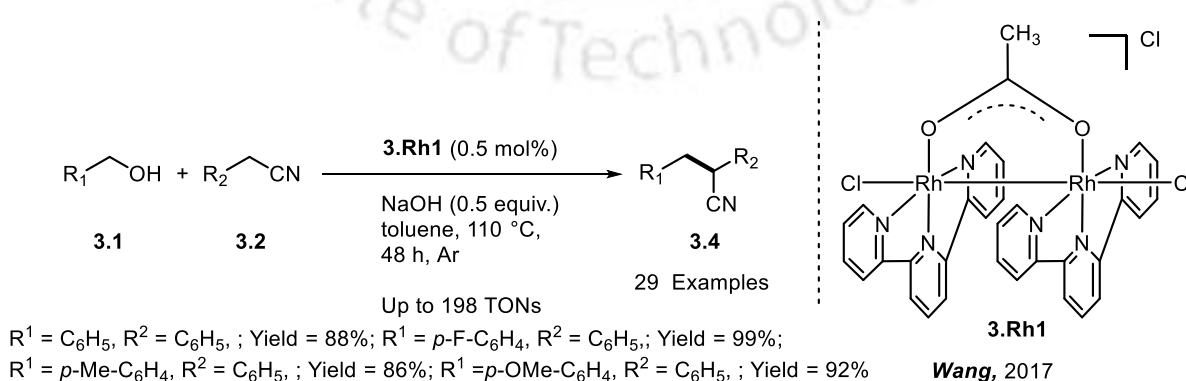
Wang demonstrated that the rhodium catalyst **3.Rh1** (0.5 mol%) could afford up to 99% yield of the desired product in presence of NaOH (50 mol%) at 110 °C in 48 hours under argon (Scheme 3.8). This binuclear Rh catalyst dehydrogenates the alcohol and generates the Rh-hydride species along with a molecule of aldehyde which undergoes condensation with the

nitrile to produce α -alkylated olefin. Under argon, the process of hydride transfer from Rh-hydride species to the α -alkylated olefin is feasible and hence the formation of the α -alkylated nitrile is observed. Whereas, it was observed that, in presence of oxygen, the reaction stops at α -alkylated olefin, because in the presence of oxygen the Rh-hydride prefers to react with oxygen rather than α -alkylated olefin.²⁰



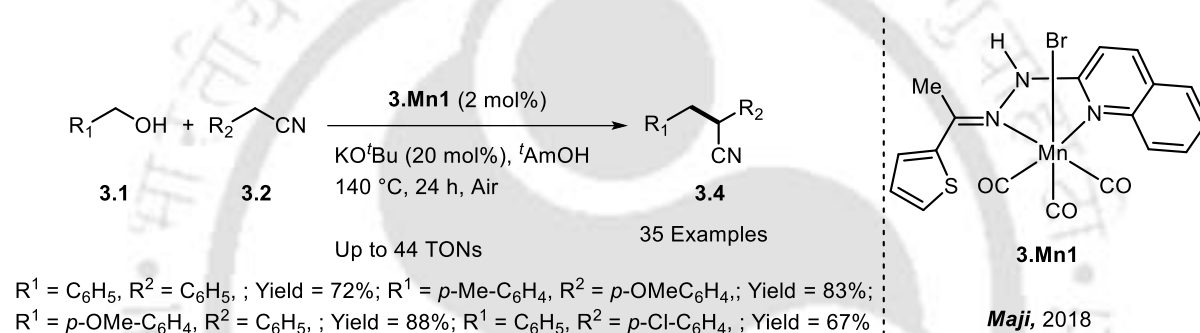
Scheme 3.7. Iridium catalysed α -alkylation of nitriles reported by Bagh.¹⁹

From the context of the current work, related reports on earth abundant, inexpensive first-row, 3d metal catalytic systems for the α -alkylation of nitriles have been discussed in greater detail.²⁶ In 2018, Maji reported a supported Mn(I)-complex **3.Mn1** (2 mol%) based on a bidentate hydrazone ligand that catalysed the α -alkylation of nitriles to afford 72% yield of α -alkylated nitrile **3.4** in presence of 20 mol% KO^tBu at 140 °C within 24 hours under an atmosphere of argon (Scheme 3.9). The presence of a bifunctional hydrazine ligand led to an outer-sphere mechanism where the (de)hydrogenation reactions involved the co-operation from the N-H group of the bidentate hydrazine ligand.²³ The following year, El-Sepelgy arrived at a condition to achieve 86% of the α -alkylated nitrile **3.4** in presence of 1 mol% PNP-Mn(I) complex **3.Mn2** and Cs₂CO₃ (10 mol%) at 135 °C after 18 hours under Ar (Scheme 3.10a).



Scheme 3.8. The pincer-rhodium catalysed α -alkylation of nitriles reported by Wang.²⁰

The reaction proceeded via an outer-sphere mechanism which was found to involve metal-ligand co-operation effect where the N-H bond of the PNP ligand actively participated in the (de)hydrogenation reactions. Initially, the precatalyst **3.Mn2** generates an imido complex in the presence of base. The dehydrogenation of **3.1** to **3.1'** occurs in presence of the active imido complex along with the formation of H-Mn-N-H species (Scheme 3.10b). Then, **3.2** coordinates to the imido species and forms the **3.Mn2A** species. Hydrogen abstraction from the **3.Mn2A** by ligand generates a highly nucleophilic **3.Mn2B**. Nucleophilic addition of **3.Mn2B** to the *in-situ* generated **3.1'** leads to the formation of an intermediate **3.Mn2C** (Scheme 3.10b). The compound **3.3** is generated from the intermediate **3.Mn2C** along with the regeneration of the imido species. The compound **3.3** is then hydrogenated by the H-Mn-N-H species to form the final product **3.4** via metal-ligand cooperation (Scheme 3.10b).²⁴

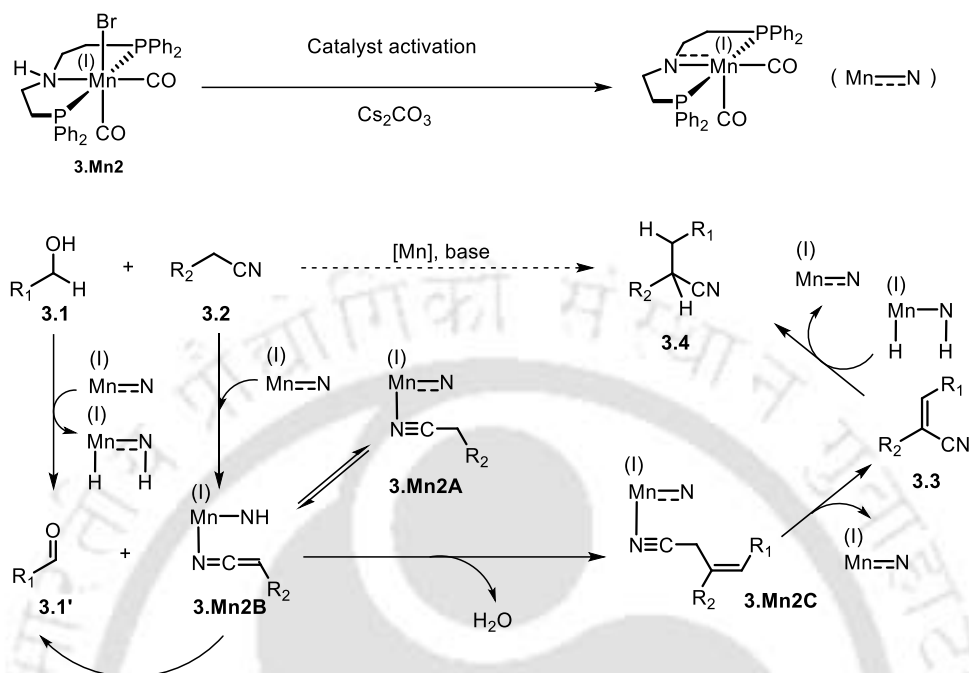


Scheme 3.9. NN bidentate-Mn catalysed α -alkylation of nitriles reported by Maji.²³

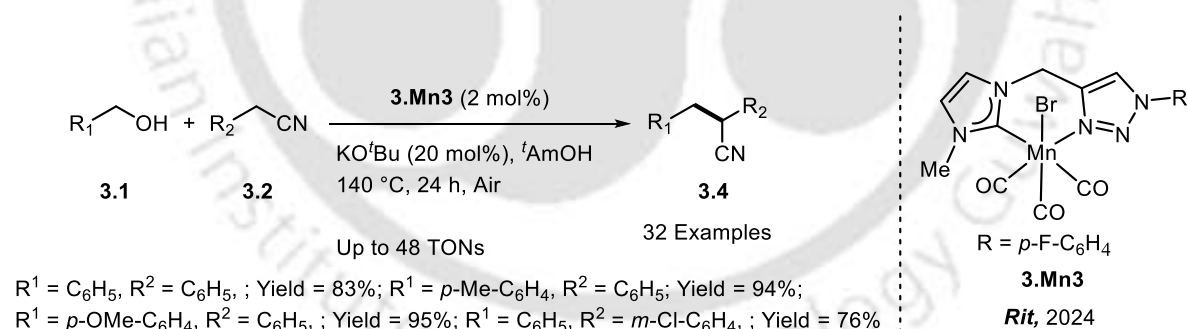
Very recently, Rit demonstrated the reactivity of an electron rich NHC-Mn(I) complex **3.Mn3** based on heteroditopic NHC ligands containing donors such as imidazol-2-ylidene (ImNHC) and 1,2,3-triazole-N (1,2,3-tz-N) or 1,2,3-triazol-5-ylidene (tzNHC), that could catalyse the synthesis of **3.4** selectively in 83% yield at 140 °C after 24 hours under inert atmosphere (Scheme 3.11). Deuterium labelling experiments suggests that the dehydrogenation of the deuterated benzyl alcohol was the key step in the catalytic cycle, which generates a Mn-D species. The transfer of the deuteride from Mn-D to the β -position of the **3.3** produces the product **3.4**. Based on the DFT studies, they have proposed the dehydrogenation of alcohol to corresponding aldehyde as the most probable rate-determining step.²⁵

Zhong in 2024, developed a protocol using a N,N-bidentate ligand based Mn(I) catalyst **3.Mn4** to selectively achieve 83% yield of **3.4** at 140 °C after 48 hours in an argon atmosphere (Scheme 3.12). They have reported a wide range of substrate scope and also developed a protocol to synthesize a natural product anipamil, which works as a calcium channel blocker. The mechanistic studies such as deuterium labelling experiments suggests the a Mn-hydride species

H **3.Fe3D** generated from **3.Fe3C** then reduces the acrylonitriles to the final product under light irradiation via a transition state **3.Fe3E** regenerating the active species **3.Fe3A** (Scheme 3.15b).³⁰

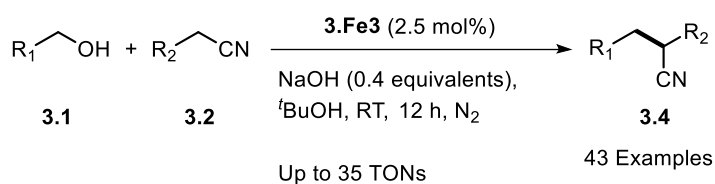


Scheme 3.10b. Proposed mechanism for the pincer-manganese catalysed α -alkylation of nitriles reported by El-Sepelgy.²⁴

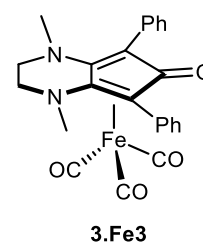


Scheme 3.11. A NHC based bidentate manganese catalyst for the α -alkylation of nitriles reported by Rit.²⁵

The α -alkylation of nitriles with alcohols using 5 mol% of Cp*Co(III) **3.Co1** and 2 equivalents of KO^tBu under an argon atmosphere was demonstrated by Sundararaju in 2020 that afforded the desired product in up to 77% yield after 24 h (Scheme 3.16).³¹ Ding on the other hand, employed a ⁱPrPPN^HPyMe-Co(I) **3.Co2** complex (1.3 mol%) to catalyse the α -alkylation of nitriles in presence of an additive, KHBET₃ (3.5 mol%) and KOH (20 mol%) at 140 °C for 24

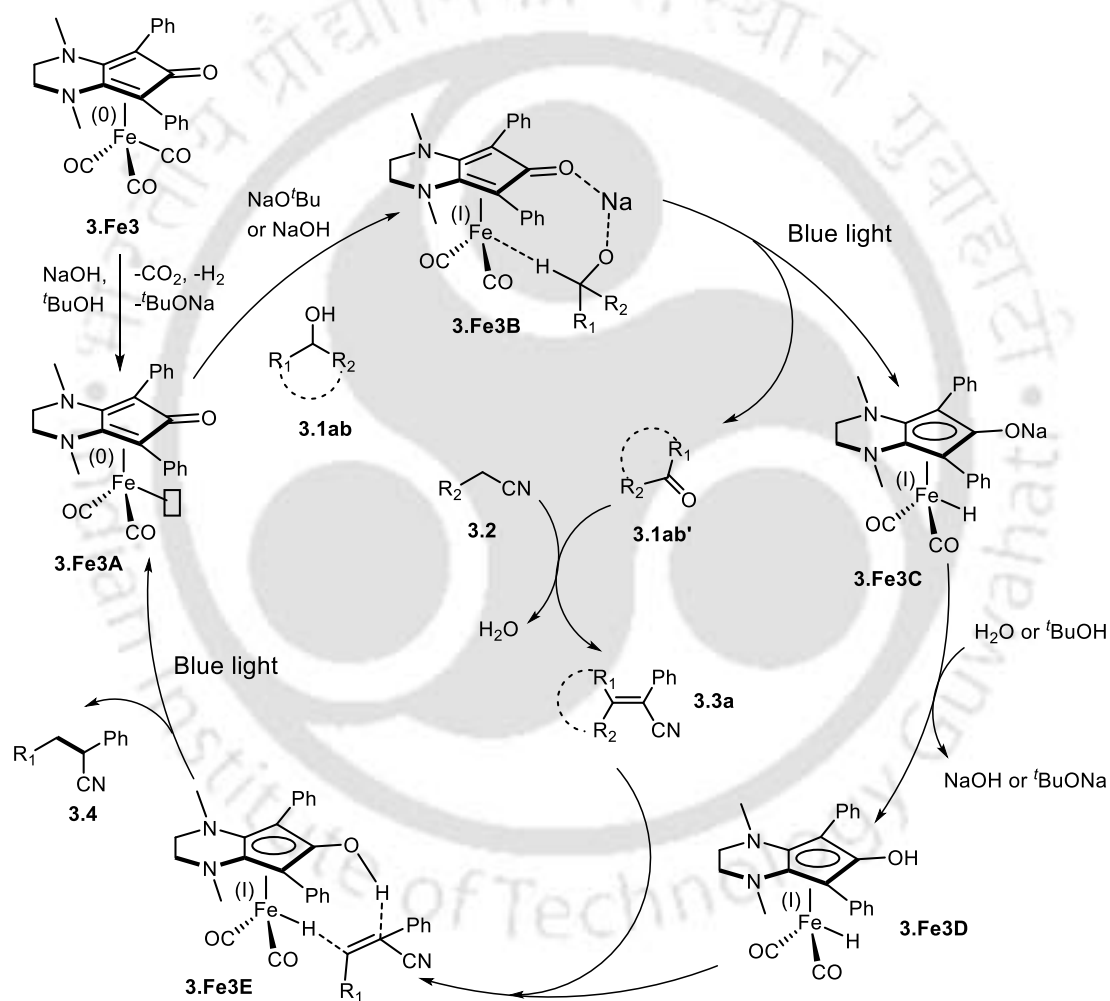


$\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = \text{C}_6\text{H}_5$, ; Yield = 85%; $\text{R}^1 = p\text{-OMe-C}_6\text{H}_4$, $\text{R}^2 = \text{C}_6\text{H}_5$; Yield = 80%;
 $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = p\text{-OMe-C}_6\text{H}_4$, ; Yield = 83%; $\text{R}^1 = \text{C}_6\text{H}_5$, $\text{R}^2 = p\text{-Me-C}_6\text{H}_4$, ; Yield = 83%



Zhong, 2023

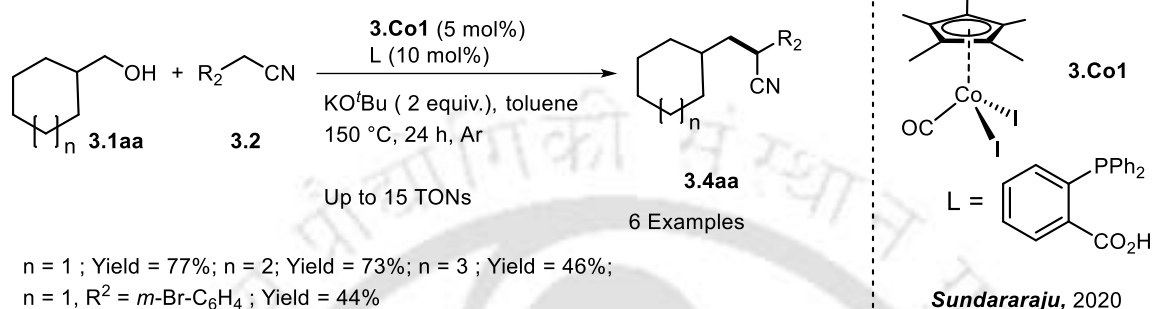
Scheme 3.15a. A half-sandwich iron complex for the catalytic α -alkylation of nitriles reported by Zhong.³⁰



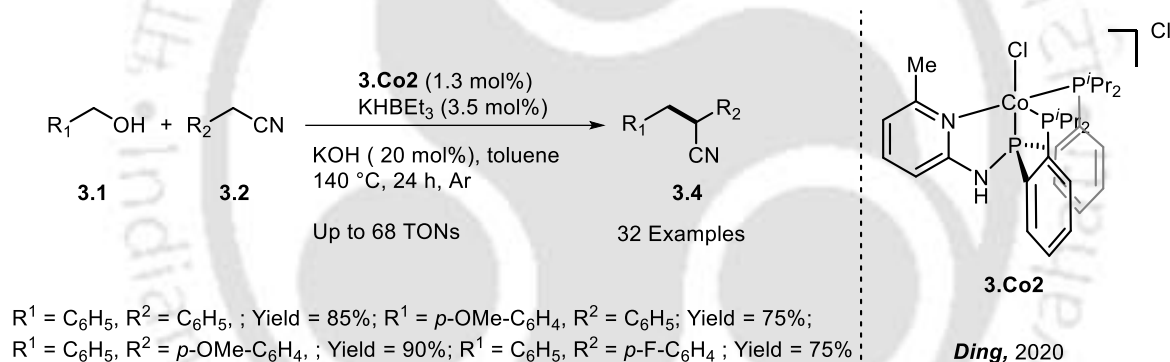
Scheme 3.15b. Plausible mechanism for the half sandwich Fe complex catalysed α -alkylation of nitriles reported by Zhong.³⁰

In 2024, Rit and co-workers reported bifunctional NHC-Co(III) complex **3.Co3** catalysed α -alkylation of nitriles where they could achieve 89% of **3.4** at 140 °C in 6 hours under Ar (Scheme 3.18). Both bifunctional and non-bifunctional NHC-Co(III) systems were

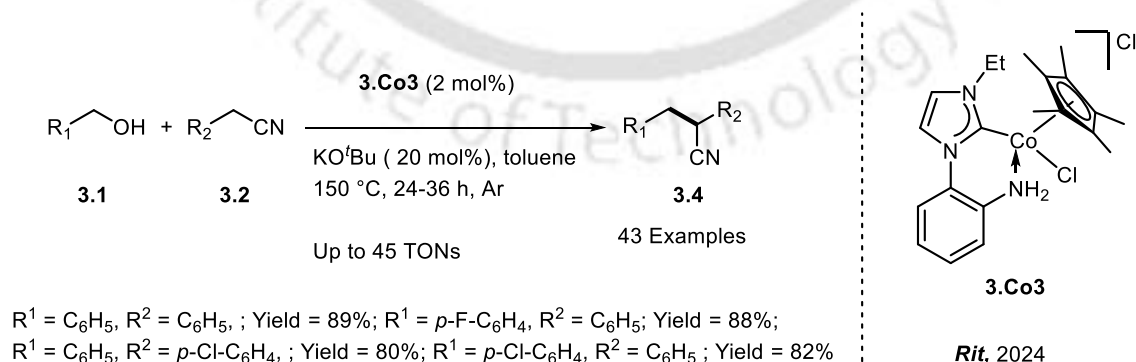
investigated for the α -alkylation of nitriles. Results suggested that the bifunctional complexes were more active than the non-bifunctional NHC-Co complexes. The k_H/k_D value of 1.3 suggests that the dehydrogenation of alcohol may not be a part of the rate determining step. The proposed mechanistic pathway for the bifunctional NHC-Co complexes showed metal-ligand cooperativity.³³



Scheme 3.16. The piano-stool cobalt complex for the catalytic α -alkylation of nitriles reported by Sundararaju.³¹

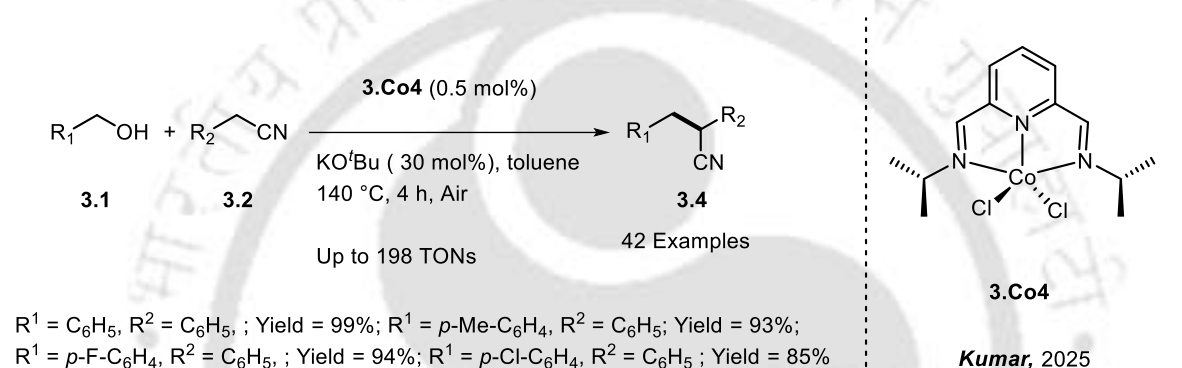


Scheme 3.17. A cobalt complex based on tetradentate PPPN ligand for the catalytic α -alkylation of nitriles reported by Ding.³²

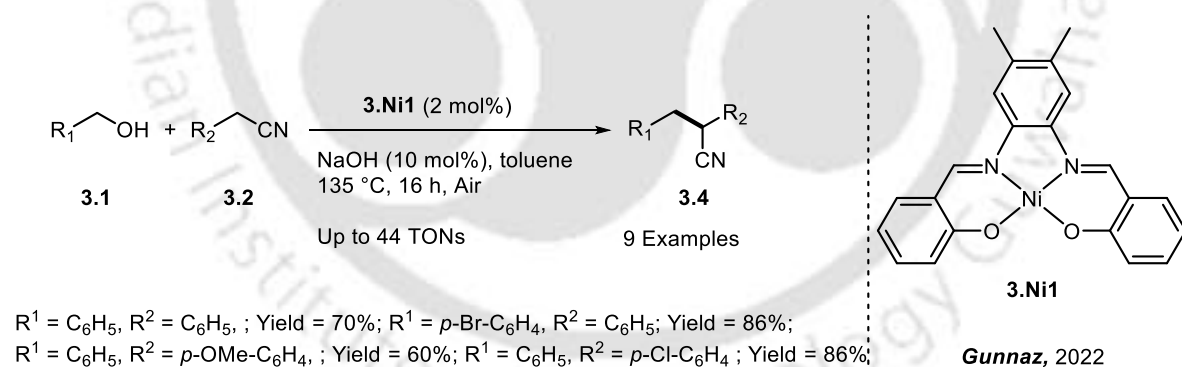


Scheme 3.18. A half-sandwich cobalt complex for the catalytic α -alkylation of nitriles reported by Rit.³³

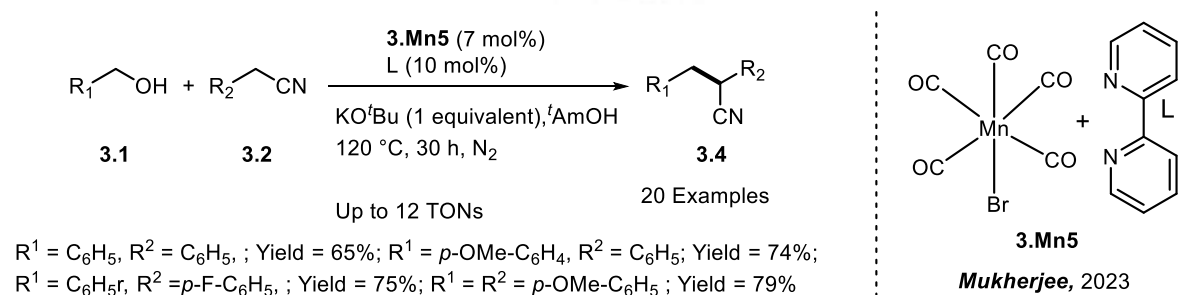
Very recently, Jagadeesh utilized cobalt nanoparticles supported on nitrogen-doped porous carbon (Co@PNC-900) as a heterogeneous catalyst at a loading of 2 mol% in the presence of an equivalent of K_3PO_4 at 140 °C, to achieve the α -alkylation of nitriles in up to 95% yield after 24 h.³⁶ Very recently, Kumar accomplished the α -alkylation of nitriles utilizing **3.Co4** (0.5 mol%) in presence of KO^tBu (30 mol%) at 140 °C and achieved 99% yield of **3.4** in 4 h under air (Scheme 3.19). Deuterium labelling studies revealed a KIE of 2.6 which suggested C-H activation might take part in the RDS. Further detailed computational studies indicated β -hydride elimination as the RDS and also suggested that the reaction proceeds via alcoholysis pathway. Moreover a good co-relation was found between the experimental (33.3 kcal/mol) and computed values (31.2 kcal/mol) of energy barrier.³⁴



Scheme 3.19. The pincer-cobalt catalysed α -alkylation of nitriles reported by Kumar.³⁴

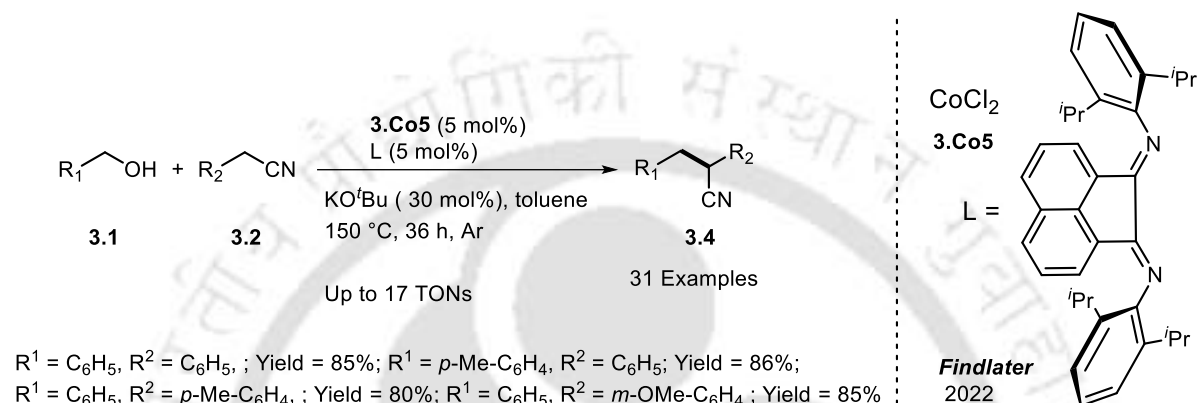


Scheme 3.20. A ONNO tetradentate Ni complex for the catalytic α -alkylation of nitriles.³⁵



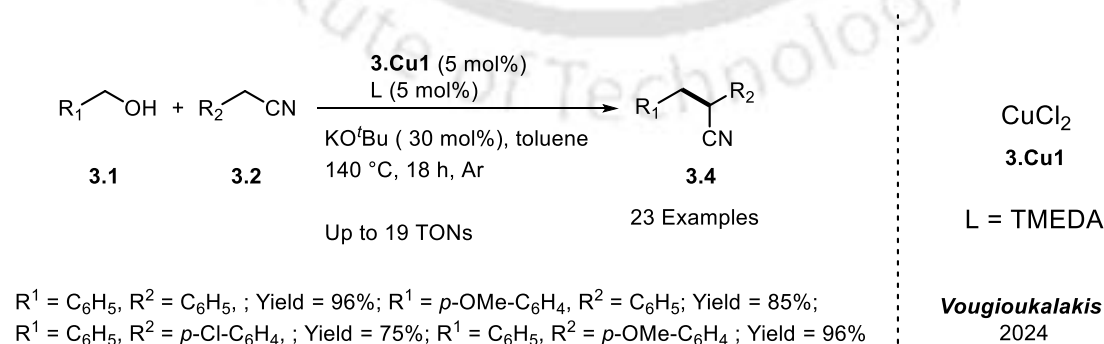
Scheme 3.21. Manganese catalysed α -alkylation of nitriles reported by Mukherjee.³⁷

In 2022, the research group of Gunnaz demonstrated the activity of Ni(II) complex **3.Ni1** derived from a tetradentate ONNO schiff-base ligand towards the α -alkylation of nitriles which afforded 88% yield of **3.4** under air (Scheme 3.20). The **3.Ni1** complex catalysed the dehydrogenation of alcohol and generated a Ni-hydride species which later takes part in hydrogenation of the unsaturated nitrile **3.3**, which is formed in a base mediated condensation of aldehyde and nitrile.³⁵



Scheme 3.22. Cobalt catalysed α -alkylation of nitriles reported by Findlater.³⁸

Mukherjee employed readily available $\text{Mn}(\text{CO})_5\text{Br}$ (7 mol%) **3.Mn5** and a bidentate NN ligand (10 mol%) to achieve 89% yield of **3.4** at 120 $^\circ\text{C}$ in 30 hours under N_2 (Scheme 3.21). Experimental analysis suggested the formation of *in-situ* generated Mn(I) complex in the presence of 1,1'-biphenyl ligand, which further generated a Mn(I)-alkoxide species in the course of reaction. This Mn(I)-alkoxide species underwent β -hydride elimination and formed a Mn(I)-hydride species which further hydrogenated the vinyl nitrile to give the α -alkylated nitrile.³⁷

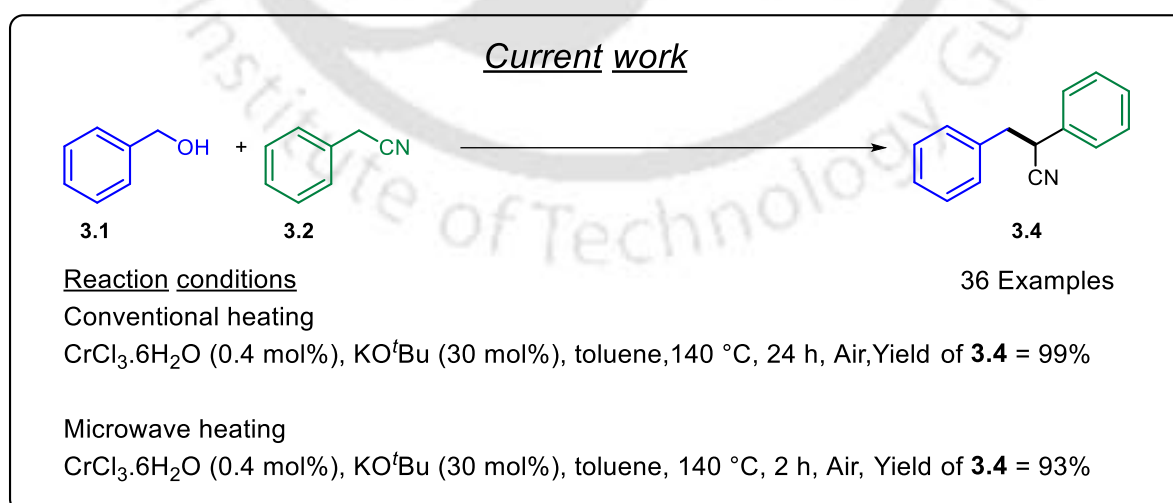


Scheme 3.23. The cuprous chloride catalysed α -alkylation of nitriles in the presence of a ligand that is reported by Vougioukalakis.³⁹

Findlater utilised readily available CoCl_2 (5 mol%) **3.Co5** along with BIAN ligand (5 mol%) to catalyse the α -alkylation of nitriles that resulted in 88% yield of **3.4** in presence of KO^tBu (30 mol%) at 150°C , in 36 hours under an atmosphere of Ar (Scheme 3.22). The iPrBIANCoCl_2 complex is expected to have formed *in-situ*, which might have carried forward this transformation of α -alkylation of nitriles. Various substrates have been screened including aliphatic alcohols.³⁸ Vougioukalakis and co-workers utilised simple CuCl_2 salt **3.Cu1** (5 mol%) along with TMEDA (5 mol%) as an additive to achieve 99% of **3.4** in presence of KO^tBu (30 mol%) at 140°C in Ar atmosphere (Scheme 3.23). The reaction proceeds via a radical pathway and both Cu(II)-hydride and Cu(III)-hydride species participate in the catalytic cycle. This proposal was supported by the results of kinetic experiments, radical trapping experiment and DFT studies.³⁹

3.2. Objectives of the current work

A comprehensive literature survey reveals that organometallic complexes, pincer complexes and metal salts aided with ligands are very active for the α -alkylation of nitriles. While the catalytic systems based on first-row transition metals as manganese,^{23-25, 27, 37} cobalt^{31-33, 36, 38} and iron²⁹⁻³⁰ have been well-explored, there are only a report each on Ni³⁵ and Cu³⁹ based catalysts with no report on any Cr based catalysts for the α -alkylation of nitriles. Considering our recent success in use of several first-transition metal salts⁴⁰⁻⁴⁴ in accomplishing various C-C bond forming reactions some of which involved dehydrogenation as a key step, the present chapter attempts to address the following questions:



Scheme 3.24. Current work.

- Can one use commercially available 3d-metal salt chromium chloride ($\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$) to catalyse for the α -alkylation of nitriles in air without any compromise on the overall performance?
- Can we also accomplish this transformation under microwave conditions similar to the work done in chapter II?

3.3. Results and Discussion

We initiated our investigation by treating the model substrates benzyl alcohol **3.1** (1 mmol) and benzyl nitrile **3.2** (0.5 mmol) with 0.4 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in presence of 10 mol% KO^tBu in toluene (1 mL) at 140 °C for 24 hours (entry 1, Table 3.1) leading to exclusive generation of α,β -unsaturated nitrile **3.3** in 11% yield. On increasing the base loading to 20 mol%, a mixture of α,β -unsaturated nitrile **3.3** and α -alkylated nitrile **3.4** was observed in 9% and 55% yield respectively (entry 2, Table 3.1). To our delight, on further increasing the KO^tBu loading to 30 mol% (entry 3, Table 3.1) and 40 mol% (entry 4, Table 3.1), the desired product α -alkylated nitrile **3.4** was selectively afforded in 99% yield. Thus, further optimizations were performed using 30 mol% base loading with various bases. Moderate yield of the α -alkylated nitrile **3.4** (74%) was obtained in presence of KOH (entry 5, Table 3.1). The yields obtained upon use of NaOH (entry 6, Table 3.1) and NaO^tBu (entry 7, Table 3.1) were comparable but lower relative to the corresponding yields provided by KO^tBu (entry 3, Table 3.1). Poor yield of **3.4** was obtained in the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.4 mol%) catalysed α -alkylation of **3.2** with **3.1** in the presence of NaOEt (entry 8, Table 3.1), while carbonate bases like Na_2CO_3 , K_2CO_3 and NaHCO_3 did not give any product under the optimized conditions (entry 9-11, Table 3.1). There was no product formation in absence of base (entry 12, Table 3.1) under otherwise identical reaction conditions.

The $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.4 mol%) catalysed α -alkylation of **3.2** with **3.1** in presence of 30 mol% KO^tBu was then carried out in various solvents like mesitylene, *o*-xylene, *m*-xylene, THF, acetonitrile (entry 13-17, Table 3.1) albeit with poor yields. The amount of the best solvent toluene was then varied. Increasing the amount of toluene to 1.5 mL did not affect the reactivity (entry 18, Table 3.1) but lowering the amount of toluene to 0.5 mL resulted in lowering of the yield (69% of **3.4**) (entry 19, table 3.1). The $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.4 mol%) catalysed α -alkylation of **3.2** with **3.1** in the presence of 30 mol% KO^tBu in the absence of any solvent yielded trace amounts of **3.4** (entry 20, Table 3.1). At higher loadings of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, the α -alkylated nitrile **3.4** was obtained in 100% yield (entry 21 and entry 22, Table 3.1). On decreasing the catalyst

Table 3.1. Optimization of the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed α -alkylation of benzyl nitrile (**3.2**) with benzyl alcohol (**3.1**) under varying conditions.^a

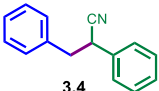
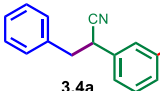
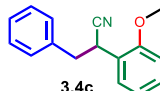
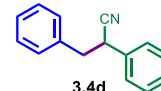
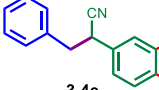
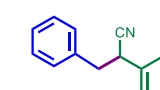
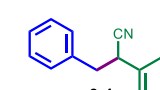
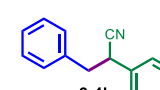
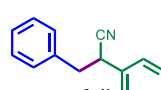
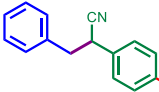
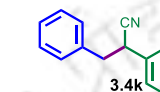
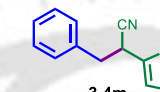
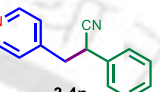
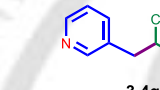
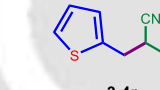
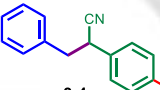
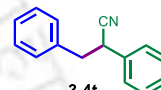
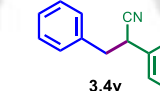
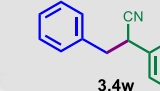
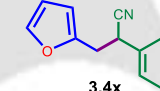
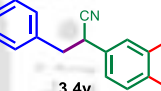
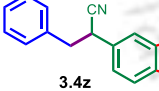
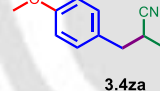
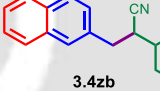
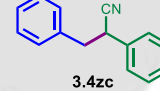
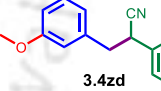
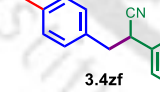
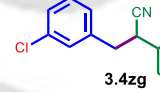
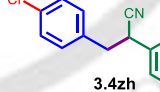
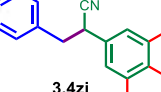
Reaction scheme: Benzyl alcohol (**3.1**) + Benzyl nitrile (**3.2**) $\xrightarrow[\text{Base (Y Mol\%), Solvent (Z mL), T } ^\circ\text{C, t h Open vessel, Air}]{\text{CrCl}_3 \cdot 6\text{H}_2\text{O (X mol\%)}}$ α -alkylated nitrile (**3.3**) + β -alkylated nitrile (**3.4**)

Entry ^a	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (X mol%)	Base (Y mol%)	Solvent (Z mL)	Yield of 3.3 (%) ^b	Yield of 3.4 (%) ^b
1	0.4 mol%	KO ^t Bu (10)	Toluene (1 mL)	11	0
2	0.4 mol%	KO ^t Bu (20)	Toluene (1 mL)	9±0	55±11
3	0.4 mol%	KO ^t Bu (30)	Toluene (1 mL)	0	99±1
4	0.4 mol%	KO ^t Bu (40)	Toluene (1 mL)	0	99±1
5	0.4 mol%	KOH (30)	Toluene (1 mL)	9±2	74±3
6	0.4 mol%	NaOH (30)	Toluene (1 mL)	10±1	58±8
7	0.4 mol%	NaO ^t Bu (30)	Toluene (1 mL)	10±2	60±1
8	0.4 mol%	NaOEt (30)	Toluene (1 mL)	7±1	42±1
9	0.4 mol%	Na_2CO_3 (30)	Toluene (1 mL)	0	0
10	0.4 mol%	K_2CO_3 (30)	Toluene (1 mL)	0	0
11	0.4 mol%	NaHCO_3 (30)	Toluene (1 mL)	0	0
12	0.4 mol%	-	Toluene (1 mL)	0	0
13	0.4 mol%	KO ^t Bu (30)	Mesitylene (1 mL)	16	Trace
14	0.4 mol%	KO ^t Bu (30)	o-xylene (1 mL)	16	17
15	0.4 mol%	KO ^t Bu (30)	m-xylene (1 mL)	21	17
16	0.4 mol%	KO ^t Bu (30)	THF (1 mL)	0	0
17	0.4 mol%	KO ^t Bu (30)	Acetonitrile (1 mL)	0	0
18	0.4 mol%	KO ^t Bu (30)	Toluene (1.5 mL)	0	100
19	0.4 mol%	KO ^t Bu (30)	Toluene (0.5 mL)	0	69
20	0.4 mol%	KO ^t Bu (30)	-	0	Trace
21	0.8 mol%	KO ^t Bu (30)	Toluene (1 mL)	0	100
22	0.6 mol%	KO ^t Bu (30)	Toluene (1 mL)	0	100
23	0.2 mol%	KO ^t Bu (30)	Toluene (1 mL)	0	91±1
24	0.02 mol%	KO ^t Bu (30)	Toluene (1 mL)	9	68
25	0.005 mol%	KO ^t Bu (30)	Toluene (1 mL)	8	64
26 ^{a,c}	0.4 mol%	KO ^t Bu (30)	Toluene (1 mL)	0	98
27 ^{a,d}	0.4 mol%	KO ^t Bu (30)	Toluene (1 mL)	19±0	14±1
28 ^{a,e}	0.4 mol%	KO ^t Bu (30)	Toluene (1 mL)	18±0	0
29	-	KO ^t Bu (30)	Toluene (1 mL)	0	32
30 ^f	0.4 mol%	KO ^t Bu (30)	Toluene (1 mL)	0	93

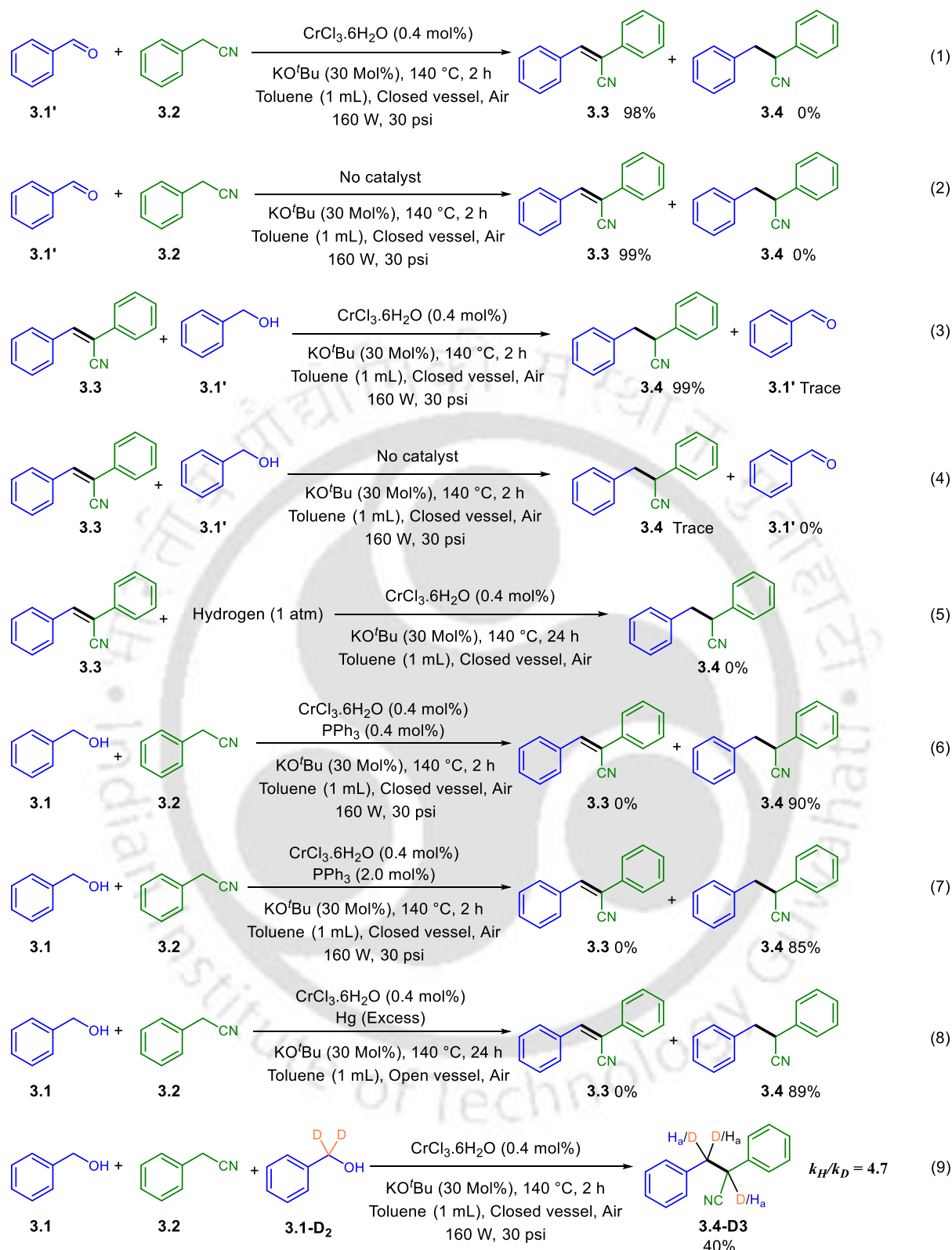
^a Reaction conditions: Benzyl alcohol **3.1** (1 mmol), benzyl cyanide **3.2** (0.5 mmol), $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (X mol%), base (Y mol%), and Solvent (Z mL) were heated together in a 5 mL flask connected to condenser under air at 140 °C for 24 hours. The mol% of base and catalyst are with respect to benzyl cyanide (**3.2**). ^bYield is determined from ^1H NMR analysis using hexamethylbenzene as a standard. Yields reported are the average of two runs. ^cReaction was done at 160 °C. ^dReaction was done at 120 °C. ^eReaction was done at 100 °C. ^fReaction was done under microwave condition (125 W, 30 psi) in a closed vessel for 2h.

loading to 0.2 mol% the yield of α -alkylated nitrile **3.4** have decreased to 91% (entry 23, Table 3.1). Further decrease in the loading of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ to 0.02 mol% and 0.005 mol% led to moderately good yields of 68% and 64% respectively (entries 24 and 25, Table 3.1). At higher temperature, there was no change in reactivity (entry 26, Table 3.1). Whereas, a sharp decrease

Table 3.2. The $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed α -alkylation of a variety of nitriles with several benzyl alcohol derivatives under conventional and microwave heating conditions

				
99% ^b [94%] ^b , 93% ^c	52% ^b , 80% ^c , 87%[80%] ^d	0% ^b , 35% ^c , 26% ^{c,g}	39% ^b , 60% ^c , 96%[87%] ^d , 44% ^f	61% ^b , 68% ^c , 79%[73%] ^e
				
0% ^b , 42%[36%] ^c	41% ^b , 40% ^c , 93%[89%] ^{c,g}	0% ^b , 30% ^c , 37% ^{e,g}	Trace ^b , 73%[68%] ^c	27% ^b , 44% ^c , 97%[90%] ^{c,g}
				
R = NO_2 ; 4j 0% ^b , 0% ^c , R = CF_3 ; 4i 0% ^b , 0% ^c	29% ^b , 45% ^c , 60%[57%] ^e , 96% ^{c,g}	0% ^b , 15% ^c	Trace ^b , 39% ^c , 36% ^d , 62%[55%] ^{c,g,h}	Trace% ^b , 77%[71%] ^c
				
Trace ^b , 42% ^c , 82%[78%] ^{c,g}	Trace ^b , 50% ^c , 92%[88%] ^{c,g}	0% ^b , 0% ^c	30% ^b , 29% ^c , 41% ^{c,g}	Trace% ^b , 87% ^c , 96%[90%] ^e
				
40% ^b , 86%[76%] ^c , 54% ^d	90% ^b , 94%[89%] ^c	0% ^b , 44% ^c , 62%[57%] ^{c,g}	0% ^b , 0% ^c	72% ^b , 96%[89%] ^c
				
64% ^b , 50%[59%] ^c	56% ^b , 70%[66%] ^c	0% ^b , 0% ^c , 0% ^{c,g}	39% ^b , 48% ^c , 85%[78%] ^d , 82% ^{c,g}	61% ^b , 85%[78%] ^c
				
64% ^b , 69%[65%] ^c	47% ^c , 91%[87%] ^e , 98% ^{c,g,h}	28% ^b , 48% ^c , 98%[91%] ^{c,g}	93% ^e , 96%[90%] ^{c,g,h}	92%[90%] ^c

^aReaction conditions: Benzyl alcohol derivatives **3.1a-z**, **3.1za-zi** (1 mmol), benzyl cyanide derivatives **3.2a-z**, **3.2za-zi** (0.5 mmol), KO^tBu (30 mol%), $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.4 mol%) and toluene (1 mL) at 140 °C. Yield determined from ^1H NMR analysis using hexamethyl benzene as a standard. ^bConventional heating conditions after 24 h. ^cMicrowave conditions 2 h (125-160 watt, 30 psi). ^dConventional heating conditions with 50 mol% KO^tBu after 24 h. ^eConventional heating conditions with 60 mol% KO^tBu after 24 h. ^fReaction with 50 mol% KO^tBu in absence of catalyst. Isolated yield is written in parenthesis. ^gDerivatives of benzyl cyanide was added in batches (0.2+0.2+0.1) mmol at an interval of 20 minute. ^hThe corresponding solid derivatives of **3.1** were melted and maintained at 140 °C for a couple of minutes prior to solubilizing $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in them.

Figure B3, Table B1, Section B3
Appendix B**Scheme 3.25.** Control Experiments.

in the yield of **3.4** was observed at 120 °C and 100 °C (entries 27 and 28, Table 3.1). A catalyst-free reaction yielded 32% of the α -alkylated nitrile **3.4** under otherwise identical reaction

conditions in 24 hours which highlights the importance of the catalyst (entry 29, Table 3.1). Various derivatives of benzyl alcohol (**3.1**) and benzyl nitrile (**3.2**) were subjected to the optimized condition under conventional heating. In most of the cases, yields of α -alkylated nitrile **3.4** were not satisfactory (footnotes b, Table 3.2). With an intention to achieve better result, we did few reactions under the optimized condition but with higher base loading (50 mol% or 60 mol%, footnotes d or e, Table 3.2) which led to improvement in the yield of α -alkylated nitrile in few cases such as **3.4a**, **3.4c**, **3.4d**, **3.4g**, **3.4k**, **3.4n**, **3.4t**, **3.4u**, **3.4zc**, **3.4zf** and **3.4zh** (Table 3.2). This protocol was not favourable for aliphatic alcohols and nitriles and needs further optimization.

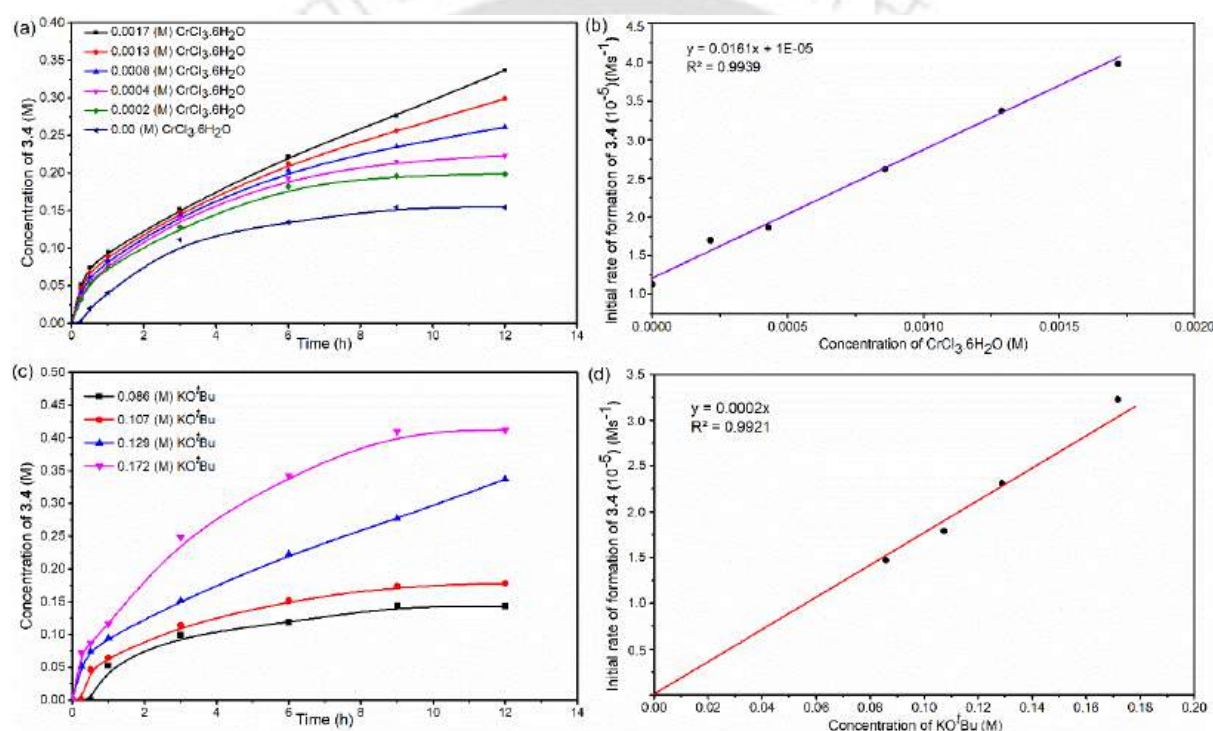


Figure 3.1. (a) Time profile of the α -alkylation of benzyl nitrile **3.2** with benzyl alcohol **3.1** under varying concentrations of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$. (b) Variation of the initial rate of formation of **3.4** with the concentration of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$. Reaction conditions for (a) and (b): $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.000013-0.00053 g, 0.00005-0.002 mmol, 0.00021-0.0017 M) benzyl alcohol (0.103 mL, 1 mmol, 0.858 M), benzyl cyanide (0.057 mL, 0.5 mmol, 0.429 M), KO^tBu (0.0168 g, 0.15 mmol, 0.129 M) in toluene (1 mL). (c) Time profile of the α -alkylation of benzyl nitrile **3.2** with benzyl alcohol **3.1** under varying concentrations of KO^tBu . (d) Variation of the initial rate of formation of **3.4** with the concentration of KO^tBu . Reaction conditions for (c) and (d): $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol, 0.0017 M), benzyl alcohol (0.103 mL, 1 mmol, 0.858 M), benzyl cyanide (0.057 mL, 0.5 mmol, 0.429 M), KO^tBu (0.014-0.025 g, 0.125-0.2 mmol, 0.107-0.172 M) in toluene (1 mL).

With an objective of achieving better yield of α -alkylated nitrile **3.4**, we continued to optimize the condition for different substrates. Based on the fact that, both benzyl alcohol **3.1** and benzyl cyanide **3.2** have permanent dipole moment (allows them to interact with the electric field of the microwave radiation making it microwave active) and from the observation of our previous

work⁴¹⁻⁴² we decided to carry out the reaction under microwave irradiation. Repeating the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.4 mol%) catalysed α -alkylation of **3.2** with **3.1** in the presence of 30 mol% KO^tBu under microwave irradiation instead of conventional heating for 2 h under air resulted in the selective formation of **3.4** in up to 93% yield. Though in many cases (**3.4a**, **3.4c-e**, **3.4h**, **3.4k**, **3.4n**, **3.4o**, **3.4p**, **3.4q**, **3.4t**, **3.4u**, **3.4w**, **3.4y**, **3.4za**, **3.4zc-ze** and **3.4zg**), use of microwave conditions resulted in a better yield in shorter duration, there were instances (**3.4b**, **3.4g**, **3.4m**, **3.4r**, **3.4x** and **3.4zb**) where the yields were still low. Encouraged by the inference of the kinetic studies that showed an inverse-first-order dependence of rate at high concentration ($> 0.17 \text{ M}$) of benzyl nitrile (*vide-infra*), the reaction of less-reactive substrates were repeated under microwave irradiation under the standard conditions but with addition of **3.2** derivatives in small portions (0.2 mmol, 0.17 M) at an interval of 20 minutes. This attempt afforded moderate to excellent yields of α -alkylated nitriles in most of the cases (**3.4f**, **3.4g**, **3.4i**, **3.4k**, **3.4n**, **3.4p**, **3.4q**, **3.4s**, **3.4w**, **3.4za**, **3.4zf**, **3.4zg** and **3.4zh** Table 3.2).

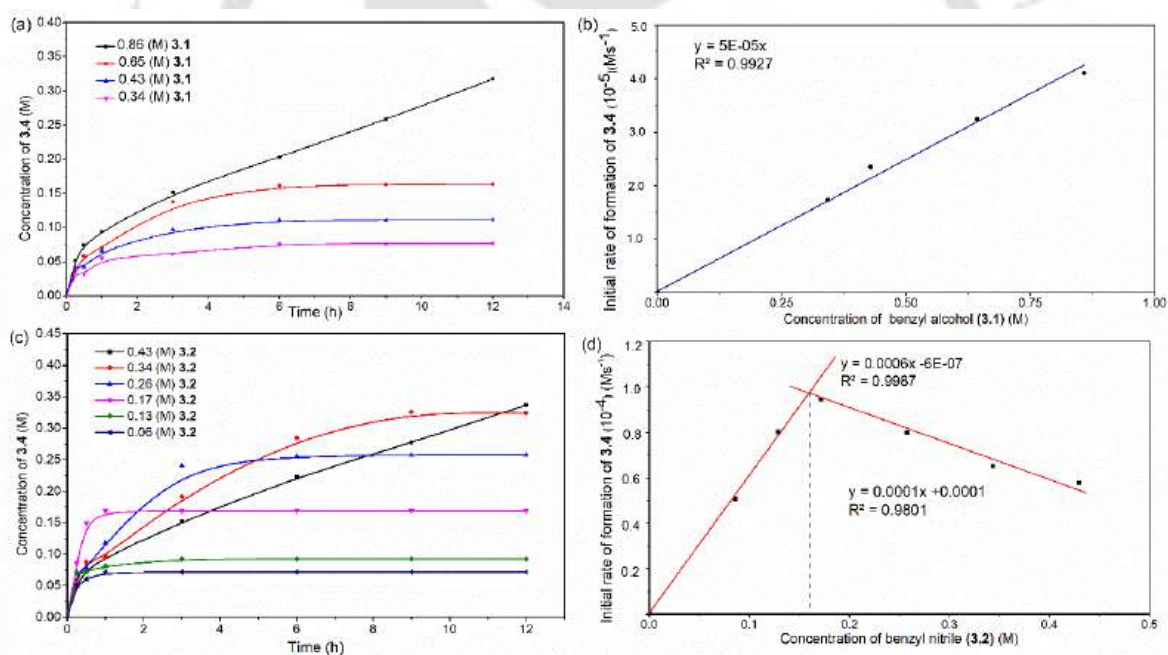


Figure 3.2. (a) Time profile of the α -alkylation of benzyl nitrile **3.2** with benzyl alcohol **3.1** under varying concentrations of **3.1**. (b) Variation of the initial rate of formation of **3.4** with the concentration of **3.1**. Reaction conditions for (a) and (b): $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol, 0.0017 M), benzyl alcohol (0.041-0.103 mL, 0.4-1 mmol, 0.343-0.858 M), benzyl cyanide (0.057 mL, 0.5 mmol, 0.429 M), KO^tBu (0.0168 g, 0.15 mmol, 0.129 M) in toluene (1 mL+ as makeup solvent). (c) Time profile of the α -alkylation of benzyl nitrile **3.2** with benzyl alcohol **3.1** under varying concentrations of **3.1**. (d) Variation of the initial rate of formation of **3.4** with the concentration of **3.1**. Reaction conditions for (c) and (d): $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol, 0.0017 M), benzyl alcohol (0.103 mL, 1 mmol, 0.858 M), benzyl cyanide (0.011-0.057 mL, 0.1-0.5 mmol, 0.06-0.429 M), KO^tBu (0.0168 g, 0.15 mmol, 0.129 M) in toluene (1 mL+ as makeup solvent).

Yet the yield was not satisfactory in the case of solid benzyl alcohol derivatives (**3.1n**, **3.1zf**, **3.1zh**) owing to the fact that $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ is only partially soluble either in toluene or in benzyl nitrile **3.2**. Hence, solid benzyl alcohol derivatives were first melted and required amount of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ was dissolved in it prior to the reaction. To our delight, this protocol helped achieve excellent yields of the α -alkylated nitriles **3.4n**, **3.4zf**, **3.4zh** (Table 3.2). Some heteroatom containing substrates gave very poor yield of **3.4b**, **3.4g**, **3.4j**, **3.4l**, **3.4m**, **3.4r**, **3.4s**, **3.4x** and **3.4zb** even up on subjecting them to various reaction conditions such as in footnotes c-f of Table 3.2. Heteroatoms in these reactants can bind to the Cr centre during catalysis thereby leading to inhibition of catalysis.

3.3.1. Mechanistic studies on the chromium catalysed α -alkylation of nitriles.

To shed light on the mechanistic insights, we started the investigation by subjecting benzaldehyde **3.1'**, with benzyl cyanide **3.2** under the optimized conditions using microwave irradiation. Selective formation of α,β -unsaturated nitrile **3.3** in 98% and 99% yields were obtained in presence of catalyst (equation 1, Scheme 3.25) and its absence (equation 2, Scheme 3.25) respectively. This indicates that the formation of **3.3** arises from the sole contribution of the KO^tBu mediated Knoevenagel type condensation of **3.1'** with **3.2**. The detection of H_2 by GC analysis (Figure B2, Appendix B) from the headspace of the reaction done under the optimized condition (entry 3, Table 3.1) along with the detection of trace amount of benzaldehyde **3.1'** in ^1H NMR (Figure B1, Appendix B) indicates that the dehydrogenation of benzyl alcohol **3.1** to benzaldehyde **3.1'** along with the extrusion of H_2 is a key step in the reaction mechanism. Treatment of α,β -unsaturated nitrile **3.3** with benzyl alcohol **3.1** in presence of catalyst under the optimized reaction conditions afforded the α -alkylated nitrile **3.4** (equation 3, Scheme 3.25) while only trace amounts of **3.4** was observed in absence of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (equation 4, Scheme 3.25). On the other hand, **3.3** did not react with hydrogen under the optimized reaction conditions (equation 5, Scheme 3.25). Collectively, equations 3-5 of Scheme 3.25 points towards the importance of the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and **3.1** in reducing the α,β -unsaturated nitrile **3.3** to α -alkylated nitrile **3.4**. The reaction done in presence of 1 equivalent PPh_3 with respect to 0.4 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (equation 6, Scheme 3.25) and in absence of PPh_3 under the optimized reaction conditions (entry 30, Table 3.1) both afforded comparable yields of the α -alkylated nitrile **3.4**. In the presence of 5 equivalents of PPh_3 with respect to 0.4 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, a slight decrease in the yield of α -alkylated nitrile **3.4** (equation 7, Scheme 3.25) was observed. PPh_3 being a well-known catalyst poison⁴⁵ for both homogeneous (where more than an equivalent relative to catalyst is required to decelerate the reaction) and

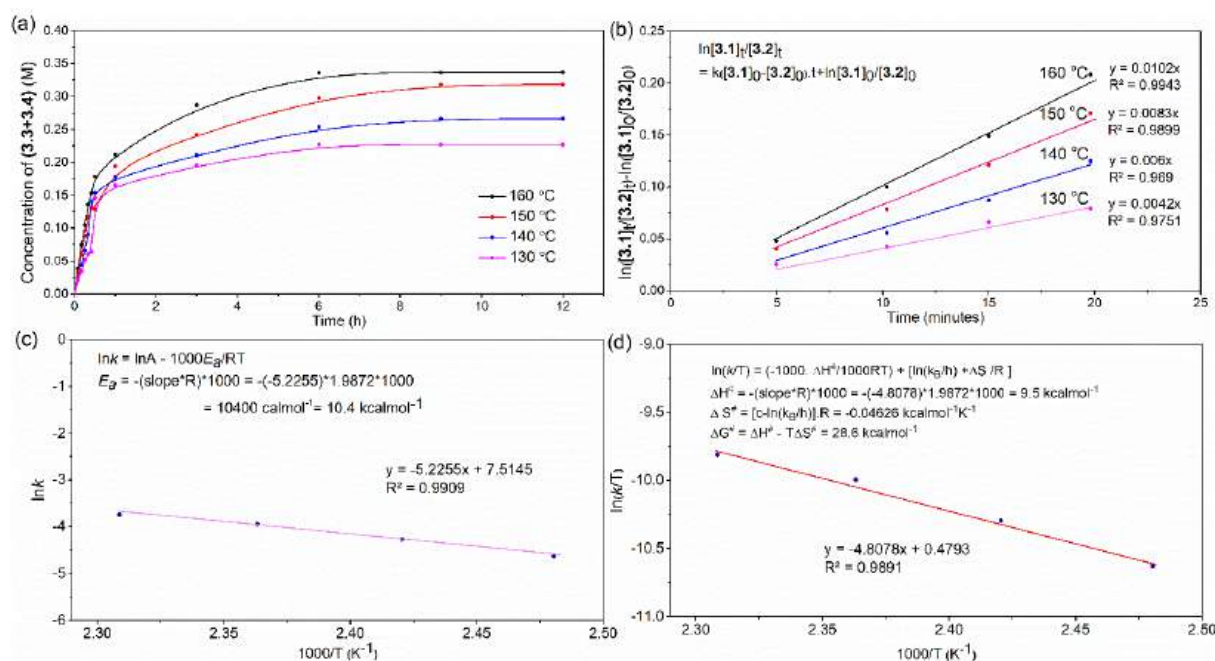


Figure 3.3. (a) Reaction profile for the formation of **3.4** with time under the optimized reaction conditions at various temperatures of 130 °C, 140 °C, 150 °C and 160 °C. (b) Plot for the calculation of the rate constant by linear fitting based on Equation in plot (b). Reaction conditions: $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol, 0.0017 M), benzyl alcohol (0.103 mL, 1 mmol, 0.858 M), benzyl cyanide (0.057 mL, 0.5 mmol, 0.429 M), and toluene (1 mL) at 130 °C, 140 °C, 150 °C and 160 °C. The first 20 min of the reaction have been considered.

heterogeneous catalyst (where addition of an equivalent with respect to catalyst is sufficient as a poison), our observation (equation 6 and equation 7, Scheme 3.25) is suggestive that the reaction is mostly homogeneous in nature. Mercury drop experiments (equation 8, Scheme 3.25) provided additional evidence for the involvement of molecular homogeneous catalytic Cr species in the reaction.

Kinetic studies performed using the initial-rate method demonstrate a linear dependence of the rate on the concentration of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, KO^tBu and **3.1**. In the case of **3.2**, while a linear dependence is observed at concentrations below 0.17 M, an inverse-first-order dependence of rate on the concentration of **3.2** (Figure 3.1 and Figure 3.2) is observed beyond 0.17 M. These observations are suggestive that the species involved in the rate-determining step (*vide-infra*) of the catalytic cycle is strongly inhibited by the presence of excess benzyl nitrile. Competitive isotope labelling experiments of **3.1** and **3.1-D₂** with **3.2** in presence of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and KO^tBu under optimized microwave conditions in air for 2h revealed a primary KIE of 4.7 (equation 9, Scheme 3.1, Table B1 and Figure B3, Appendix B) which further fortifies the possibility of β -hydride elimination as a possible RDS. This activation Gibbs free energy could experimentally be determined by using Eyring plot. For this purpose the kinetic profile of the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$

catalysed α -alkylation of **3.2** with **3.1** was obtained at various temperatures (130-160 °C, Figure 3.3a). The rate constants at various temperatures were then deduced from the slope of the plot of $\ln ([\mathbf{3.1}]_t/[\mathbf{3.2}]_t) - \ln([\mathbf{3.1}]_0/[\mathbf{3.2}]_0)$ vs. time (equation 3.10 and Figure 3.3b).

Additionally, the activation energy (E_a) was calculated as 10.4 kcal/mol (Figure 3.3c) using the equation (11), by determining the slope of the linear fit obtained from the plot of $\ln k$ vs. $1000/T$ (where k is the rate constant at a particular temperature T and R is the gas constant).

$$\ln ([\mathbf{3.1}]_t/[\mathbf{3.2}]_t) = k([\mathbf{3.1}]_0 - [\mathbf{3.2}]_0).T + \ln ([\mathbf{3.1}]_0/[\mathbf{3.2}]_0) \quad (10)$$

$$\ln k = \ln A - (1000[E_a]/1000RT) \quad (11)$$

$$\ln (k/T) = \ln (K_B/h) + \Delta S^\ddagger/R + \Delta H^\ddagger/RT \quad (12)$$

Ultimately, the thermodynamic parameters, such as the activation enthalpy ($\Delta H^\ddagger$), activation entropy ($\Delta S^\ddagger$) and activation Gibbs free energy ($\Delta G^\ddagger$), were derived from the Eyring equation (12). The values of $\Delta H^\ddagger = 9.5$ kcal/mol and $\Delta S^\ddagger = -0.04$ kcal/mol.K were obtained from the plot of $\ln(k/T)$ vs. $1000/T$. The activation Gibbs free energy at 140 °C ($\Delta G_{140}^\ddagger$) was calculated as 28.6 kcal/mol (Figure 3.2d) using the Eyring equation (where k is the rate constant, K_B is the Boltzmann constant, h is the Planck's constant and R is the gas constant and T = temperature in K).

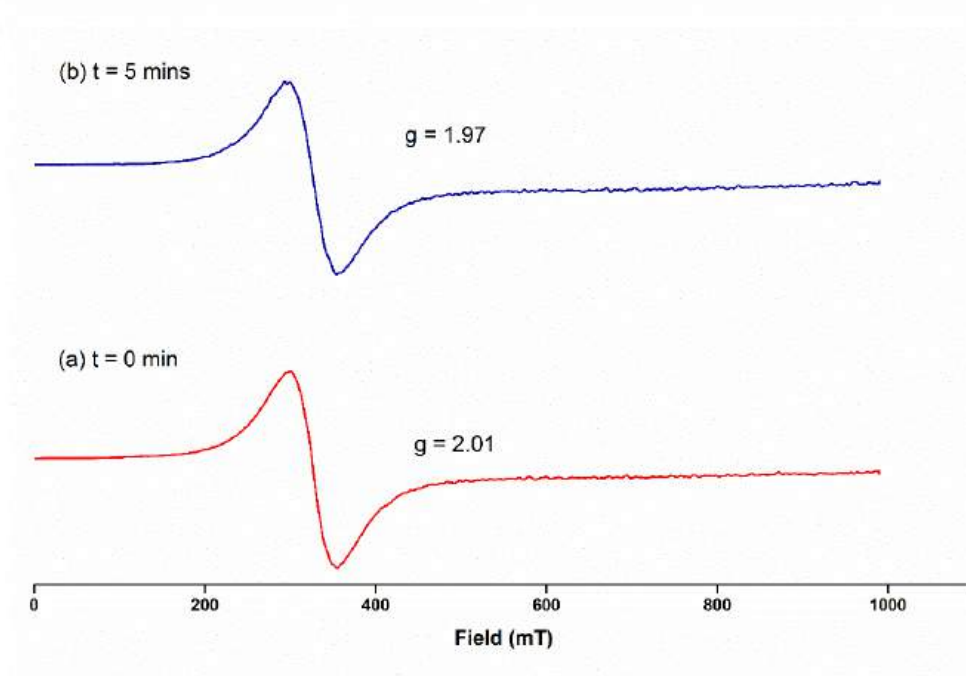


Figure 3.4. EPR analysis of the reaction mixture containing (a) $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%) at 0 min in absence of base at room temperature. (b) $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%), KO^tBu (0.15 mmol) at 5 mins, at 140 °C. The X-band EPR were recorded on a JES-FA200 ESR spectrometer at 77 K with a microwave power of 0.998 mW and a microwave frequency of 9.14 GHz.

The EPR analysis (Figure 3.4) of the reaction mixture containing $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%) in the absence of KO^tBu at room temperature, shows $g = 2.01$ which corresponds to Cr(III) ⁴⁷ and the EPR analysis (Figure 3.4) of the same reaction mixture in the presence of KO^tBu (30 mol%) after heating it at 140°C for 5 minutes, shows $g = 1.97$ which corresponds to Cr(II) .⁴⁸⁻⁵¹ This transformation of Cr(III) to Cr(II) during the catalysis was further confirmed by magnetic moment measurements using Evan's method (Figure 3.5). A magnetic moment of $\mu_{\text{eff}} = 3.8 \mu_B$ was obtained for the reaction mixture containing $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%) in the absence of KO^tBu at room temperature which corresponds to Cr(III) species.⁵² On the other hand, a magnetic moment of $\mu_{\text{eff}} = 4.5 \mu_B$ was obtained for the reaction mixture containing $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (5 mol%) in the presence of KO^tBu (30 mol%) at room temperature which corresponds to Cr(II) species (Figure 3.5).⁵² Thus both EPR (Figure 3.4) and Evan's measurements (Figure 3.5) provide conclusive evidence for the transformation of Cr(III) to Cr(II) under the basic reaction conditions. It is noteworthy that the reaction attempted with 0.4 mol% anhydrous CrCl_2 under the optimized reaction conditions, resulted in 62% yield of **3.4** (equation 10, Scheme 3.25)

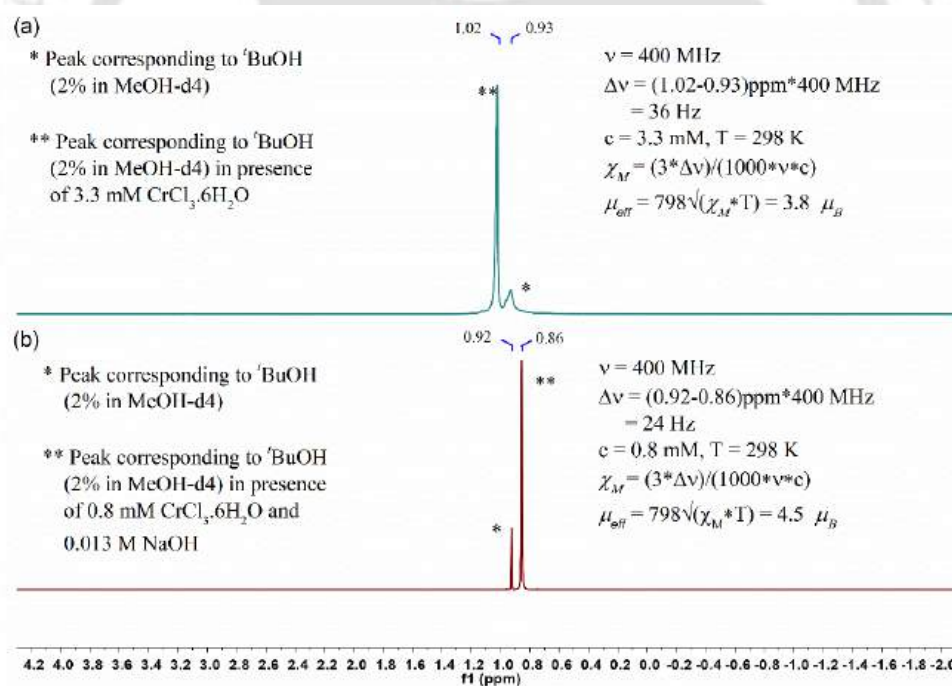
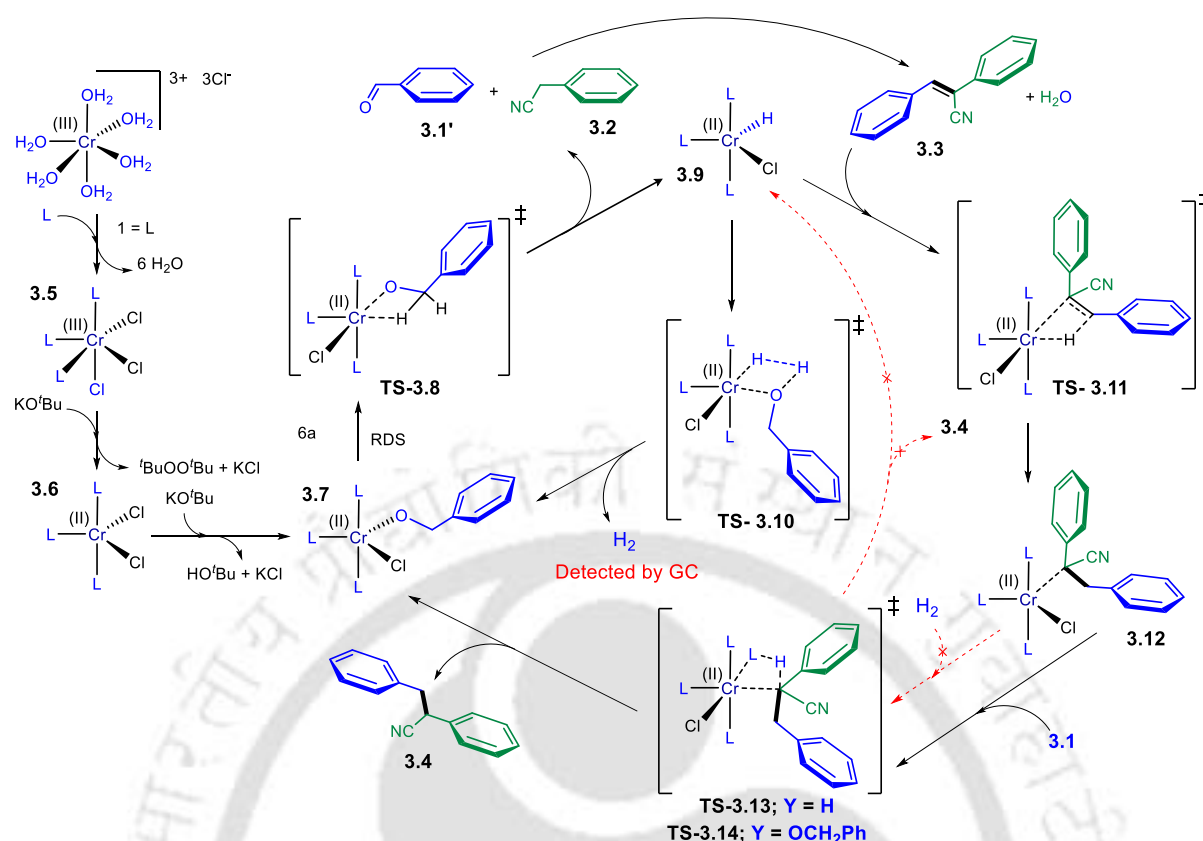


Figure 3.5. Magnetic moment in solution of (a) the mixture of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.02 mmol), **3.1** (1 mmol) and **3.2** (0.5 mmol) at room temperature (b) the mixture of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.02 mmol), **3.1** (1 mmol), **3.2** (0.5 mmol) and KO^tBu (0.15 mmol) at room temperature.

The inference of the control experiments (Scheme 3.25, Figure 3.1 -3.5) form the basis of the proposed mechanism. In the presence of benzyl alcohol **3.1**, $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ will undergo solvation to form an octahedral Cr (III) species **3.5** (Scheme 3.26). Under the basic conditions, Cr(III) species **3.5** will react with KO^tBu , to generate the Cr(II) species **3.6** with concomitant formation of the peroxide $^t\text{BuOO}^t\text{Bu}$ (Figure). While qualitative evidence has been obtained from EPR studies (Figure 3.4) and Evan's measurements (Figure 3.5). The cycle is then driven by Cr (II) species which is essentially molecular in nature as inferred from experiments with catalyst poison (equations 6-8, Scheme 3.25).

This Cr (II) active species will then readily undergo salt metathesis in the presence of benzyl alcohol **3.1** and KO^tBu along with the release of one molecule of *t*-butanol and one molecule of KCl to give rise to Cr (II)-alkoxide species **3.7**. The species **3.7** then undergoes β -hydride elimination leading to the formation of a Cr (II)-hydride species **3.9** via **TS-3.8** along with the extrusion of a benzaldehyde **3.1'** molecule. As per the observed KIE of 4.7 (equation 9, Scheme 3.25), the step **3.7**→**TS-3.8**→**3.9** is likely to be the rate-determining step (RDS) with a barrier of 28.6 kcal/mol (Figure 3.3). The dependence of rate of the reaction on the concentration of **3.1** and **3.2** (Figure 3.2) indicate that the L groups on species **3.7** are mainly **3.1** at lower concentration of **3.2** and at high concentrations, the latter strongly competes with the former and inhibits **3.7** resulting in the observed inverse first-order dependence of rate at concentration of **3.2** beyond 0.17 M. Hence, this threshold concentration was chosen for sequential addition wherein 0.2 mmol [0.17 M] of **3.2** was added in portions. This ensured that the reaction proceeded in a facile manner and was not inhibited by **3.2** as at any instant of time during the course of the reaction, the concentration of **3.2** was well below 0.17 M.

The intermediate **3.9** upon alcoholysis with **3.1** via **TS-3.10** regenerates **3.7** along with the extrusion of hydrogen. Experimentally, H_2 is detected (Figure B2, Appendix B) by the GC analysis of the head-space of the reaction mixture. In presence of KO^tBu , **3.1'** undergoes Knoevenagel type condensation with **3.2** to give α,β -unsaturated nitrile **3.3** (equations 1 and 2, Scheme 3.25). It is followed by the insertion of **3.3** into the Cr-H bond of the intermediate **3.9** to generate intermediate **3.12** via **TS-3.11**. The species **3.12** then readily undergoes σ -bond metathesis with benzyl alcohol **3.1** (alcoholysis) to regenerate the Cr(II)-alkoxide species **3.7** along with the release of the desired product **3.4** via **TS-3.14** (green arrows, Scheme 3.26). Formation of **3.4** upon starting from **3.3** under the standard experimental conditions (equation 3, Scheme 3.25) fortifies the existence of the alcoholysis step.



Scheme 3.26. Plausible mechanism of the α -alkylation of nitriles catalysed by $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$.

The alternative path involving the σ -bond metathesis of **3.12** with H_2 (hydrogenolysis) to yield Cr (II)-hydride species **3.9** and product **3.4** via **TS-3.13** (red dashed arrows, Scheme 3.26) is highly unlikely owing to the lack of reactivity of **3.3** with H_2 (equation 5, Scheme 3.26). These factors along with the fact that the reaction occurs in both open vessel (entry 3, Table 3.1) as well as under closed vessel conditions (entry 30, Table 3.1) highlights the sole involvement of alcoholysis in the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed α -alkylation of **3.2** with **3.1**. As inferred from control experiments, equation 1-5, Scheme 3.25 and equation 9, Scheme 3.25 where only 2% D incorporation was observed on the carbon α to the nitrile, the contribution to the overall reactivity from any other competing mechanisms including those like nitrile metalation pathways are negligibly small.

3.4. Conclusions

Commercially available first-row, 3d transition metal salt chromium (III) chloride (0.4 mol%) was employed for catalysing the selective α -alkylation of nitriles with benzyl alcohol in excellent yields (ca. 99%) in the presence of 30 mol% KO^tBu at 140°C after 24 h using

conventional heating in air. Under otherwise identical conditions, use of microwave heating resulted in comparable yields (ca. 93%) within 2 h of reaction in air. The formulated synthetic protocol was utilized to bring about the selective α -alkylation of a range of benzyl nitriles with various benzyl alcohols.

While reactions with catalyst poisons such as triphenyl phosphine and elemental mercury are suggestive of the molecular nature of the Cr catalytic system, EPR experiments reveal these molecular Cr species to be in the +2 oxidation state. The reaction demonstrates as linear dependence of rate on concentration of the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, KO^tBu and on the concentration of benzyl alcohol, in addition to an inverse-first-order dependence of rate relative to the concentration of benzyl nitrile at concentration > 0.17 M. This indicates the likely involvement of a Cr-benzyloxide species undergoing β -hydride elimination to be the RDS of the catalytic cycle which is apparently inhibited by an increase in the concentration of benzyl nitrile. This is very nicely complemented by the observed primary KIE of 4.7. The activation Gibbs free energy barrier for this β -hydride elimination is experimentally calculated to be about 28.6 kcal/mol. Thus, detailed mechanistic studies are suggestive of a sole contribution from the alcoholysis path in the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed α -alkylation of benzyl nitrile with benzyl alcohol with β -hydride elimination as the RDS having a rate-determining barrier of 28.6 kcal/mol.

From a sustainable point of view, this work utilises a commercially available 3d-metal salt $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ at a very low loading of 0.4 mol%, making it cost effective. There is no requirement of any ligand synthesis which further cuts down the use of extra solvents required in the process of extraction and making it more sustainable. Further, the reaction is very selective and is accomplished under microwave irradiation, which minimises the reaction time resulting in the lowering of overall energy consumption. The reaction is under air and does not require special handling. The overall E-factor of this catalytic α -alkylation of nitriles calculated in the absence and in the presence of toluene as solvent is 0.88 and 9.85 respectively (see page 187). To the best of our knowledge, this is first report on a Cr based catalytic system for the α -alkylation of nitriles.

3.5. Experimental section

3.5.1. General Procedure and Materials

All manipulations were performed under air. The chemicals $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, benzyl alcohol, benzyl nitrile, and their derivatives, toluene, and CDCl_3 along with all the additives (KO^tBu ,

NaO^tBu, NaOEt, KOH, NaOH, K₂CO₃, Na₂CO₃ and NaHCO₃) were purchased either from Sigma-Aldrich, MERCK, or Alfa Aesar and used as such.

3.5.2. Physical Measurements

¹H, ¹³C{H}, ¹⁹F, and ³¹P NMR spectra were recorded on a Bruker ASCEND 600 operating at 600 MHz for ¹H, 150 MHz for ¹³C{H}, 564 MHz for ¹⁹F; or on a Bruker AVANCE 500 operating at 500 MHz for ¹H, 125 MHz for ¹³C{H}, 470 MHz for ¹⁹F; or on a Bruker AVANCE 400 operating at 400 MHz for ¹H, 100 MHz for ¹³C{H}, 377 MHz for ¹⁹F. Chemical shifts (δ) are reported here in ppm, spin-spin coupling constant (J) is expressed in Hz, and other data are reported as s-singlet, d-doublet, t-triplet, m-multiple, and q-quartet. GC analyses were performed on an Agilent 7820-GC instrument fitted with an Agilent Front SS7 inlet N2 HP-PLOT Q column (30 m $\times$ 530 μ m $\times$ 40 μ m) using the following methods; Agilent 7820-GC back detector, detector temperature (TCD): 250 °C, detector temperature (FID): 300 °C, inlet temperature: 40 °C, time at starting temp: 0 min, ramp: 40 °C/min up to 250 °C, hold time = 5 min, flow rate (carrier): 25 mL/min (N₂), split ratio: 195. Fourier Transform Infrared (FT-IR) was recorded using a Perkin Elmer IR spectrometer at room temperature. All microwave reactions were performed using a CEM Discover microwave system unit (operating at 110 V, microwave irradiation of 2.45 GHz, and maximum microwave output of 300 W) in a 10 mL microwave sealed tube using the following parameters: temperature: 140 °C, power: 160 W (the instrument auto-adjusted the power in the range of 125 W – 160 W to maintain the temperature constant at 140 °C), pressure: 30 psi (this was set for all the substrates because toluene that has the lowest boiling point among the reagents used in the reaction can generate up to 20 psi at 140 °C), hold time: 10 mins, run time: 2 h (consisted of three segments of 20 minutes run after each of the three batch wise addition of benzyl nitrile which was then followed by a one hour run). Melting points were recorded in Buchi melting point B-540 apparatus in an open capillary tube. The derivatives of **3.3** and **3.4** were separated by column chromatography, using a solvent mixture of *n*-hexane and ethyl acetate as eluent.

3.5.3. General procedure for the optimization of chromium catalysed α -alkylation of nitriles under conventional heating. In a 5 mL pear-shaped flask, 1 mL toluene was added. Required amount of CrCl₃.6H₂O was withdrawn from a stock solution in benzyl alcohol and added to the flask, so that ultimately, the flask contained CrCl₃.6H₂O (0.00053 g, 0.002 mmol), benzyl alcohol (0.103 mL, 1 mmol), benzyl cyanide (0.057 mL, 0.5 mmol) and 30 mol% KO^tBu

(0.0168 g, 0.15 mmol). The reaction mixture was stirred well with an intention to achieve a homogeneous solution. It was then allowed to stir at 140 °C using a preheated oil-bath, for 24 h, under air. After 24 h, the reaction mixture was brought to room temperature and hexamethyl benzene (10 mg, 0.062 mmol) was added as a standard. It was mixed properly and 0.02 mL of the resulting mixture was withdrawn to a vial and the toluene was evaporated off. The yield of **3.4** was determined from ^1H NMR analysis using hexamethyl benzene as an standard and CDCl_3 as NMR solvent. The product **3.4** was purified by silica gel chromatography using 1-3% ethyl acetate in *n*-hexane as an eluent.

3.5.4. General procedure for the chromium catalysed α -alkylation of various nitrile derivatives and benzyl alcohol derivatives under microwave heating. In a microwave tube, 1 mL toluene was added. Required amount of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ was withdrawn from a stock solution in benzyl alcohol and added to the flask, so that ultimately, the flask contained $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol), benzyl alcohol or benzyl alcohol derivative (1 mmol), benzyl cyanide or nitriles derivative (0.5 mmol) and 30 mol% KO^tBu (0.0168 g, 0.15 mmol). The reaction mixture was stirred well with an intention to achieve a homogeneous solution. It was then allowed to stir at 140 °C using a preheated oil-bath, for 2 h, under microwave conditions (125-160 W, 30 psi). After 2 h, the reaction mixture was brought to room temperature and hexamethyl benzene (10 mg, 0.062 mmol) was added as a standard. It was mixed properly and 0.02 mL of the resulting mixture was withdrawn to a vial and the toluene was evaporated off out. The yield of derivatives of **3.4** was determined from ^1H NMR analysis using hexamethyl benzene as a standard and CDCl_3 as NMR solvent. The derivatives of product **3.4** were purified by silica gel chromatography using 1-3% ethyl acetate in *n*-hexane as an eluent.

[**Note:** Based on the requirement, in some cases, the benzyl cyanide or nitriles derivative (0.5 mmol) were added batch wise (0.2+0.2+0.1 mmol) in 20 minute intervals. Also in the cases, where the benzyl alcohol derivatives were solids, they were melted at 140 °C before preparing the stock solution of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in them.]

3.5.5. General procedure for the $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ catalysed α -alkylation of nitriles under conventional heating on a larger scale. In a 50 mL one-necked round-bottom flask, benzyl alcohol (1.035 mL, 10 mmol, 8.58 M) was added. Required amount of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.005 g, 0.02 mmol, 0.017 M) was added to the RB and was stirred at room temperature until a homogeneous solution was obtained. Required amount of KO^tBu (0.168 g, 1.5 mmol, 1.29 M)

was added and the reaction mixture was again stirred at room temperature. Then, toluene (10 mL) was added. Finally, benzyl nitrile (0.574 mL, 5 mmol, 4.29 M) was added batch wise (1 mmol each five times in an interval of 20 minutes). It was then allowed to stir at 140 °C (preheated oil bath), for 48 h, under air. After 48 h, the reaction mixture was brought to room temperature. The product was purified by silica gel chromatography using 1% ethyl acetate in n-hexane as an eluent to obtain 900 mg of **3.4** in 85 %yield.

3.5.6. General procedure for Kinetic Studies

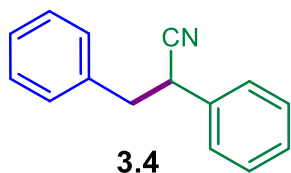
(a) Variation of loading of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$: To each of the six 5 mL pear-shaped flask, 1 mL toluene was added. Required amount of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ was withdrawn from a stock solution in benzyl alcohol and added to the flask, so that ultimately, the flask contained $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.000013-0.00053 g, 0.00005-0.002 mmol, 0.00021-0.0017 M), benzyl alcohol (0.103 mL, 1 mmol, 0.858 M), benzyl cyanide (0.057 mL, 0.5 mmol, 0.429 M), 30 mol% KO^tBu (0.0168 g, 0.15 mmol, 0.129 M) and hexamethyl benzene (0.01 g, 0.062 mmol, 0.053 M) as a standard. The reaction mixture was stirred well with an intention to achieve a homogeneous solution. It was then allowed to stir at 140 °C using a preheated oil-bath, for 12 h, under air. At regular intervals, 0.02 mL of the resulting mixture was withdrawn to a vial and the toluene was evaporated off. The yield of **3.4** was determined from ^1H NMR analysis using hexamethyl benzene as a standard and CDCl_3 as NMR solvent.

(b) Variation of loading of KO^tBu: To each of the four 5 mL pear-shaped flask, 1 mL toluene was added. Required amount of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ was withdrawn from a stock solution in benzyl alcohol and added to the flask, so that ultimately, the flask contained $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol, 0.0017 M), benzyl alcohol (0.103 mL, 1 mmol, 0.858 M), benzyl cyanide (0.057 mL, 0.5 mmol, 0.429 M), KO^tBu (0.014-0.025 g, 0.125-0.2 mmol, 0.107-0.172 M) and hexamethyl benzene (0.01 g, 0.062 mmol, 0.053 M) as a standard. The reaction mixture was stirred well with an intention to achieve a homogeneous solution. It was then allowed to stir at 140 °C using a preheated oil-bath, for 12 h, under air. At regular intervals, 0.02 mL of the resulting mixture was withdrawn to a vial and the toluene was evaporated off. The yield of **3.4** was determined from ^1H NMR analysis using hexamethyl benzene as a standard and CDCl_3 as NMR solvent.

(c) Variation in the concentration of benzyl alcohol (3.1): To each of the four 5 mL pear-shaped flask, 1 mL toluene was added. Required amount of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ was withdrawn from a stock solution in benzyl alcohol and added to the flask, so that ultimately, the flask contained $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol, 0.0017 M), benzyl alcohol (0.041-0.103 mL, 0.4-1 mmol, 0.343-0.858 M), benzyl cyanide (0.057 mL, 0.5 mmol, 0.429 M), 30 mol% KO^tBu (0.0168 g, 0.15 mmol, 0.129 M), toluene was added as a makeup solvent and hexamethyl benzene (0.01 g, 0.062 mmol, 0.053 M) as a standard. The reaction mixture was stirred well with an intention to achieve a homogeneous solution. It was then allowed to stir at 140 °C using a preheated oil-bath, for 12 h, under air. At regular intervals, 0.02 mL of the resulting mixture was withdrawn to a vial and the toluene was evaporated off. The yield of **3.4** was determined from ^1H NMR analysis using hexamethyl benzene as a standard and CDCl_3 as NMR solvent.

(d) Variation in the concentration of benzyl cyanide (3.2): To each of the six 5 mL pear-shaped flask, 1 mL toluene was added. Required amount of $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ was withdrawn from a stock solution in benzyl alcohol and added to the flask, so that ultimately, the flask contained $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00053 g, 0.002 mmol, 0.0017 M), benzyl alcohol (0.103 mL, 1 mmol, 0.858 M), benzyl cyanide (0.011-0.057 mL, 0.1-0.5 mmol, 0.06-0.429 M), 30 mol% KO^tBu (0.0168 g, 0.15 mmol, 0.129 M) toluene as a makeup solvent and hexamethyl benzene (0.01 g, 0.062 mmol, 0.053 M) as an internal standard. The reaction mixture was stirred well with an intention to achieve a homogeneous solution. It was then allowed to stir at 140 °C using a preheated oil-bath, for 12 h, under air. At regular interval, 0.02 mL of the resulting mixture was withdrawn to a vial and the toluene was evaporated off. The yield of **3.4** was determined from ^1H NMR analysis using hexamethyl benzene as a standard and CDCl_3 as NMR solvent.

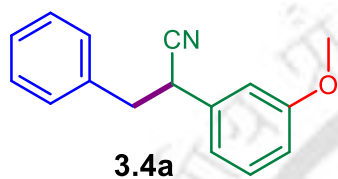
2,3-Diphenylpropanenitrile (**3.4**):²⁵



Following the general procedure, the titled compound was isolated as a white solid (97 mg, yield: 94%) using silica gel column chromatography (1% ethyl acetate in hexane). ^1H NMR (400 MHz, Chloroform- d) δ 7.38 – 7.31 (m, 3H), 7.31 – 7.23 (m, 5H), 7.13 (dd, J = 7.6, 1.6 Hz, 2H), 3.99 (dd, J = 8.3, 6.5 Hz, 1H), 3.19 (dd, J = 13.6, 8.3 Hz, 1H), 3.13 (dd, J = 13.6, 6.5 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [136.4, 135.3, 129.3, 129.1, 128.7, 128.3, 127.6, 127.5, 120.5](Ar), 42.2 (CH_2),

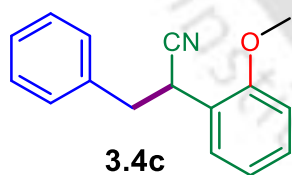
39.8 (CH(CN)). mp 56-58 °C;⁵³ ν_{max} (neat) 2242 (-CN), 1599, 1495, 1455 (aromatics) cm^{-1} .

2-(3-Methoxyphenyl)-3-phenylpropanenitrile (3.4a):³⁸

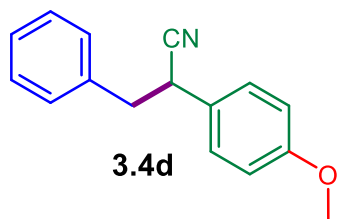


Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (95 mg, yield: 80 %). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.23 (m, 5H), 7.17 – 7.13 (m, 2H), 6.85 (dd, J = 8.3, 2.3 Hz, 2H), 6.77 (t, J = 2.0 Hz, 1H), 3.97 (dd, J = 8.2, 6.5 Hz, 1H), 3.77 (s, 3H), 3.19 (dd, J = 13.6, 8.3 Hz, 1H), 3.13 (dd, J = 13.6, 6.5 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform-*d*) δ [159.9, 136.7, 136.3, 130.1, 129.2, 128.7, 127.4, 120.3, 119.8, 113.8, 113.2] (Ar), 55.3 (OCH₃), 42.1 (CH₂), 39.8 (CH(CN)).

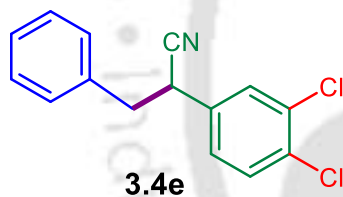
2-(2-Methoxyphenyl)-3-phenylpropanenitrile (3.4c):³⁸



Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (107 mg, yield: 87 %). ^1H NMR (600 MHz, Chloroform-*d*) δ 7.38 – 7.27 (m, 6H), 7.23 (d, J = 7.3 Hz, 2H), 7.01 – 6.92 (m, 2H), 4.44 (dd, J = 9.0, 5.3 Hz, 1H), 3.88 (s, 3H), 3.17 (dd, J = 13.5, 5.3 Hz, 1H), 3.10 (dd, J = 13.5, 9.1 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform-*d*) δ [156.0, 137.1, 129.5, 129.2, 128.5, 127.2, 123.7, 120.9, 120.7, 110.8] (Ar), 55.6 (OCH₃), 39.9 (CH₂), 34.2 (CH(CN)).

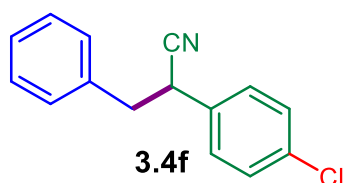
2-(4-Methoxyphenyl)-3-phenylpropanenitrile (3.4d):³⁹

Following the general procedure, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (87 mg, yield: 73%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.24 (m, 3H), 7.18 – 7.11 (m, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.94 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.80 (s, 3H), 3.17 (dd, *J* = 13.5, 8.2 Hz, 1H), 3.09 (dd, *J* = 13.6, 6.5 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [159.4, 136.4, 129.3, 128.6, 127.3, 127.2, 120.7, 114.4] (Ar), 55.4 (OCH₃), 42.3 (CH₂), 39.0 (CH(CN)). mp 74-75 °C.⁵³

2-(3,4-Dichlorophenyl)-3-phenylpropanenitrile (3.4e):¹⁷

Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (50 mg, yield: 36%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 8.3 Hz, 1H), 7.39 – 7.28 (m, 5H), 7.14 (d, *J* = 7.0 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 4.00 (t, *J* = 7.3 Hz, 1H), 3.22 (dd, *J* = 13.6, 8.1 Hz, 1H), 3.14 (dd, *J* = 13.6, 6.5 Hz, 1H).

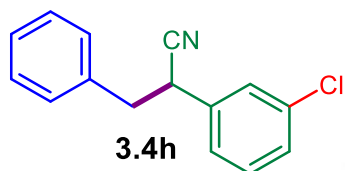
$\nu_{\max}$ (neat) 2241 (-CN), 1600, 1439, 1463, 1455, 1493 (aromatics) cm⁻¹

2-(4-Chlorophenyl)-3-phenylpropanenitrile (3.4f):²⁵

Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (107 mg, yield: 89%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.37 – 7.27 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 4.05 – 3.99 (m, 1H), 3.21 (dd, *J* = 13.6, 8.0 Hz, 1H), 3.14 (dd, *J* = 13.6, 6.6 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [135.8, 134.3, 133.6, 129.3, 129.2, 128.9, 128.7, 127.6, 120.0]

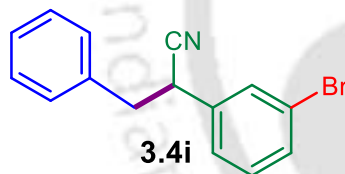
(Ar), 42.0 (CH₂), 39.2 (CH(CN)). $\nu_{\max}$ (neat) 2241 (-CN), 1409, 1453, 1489 (aromatics) cm⁻¹.

2-(3-Chlorophenyl)-3-phenylpropanenitrile (3.4h):¹⁷



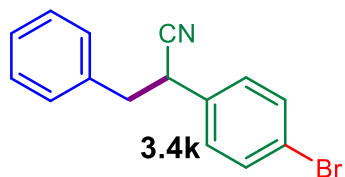
Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (82 mg, yield: 68%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.37 – 7.27 (m, 8H), 7.16 (s, 1H), 4.01 (dd, *J* = 8.1, 6.7 Hz, 1H), 3.22 (dd, *J* = 13.6, 8.4 Hz, 1H), 3.16 (dd, *J* = 13.6, 6.4 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [137.1, 135.8, 134.9, 130.3, 129.2, 128.8, 128.6, 127.7, 127.6, 125.8, 119.9] (Ar), 42.0 (CH₂), 39.4 (CH(CN)).

2-(3-Bromophenyl)-3-phenylpropanenitrile (3.4i):¹⁵



Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (129 mg, yield: 90%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.45 (s, 1H), 7.39 – 7.26 (m, 4H), 7.25 – 7.14 (m, 3H), 4.03 – 3.97 (m, 1H), 3.21 (dd, *J* = 13.6, 8.4 Hz, 1H), 3.15 (dd, *J* = 13.6, 6.4 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [137.3, 135.8, 131.5, 130.6, 130.56, 129.2, 128.8, 127.6, 126.2, 123.0, 119.7] (Ar), 42.0 (CH₂), 39.4 (CH(CN)).

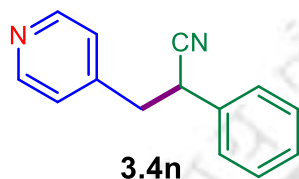
2-(4-Bromophenyl)-3-phenylpropanenitrile (3.4k):¹⁷



Following the general procedure, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (81 mg, yield: 57%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.31 (p, *J* = 7.0 Hz, 3H), 7.14 (d, *J* = 8.0

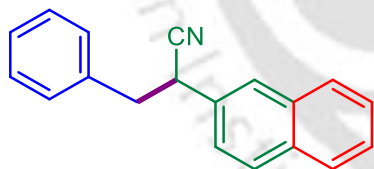
Hz, 4H), 4.00 (t, $J = 7.3$ Hz, 1H), 3.21 (dd, $J = 13.6, 8.0$ Hz, 1H), 3.13 (dd, $J = 13.6, 6.6$ Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [135.8, 134.1, 132.2, 129.2, 128.7, 127.6, 122.3, 119.9] (Ar), 41.9 (CH_2), 39.2 ($\text{CH}(\text{CN})$). mp 82-83 $^\circ\text{C}$.⁵³

2-Phenyl-3-(pyridin-4-yl)propanenitrile (3.4n):³⁸

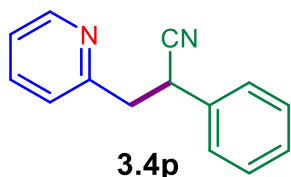


Following the general procedure, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 30% ethyl acetate in hexane (57 mg, yield: 55%). ^1H NMR (400 MHz, Chloroform- d) δ 8.53 (dd, $J = 4.5, 1.5$ Hz, 2H), 7.41 – 7.31 (m, 3H), 7.31 – 7.21 (m, 3H), 7.08 – 7.02 (m, 2H), 4.09 – 4.01 (m, 1H), 3.23 – 3.11 (m, 2H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [150.1, 144.8, 134.3, 129.2, 128.6, 127.4, 124.4] (Ar), 41.2 (CH_2), 38.6 ($\text{CH}(\text{CN})$).

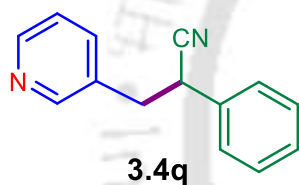
2-(Naphthalen-2-yl)-3-phenylpropanenitrile (3.4o):²⁵



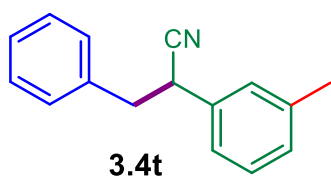
Following the general procedure, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (91 mg, yield: 71%). ^1H NMR (600 MHz, Chloroform- d) δ 7.89 (d, $J = 8.3$ Hz, 2H), 7.87 – 7.83 (m, 1H), 7.79 (s, 1H), 7.56 (dd, $J = 6.2, 3.2$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 1H), 7.33 (q, $J = 8.7, 7.6$ Hz, 3H), 7.21 (d, $J = 6.8$ Hz, 2H), 4.23 – 4.19 (m, 1H), 3.32 (dd, $J = 13.7, 8.4$ Hz, 1H), 3.27 (dd, $J = 13.7, 6.4$ Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [136.3, 133.3, 132.9, 132.5, 129.3, 129.0, 128.7, 128.0, 127.8, 127.5, 126.8, 126.7, 126.6, 125.0, 120.4] (Ar), 42.1 (CH_2), 40.0 ($\text{CH}(\text{CN})$).

2-Phenyl-3-(pyridin-2-yl)propanenitrile (3.4p):²⁴

Following the general procedure, the title compound was isolated as a brownish liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (81 mg, yield: 78%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 4.7 Hz, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.39 – 7.10 (m, 7H), 4.49 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.41 – 3.22 (m, 2H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [156.2, 149.7, 136.8, 135.5, 129.1, 128.2, 127.4, 123.9, 122.4, 120.6] (Ar), 44.2 (CH₂), 37.3 (CH(CN)).

2-Phenyl-3-(pyridin-3-yl)propanenitrile (3.4q):³⁸

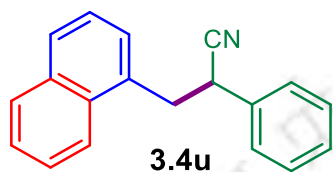
Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 30% ethyl acetate in hexane (92 mg, yield: 88%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.32 (d, *J* = 1.9 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.39 – 7.20 (m, 6H), 4.04 (t, *J* = 7.1 Hz, 1H), 3.23-3.13 (m, 2H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [150.4, 148.9, 134.3, 131.6, 129.2, 128.6, 127.5, 123.4, 119.8], 39.2 (CH(CN)). *v*_{max} (neat) 2241 (-CN), 1594, 1576, 1497, 1479, 1454, 1424 (aromatics) cm⁻¹.

3-Phenyl-2-(m-tolyl)propanenitrile (3.4t):³⁹

Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (99 mg, yield: 90%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.32 (dd, *J* = 15.3, 7.3 Hz, 3H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 14.1, 7.0 Hz, 3H), 7.13 (s, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 4.01 – 3.96 (m, 1H), 3.22-3.13 (m, 2H), 2.38 (s, 3H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [138.9,

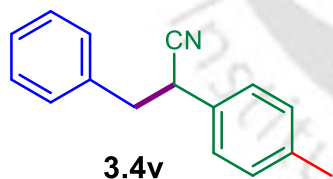
136.5, 135.2, 129.2, 129.0, 128.9, 128.6, 128.1, 127.4, 124.5, 120.5] (Ar), 42.3 (CH₂), 39.8 (CH(CN)), 21.4 (CH₃).
 $\nu_{\max}$ (neat) 2240 (-CN), 1607, 1496, 1454 (aromatics) cm⁻¹.

3-(Naphthalen-1-yl)-2-phenylpropanenitrile (3.4u):²⁵

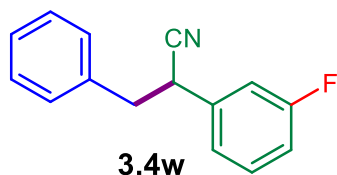


Following the general procedure, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (98 mg, yield: 76%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.46 – 7.33 (m, 7H), 4.21 (dd, *J* = 8.8, 6.6 Hz, 1H), 3.69 (dd, *J* = 14.1, 8.9 Hz, 1H), 3.64 (dd, *J* = 14.1, 6.6 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [135.6, 134.0, 132.2, 131.3, 129.3, 129.2, 128.4, 128.3, 127.4, 126.6, 125.8, 125.5, 122.6, 120.5] (Ar), 39.6 (CH₂), 38.9 (CH(CN)).

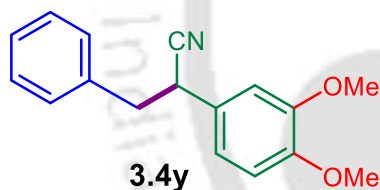
3-Phenyl-2-(p-tolyl)propanenitrile (3.4v):²⁵



Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane (98 mg, yield: 89%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.35 – 7.28 (m, 3H), 7.18 (d, *J* = 7.3 Hz, 6H), 4.02 – 3.96 (m, 1H), 3.20 (dd, *J* = 13.6, 8.6 Hz, 1H), 3.14 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.38 (s, 3H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [138.0, 136.5, 132.2, 129.7, 129.2, 128.6, 127.7, 120.6] (Ar), 42.3 (CH₂), 39.5 (CH(CN)), 21.1 (CH₃).
 mp 77-79 °C; ⁵³ $\nu_{\max}$ (neat) 2240 (-CN), 1600, 1514, 1495, 1456 (aromatics) cm⁻¹.

2-(3-Fluorophenyl)-3-phenylpropanenitrile (3.4w):¹⁷

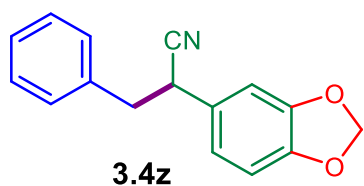
Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (62 mg, yield: 57%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.38 – 7.28 (m, 4H), 7.16 (d, *J* = 7.0 Hz, 2H), 7.06 (dd, *J* = 13.0, 8.0 Hz, 2H), 7.01 (d, *J* = 9.4 Hz, 1H), 4.05 – 4.01 (m, 1H), 3.23 (dd, *J* = 13.6, 8.3 Hz, 1H), 3.16 (dd, *J* = 13.6, 6.4 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [163.7, 137.5, 135.8, 130.7, 130.6, 129.2, 128.7, 127.6, 123.3, 119.8, 115.4, 115.3, 114.8, 114.7] (Ar), 42.0 (CH₂), 39.5 (CH(CN)). ¹⁹F NMR (565 MHz, Chloroform-*d*) δ -111.6.

2-(3,4-Dimethoxyphenyl)-3-phenylpropanenitrile (3.4y):³⁹

Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (119 mg, yield: 89%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 4.4 Hz, 2H), 7.31 (dt, *J* = 12.3, 6.8 Hz, 4H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.86 – 6.82 (m, 2H), 6.66 (s, 1H), 3.97 (t, *J* = 7.3 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.21 (dd, *J* = 13.5, 8.0 Hz, 1H), 3.14 (dd, *J* = 13.6, 6.6 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [149.1, 148.9, 136.3, 129.3, 128.62, 128.57, 127.6, 127.5, 127.4, 120.6, 119.8, 111.34, 110.6] (Ar), 65.3 (OCH₃), 55.9 (OCH₃), 42.2 (CH₂), 39.3 (CH(CN)).

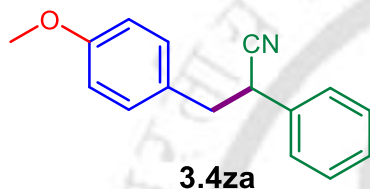
2-(benzo[d][1,3]dioxol-5-yl)-3-phenylpropanenitrile (3.4z):¹⁵

Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (74 mg, yield: 59%). ¹H NMR (400 MHz, Chloroform-*d*)



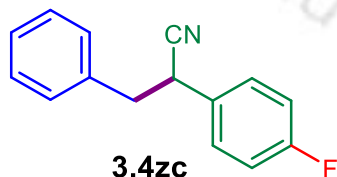
δ 7.33 – 7.23 (m, 3H), 7.14 (d, J = 6.3 Hz, 2H), 6.78 – 6.73 (m, 2H), 6.71 – 6.65 (m, 1H), 5.97 (s, 2H), 3.90 (dd, J = 8.1, 6.7 Hz, 1H), 3.16 (dd, J = 13.6, 8.2 Hz, 1H), 3.08 (dd, J = 13.6, 6.6 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [148.2, 147.6, 136.3, 129.2, 128.9, 128.7, 127.4, 120.5, 108.6, 107.9] (Ar), 101.4 (OCH₂O), 42.3 (CH₂), 39.5 (CH(CN)).

3-(4-Methoxyphenyl)-2-phenylpropanenitrile (3.4za):³⁹



Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (78 mg, yield: 66%). ^1H NMR (400 MHz, Chloroform- d) δ 7.38 – 7.31 (m, 3H), 7.25 (d, J = 7.0 Hz, 3H), 7.04 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.96 (dd, J = 8.0, 6.6 Hz, 1H), 3.79 (s, 3H), 3.17 – 3.04 (m, 2H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [158.9, 135.3, 130.3, 129.0, 128.2, 127.5, 120.5] (Ar), 55.3 (OCH₃), 41.4 (CH₂), 40.1 (CH(CN)). ν_{max} (neat) 2242 (–CN), 1583, 1611, 1455, 1411 (aromatics) cm^{–1}.

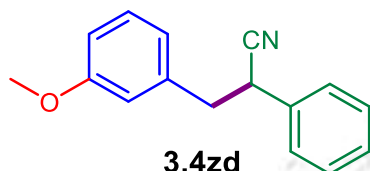
3-(4-Fluorophenyl)-2-phenylpropanenitrile (3.4zc):²⁵



Following the general procedure, the titled compound was isolated as white solid (88 mg, yield: 78%) using silica gel column chromatography (2.5% ethyl acetate in hexane). ^1H NMR (400 MHz, Chloroform- d) δ 7.35 – 7.24 (m, 3H), 7.23 – 7.17 (m, 2H), 7.13 – 6.98 (m, 4H), 4.03 – 3.96 (m, 1H), 3.19 (dd, J = 13.6, 8.0 Hz, 1H), 3.10 (dd, J = 13.6, 6.6 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [163.3, 161.6, 135.9, 131.0, 129.3, 128.7, 127.5, 120.2, 115.9] (Ar), 42.2 (CH₂), 39.0 (CH(CN)). ^{19}F

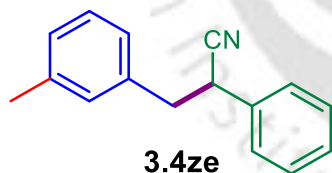
NMR (565 MHz, Chloroform-*d*) δ -113.5. $\nu_{\max}$ (neat) 2240 (-CN), 1601, 1507, 1455, 1419 (aromatics) cm^{-1} .

2-Phenyl-3-(*m*-tolyl) propanenitrile (3.4zd):³⁸

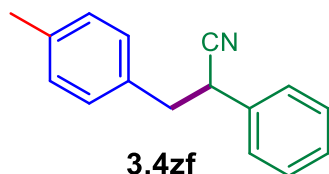


Following the general procedure, the titled compound was isolated as a colorless liquid (86 mg, yield: 78%) using silica gel column chromatography (2% ethyl acetate in hexane). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34(ddd, J = 8.7, 6.0, 3.1 Hz, 3H), 7.26 (dd, J = 8.1, 1.9 Hz, 2H), 7.24 – 7.17 (m, 1H), 6.80 (dd, J = 8.0, 2.1 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.64 (d, J = 3.8 Hz, 1H), 3.99 (dd, J = 8.3, 6.5 Hz, 1H), 3.74 (s, 3H), 3.17 (dd, J = 13.6, 8.3 Hz, 1H), 3.10 (dd, J = 13.6, 6.5 Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform-*d*) δ [159.7, 137.8, 135.2, 129.7, 129.0, 128.2, 127.5, 121.5, 120.4, 114.8, 113.0] (Ar), 55.2 (OCH₃), 42.2 (CH₂), 39.7(CH(CN)).

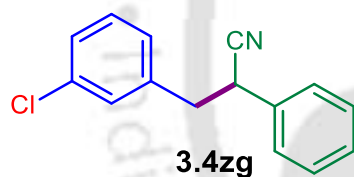
2-Phenyl-3-(*m*-tolyl) propanenitrile (3.4ze):³⁸



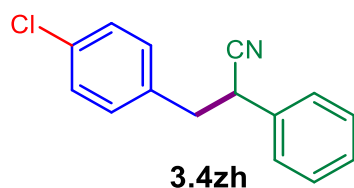
Following the general procedure, the titled compound was isolated as a colorless liquid (104 mg, yield: 95%) using silica gel column chromatography (2% ethyl acetate in hexane). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.35 (ddt, J = 9.3, 6.5, 3.5 Hz, 3H), 7.29 – 7.24 (m, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 11.5 Hz, 2H), 3.98 (dd, J = 8.5, 6.4 Hz, 1H), 3.15 (dd, J = 13.6, 8.6 Hz, 1H), 3.08 (dd, J = 13.6, 6.4 Hz, 1H), 2.31 (s, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform-*d*) δ [138.3, 136.3, 135.4, 130.0, 129.0, 128.5, 128.2, 128.1, 127.5, 126.2, 120.4] (Ar), 42.2 (CH₂), 39.9 (CH(CN)), 21.4 (CH₃). $\nu_{\max}$ (neat) 2240 (-CN), 1609, 1495, 1454 (aromatics) cm^{-1} .

2-Phenyl-3-(p-tolyl)propanenitrile (3.4zf):³⁸

Following the general procedure, the titled compound was isolated as colorless liquid (96 mg, yield: 87%) using silica gel column chromatography (2% ethyl acetate in hexane). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.38 (dp, *J* = 14.4, 7.4, 6.6 Hz, 3H), 7.31-7.28 (m, 3H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 4.02-3.98 (m, 1H), 3.18 (dd, *J* = 13.7, 8.5 Hz, 1H), 3.13 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.36 (s, 3H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [137.0, 135.4, 133.2, 129.3, 129.1, 129.0, 128.2, 127.5, 120.5] (Ar), 41.9 (CH₂), 40.0 (CH(CN)), 21.1 (CH₃). ν_{max} (neat) 2240 (-CN), 1600, 1495, 1515, 1454 (aromatics) cm⁻¹.

3-(3-Chlorophenyl)-2-phenylpropanenitrile (4zg):²⁵

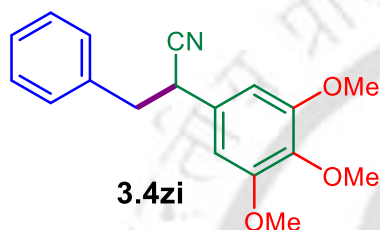
Following the general procedure, the title compound was isolated as a colorless liquid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (110 mg, yield: 91%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.39 (dq, *J* = 14.2, 7.0 Hz, 3H), 7.32 – 7.24 (m, 4H), 7.15 (s, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 4.05 – 4.01 (m, 1H), 3.19 (dd, *J* = 13.7, 8.4 Hz, 1H), 3.14 (dd, *J* = 13.7, 6.4 Hz, 1H). ¹³C{H} NMR (151 MHz, Chloroform-*d*) δ [138.2, 134.8, 134.4, 129.9, 129.4, 129.2, 128.4, 127.7, 127.53, 127.48, 120.1], 41.7 (CH₂), 39.5 (CH(CN)). ν_{max} (neat) 2241 (-CN), 1598, 1574, 1496, 1477, 1454, 1431 (aromatics) cm⁻¹.

3-(4-chlorophenyl)-2-phenylpropanenitrile (4zh):^{6a}

Following the general procedure, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 2% ethyl acetate in hexane (109 mg, yield: 90%). ¹H NMR (600 MHz, Chloroform-*d*) δ 7.38 (dq, *J* = 14.1, 7.0 Hz, 3H), 7.28 (dd, *J* = 13.3, 7.7 Hz, 4H), 7.07 (d, *J* = 8.2 Hz, 2H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.19

(dd, $J = 13.7, 8.1$ Hz, 1H), 3.15 (dd, $J = 13.7, 6.5$ Hz, 1H).
 $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [134.8, 134.6, 133.4, 130.6, 129.1, 128.8, 128.4, 127.50 120.1] (Ar), 41.4 (CH₂), 39.6 (CH(CN)). ν_{max} (neat) 2243 (-CN), 1599, 1489, 1453, 1444, 1408 (aromatics) cm⁻¹.

3-Phenyl-2-(3,4,5-trimethoxyphenyl)propanenitrile (3.4zi):¹⁵



Following the general procedure, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 15% ethyl acetate in hexane (134 mg, yield: 90%). ^1H NMR (400 MHz, Chloroform- d) δ 7.34 – 7.24 (m, 3H), 7.17 – 7.10 (m, 2H), 6.39 (s, 2H), 3.95 – 3.90 (m, 1H), 3.84 (s, 3H), 3.80 (s, 6H), 3.20 (dd, $J = 13.5, 8.0$ Hz, 1H), 3.12 (dd, $J = 13.5, 6.6$ Hz, 1H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Chloroform- d) δ [153.5, 136.2, 130.6, 129.3, 128.6, 127.4, 120.4, 104.7] (Ar), 60.9 (OCH₃), 56.2 (OCH₃), 42.2 (CH₂), 39.9 (CH(CN)).

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Appendix B

B1.NMR spectra of the reaction mixture:

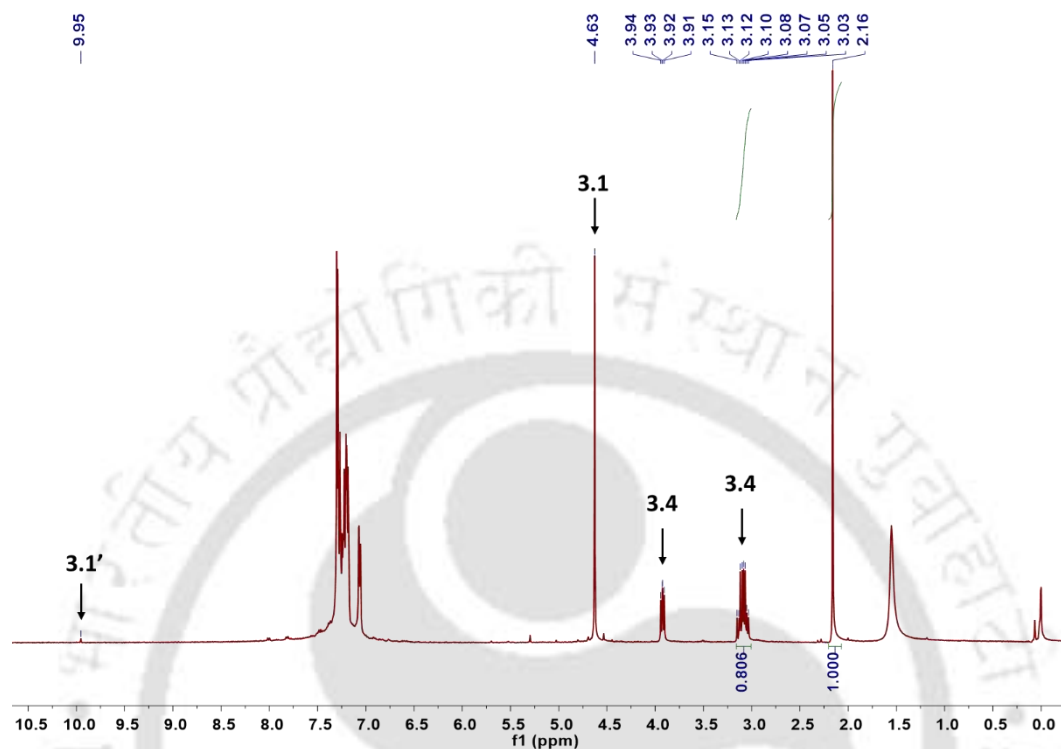


Figure B1: ^1H NMR of the crude reaction mixture (entry 3, Table 3.1) in CDCl_3 .

B2. Gas-GC Spectra

GC analysis (TCD detection) was performed on a Agilent 7820-GC instrument fitted with Agilent Front SS7 inlet N2 HP-PLOT Q column (30 m length x 530 μm x 40 μm ID) using the following method:

Agilent 7820-GC Detector

TCD starting temperature 40 $^\circ\text{C}$

Oven temperature 70 $^\circ\text{C}$

Time at starting temp: 0 min

Hold time = 5 min

Ramp: 40 $^\circ\text{C}/\text{min}$ up to 250 $^\circ\text{C}$

Flow rate (carrier): 25 mL/min (N_2)

Split ratio: 195

Inlet temperature: 40 °C

Detector temperature: TCD: 250 °C

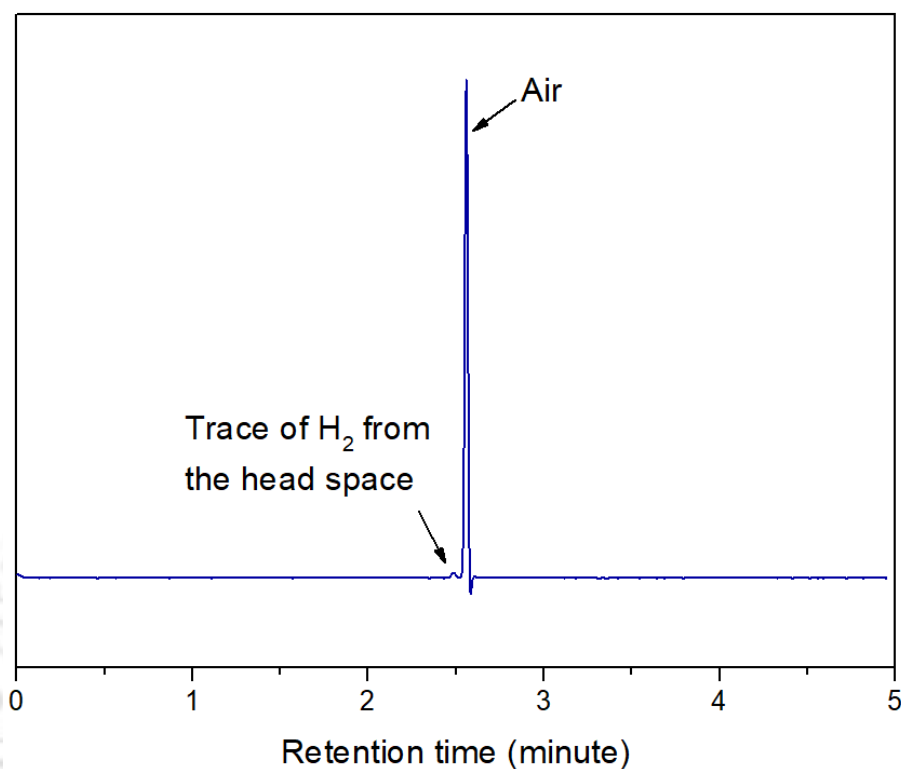


Figure B2. GC-TCD analysis of H₂ gas evolved from alpha alkylation of **3.1** with **3.2** (entry 3, Table 3.1). Reaction condition: 1 mmol of **3.1**, 0.5 mmol of **3.2**, 0.002 mmol of CrCl₃·6H₂O, and 0.15 mmol of KO^tBu in 1mL toluene at 140 °C.

B3. Deuterium labelling experiment:

The deuterium labelling experiment for α -alkylation of nitriles was performed by using **3.1** (0.5 mmol), **1-D₂** (91% D) (0.5 mmol) and **3.2** (0.5 mmol), under the optimized reaction condition (microwave). The product was separated by column chromatography using 1% EtOAc in hexane as an eluent. 42 mg (40%) of the product was obtained. The KIE was determined from ¹H NMR using CDCl₃ as a solvent.¹

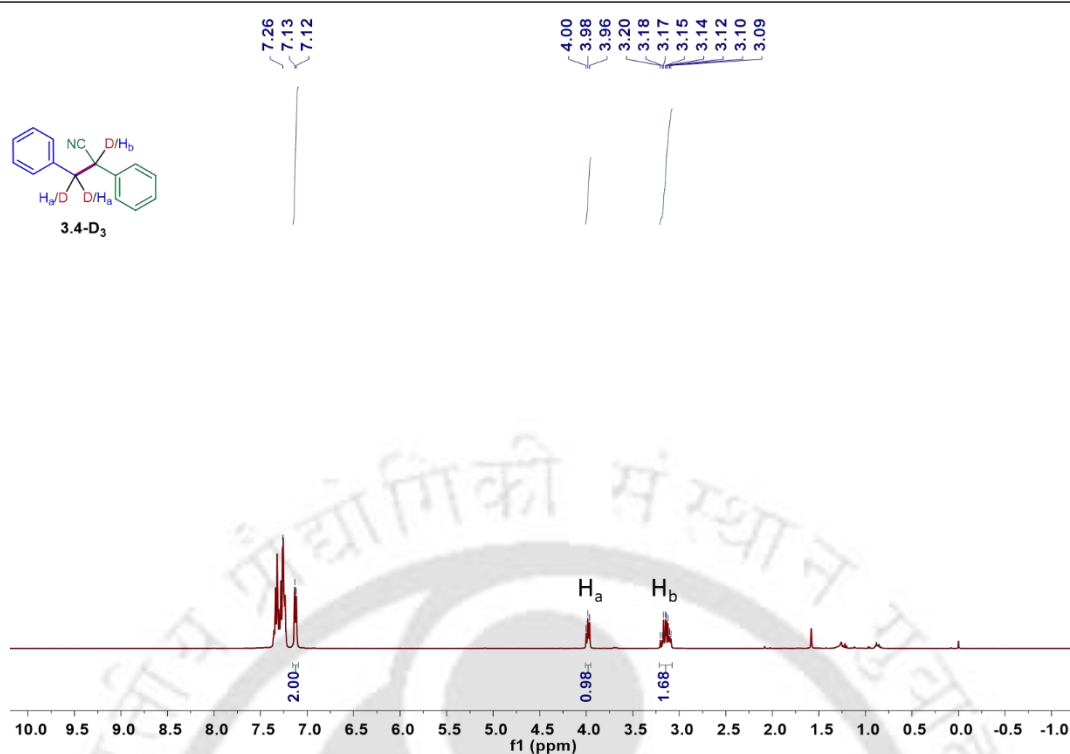


Figure B3: ^1H NMR of **3.4-D₃** in CDCl_3 .

Table B1: Kinetic labelling experiment

		Deuterium incorporation in H_a position	Deuterium incorporation in H_b position
Signal δ ppm	7.13 [2H]	9.98 [1H]	3.15 [2H]
Integral Value	2.0	0.98	1.68
Calculated ratio		$\{(1-0.98)/1\} \times 100 = 2\%$	$\{(2-1.68)/2\} \times 100 = 16\%$

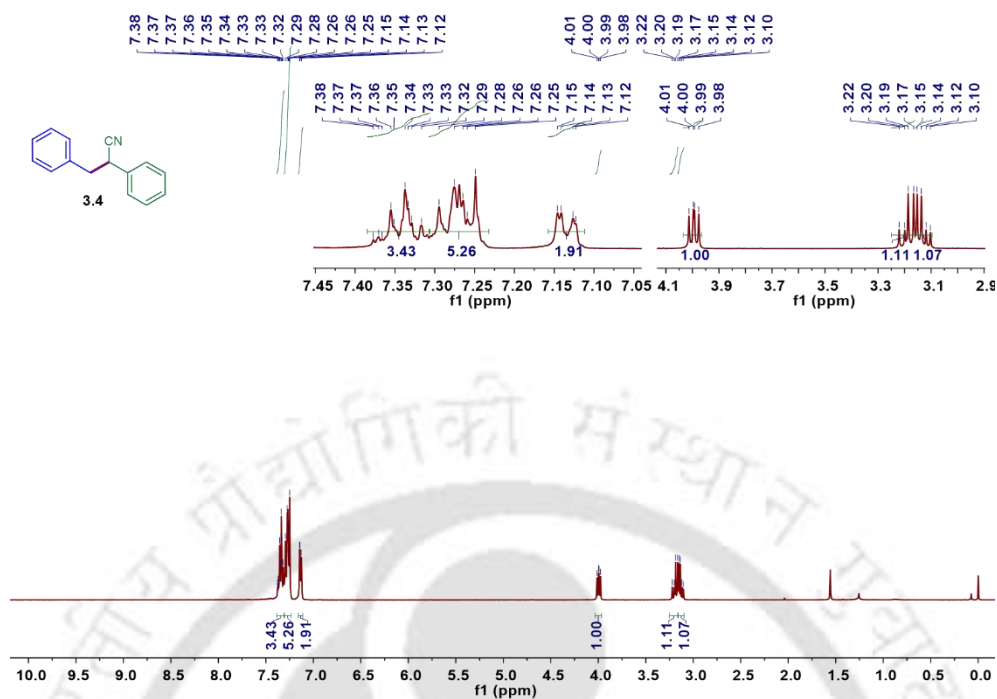
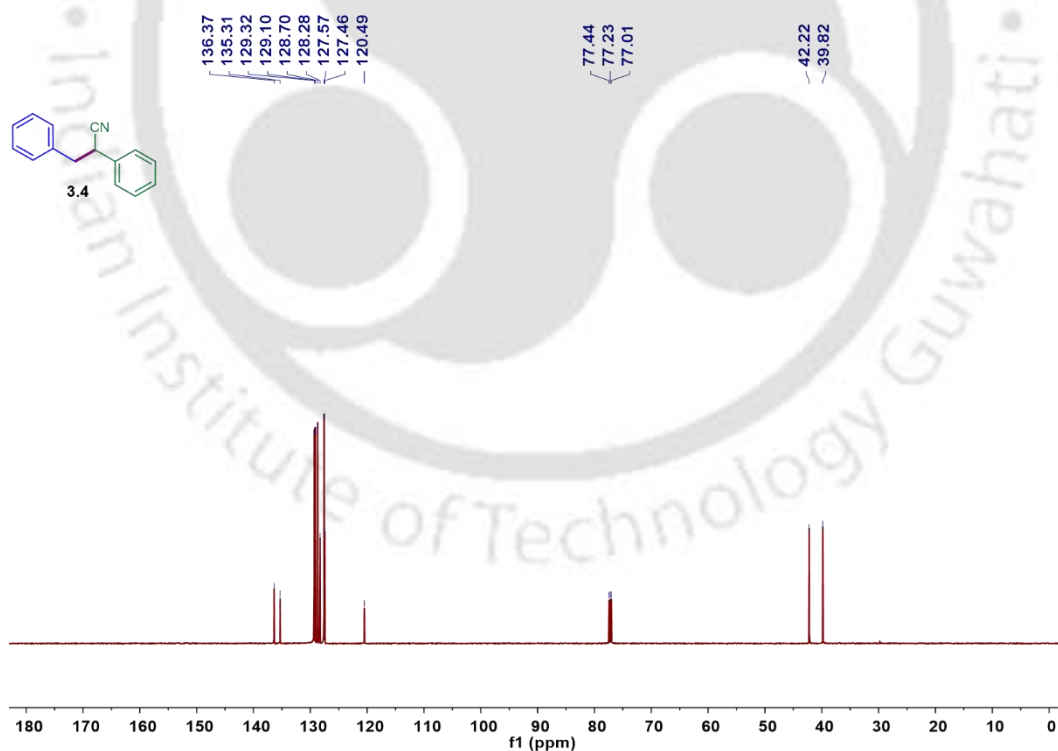
Calculation of K_H/K_D

For 91% 1-D_2 , deuterium incorporation in the product = 16%

For 100% 1-D_2 , deuterium incorporation in the product = 17.5% D

Therefore, proton incorporation = $(100-17.5)\% = 82.5\% \text{ H}$

$K_H/K_D = 82.5\%/17.5\% = 4.7$

B4. NMR spectra of purified compounds:**Figure B4.** ¹H NMR of 3.4 in CDCl₃.**Figure B5.** ¹³C{¹H} NMR of 3.4 in CDCl₃.

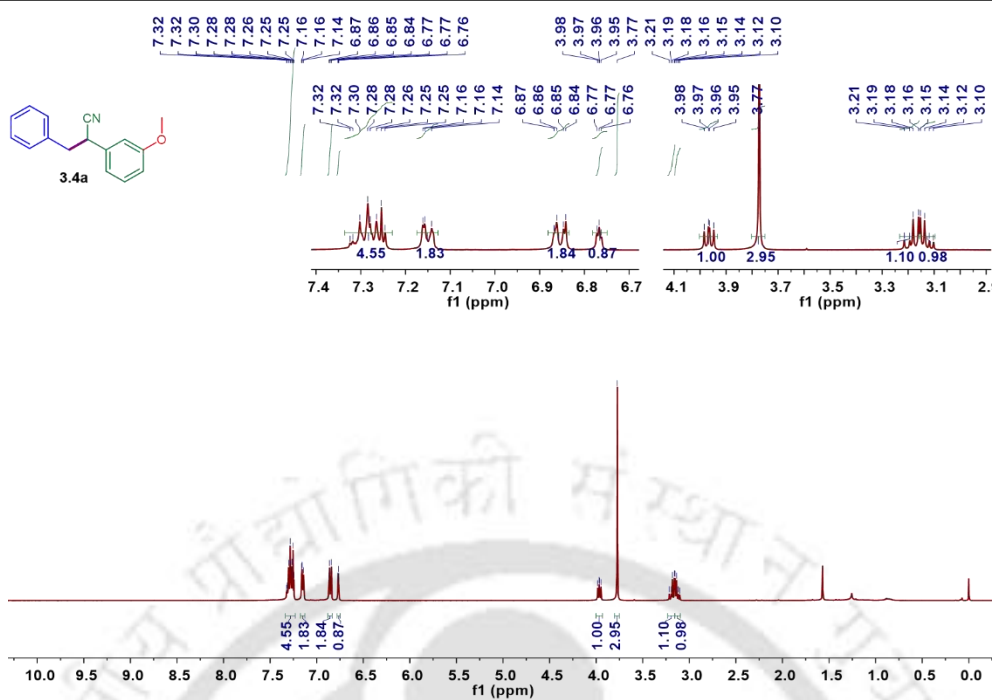


Figure B6. ¹H NMR of 3.4a in CDCl₃.

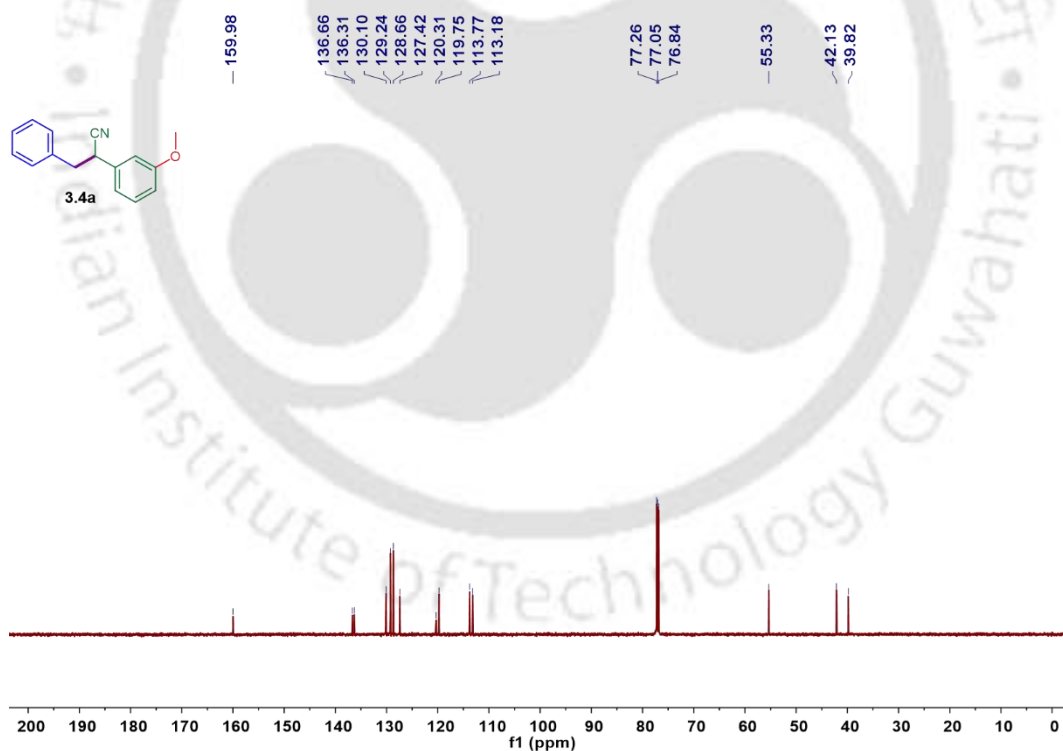


Figure B7. ¹³C{H} NMR of 3.4a in CDCl₃.

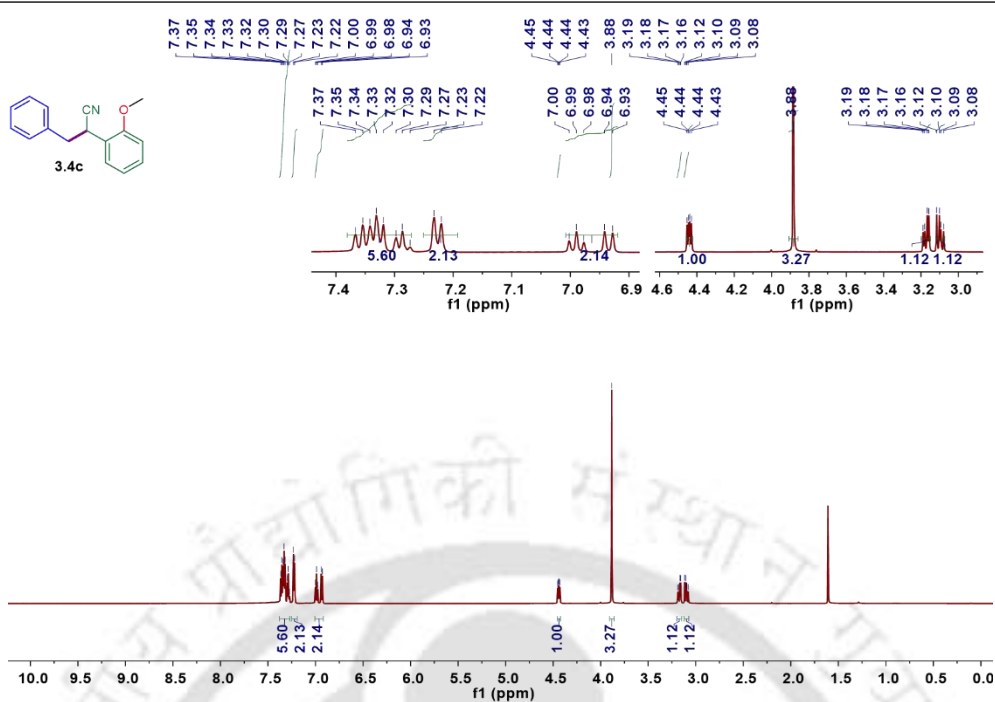


Figure B8. ¹H NMR of 3.4c in CDCl₃.

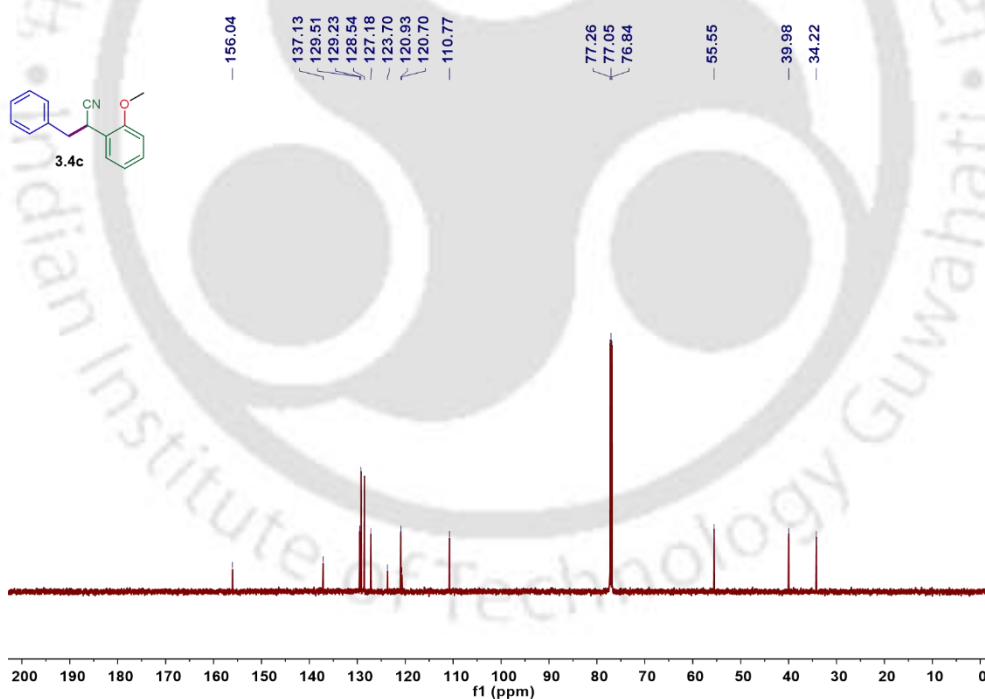


Figure B9. ¹³C{¹H} NMR of 3.4c in CDCl₃.

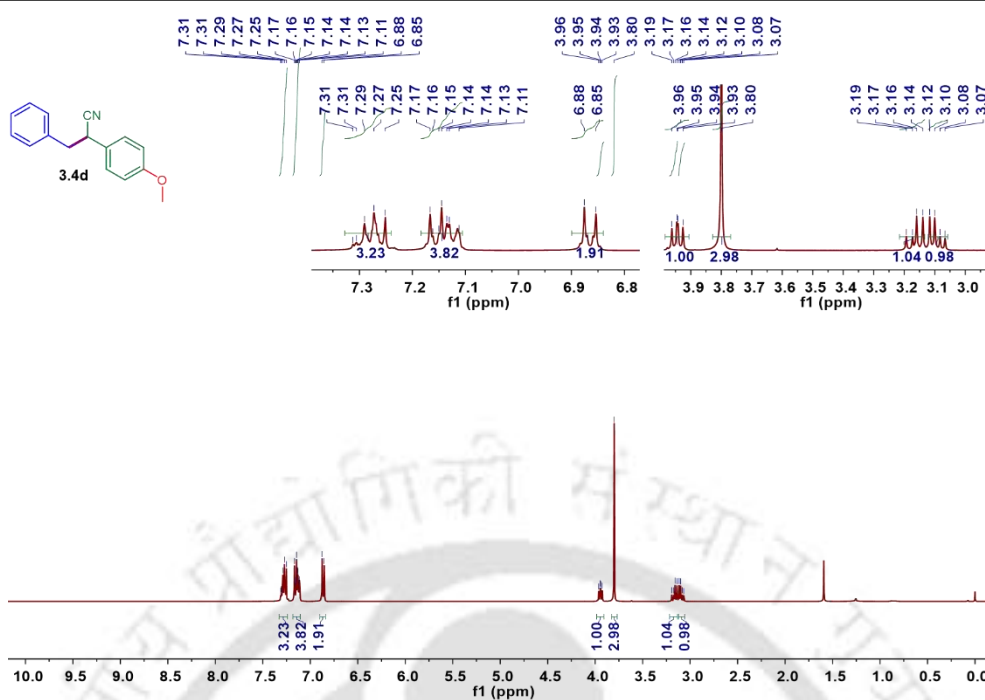


Figure B10. ¹H NMR of 3.4d in CDCl₃.

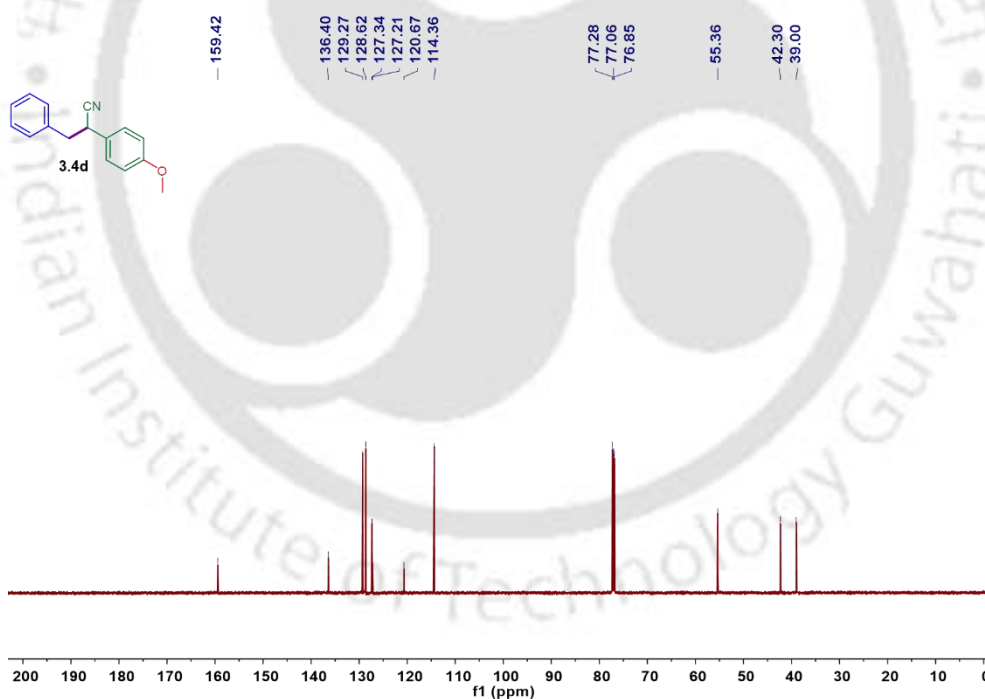


Figure B11. ¹³C{H} NMR of 3.4d in CDCl₃.

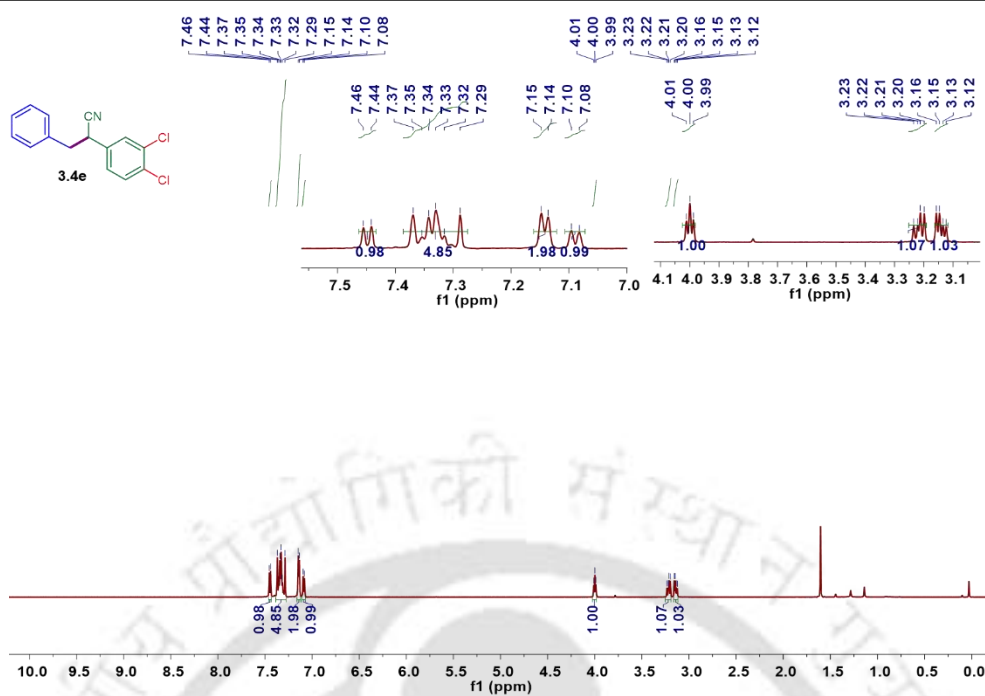


Figure B12. ¹H NMR of **3.4e** in CDCl₃.

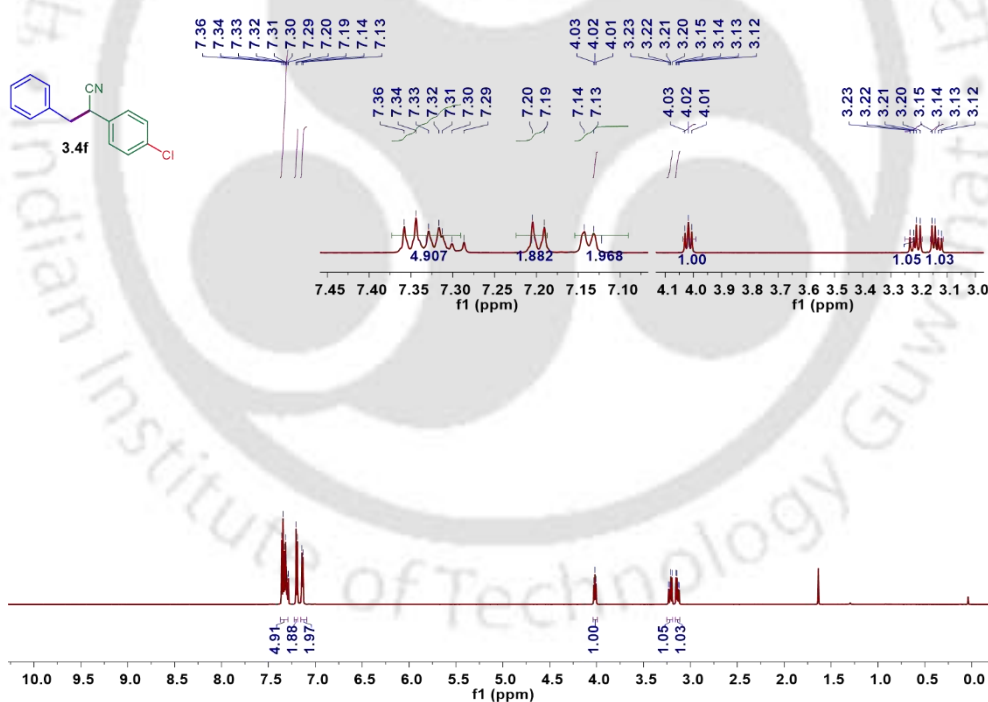


Figure B13. ¹H NMR of **3.4f** in CDCl₃.

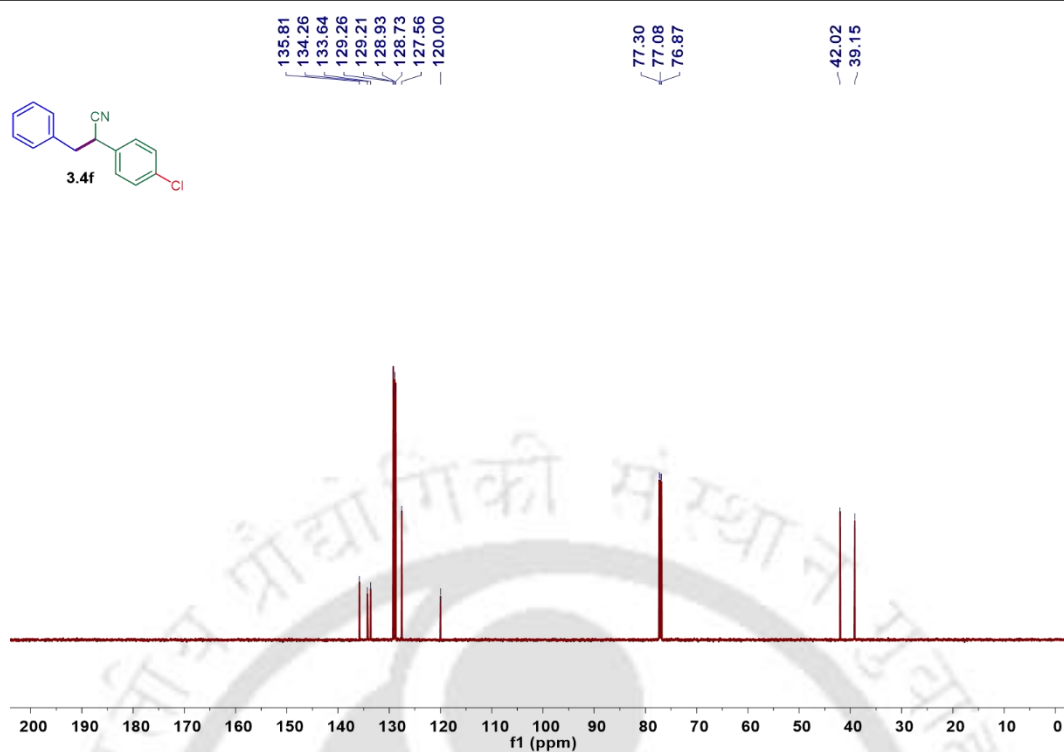


Figure B14. $^{13}\text{C}\{^1\text{H}\}$ NMR of **3.4f** in CDCl_3 .

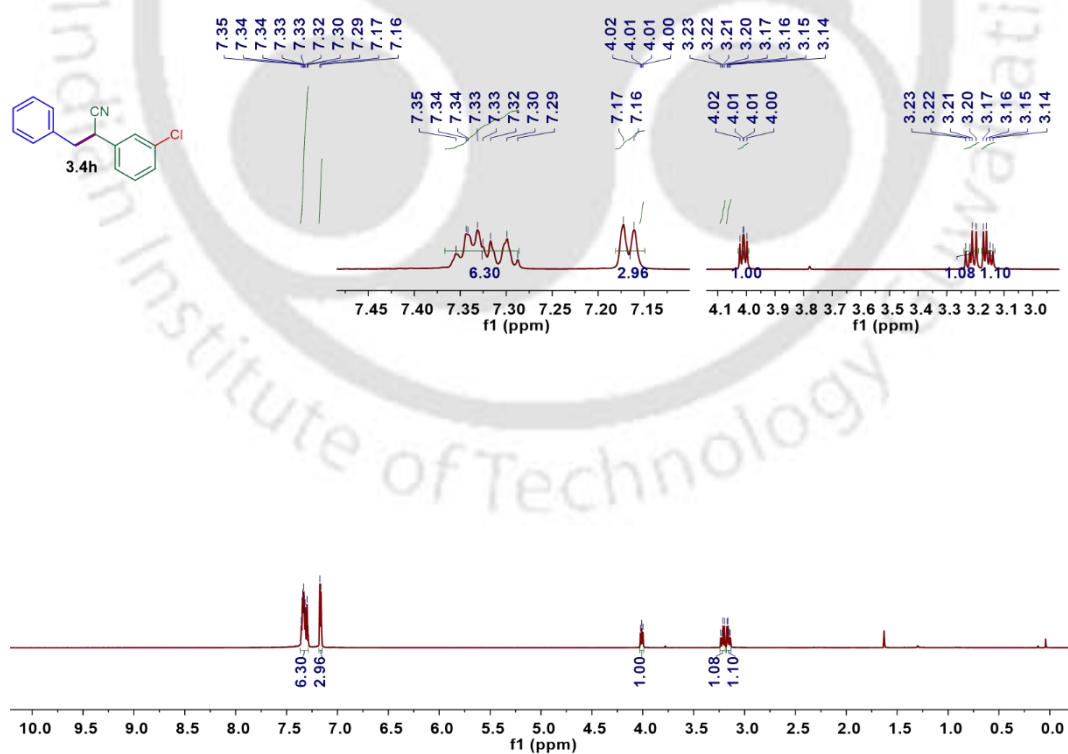
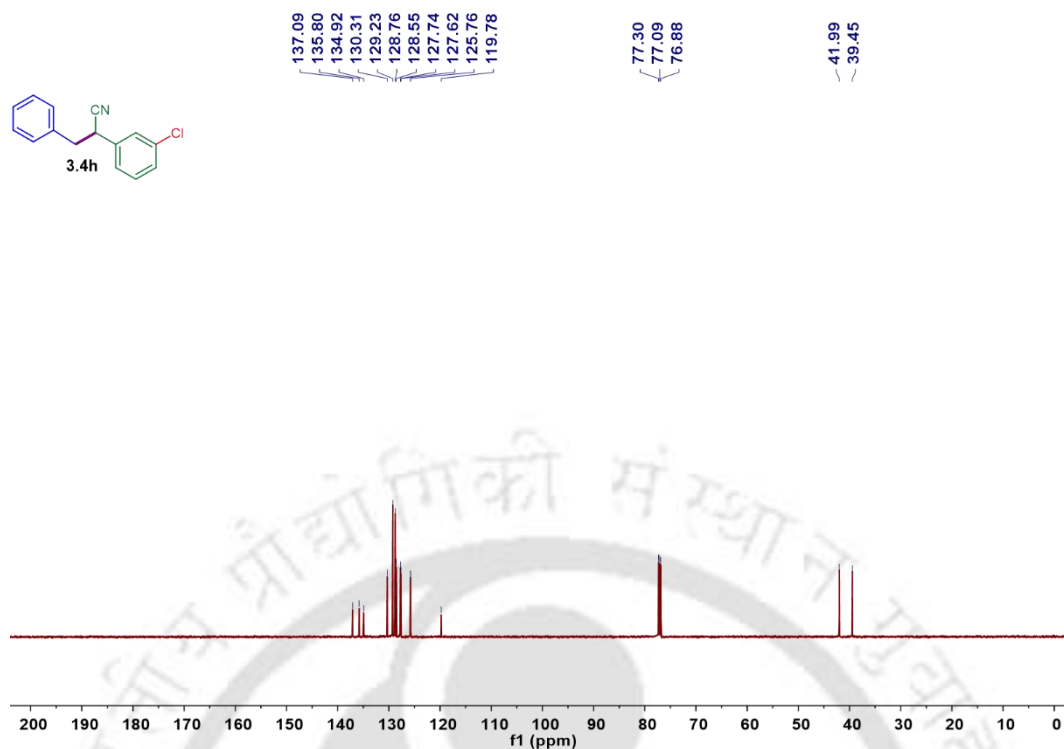
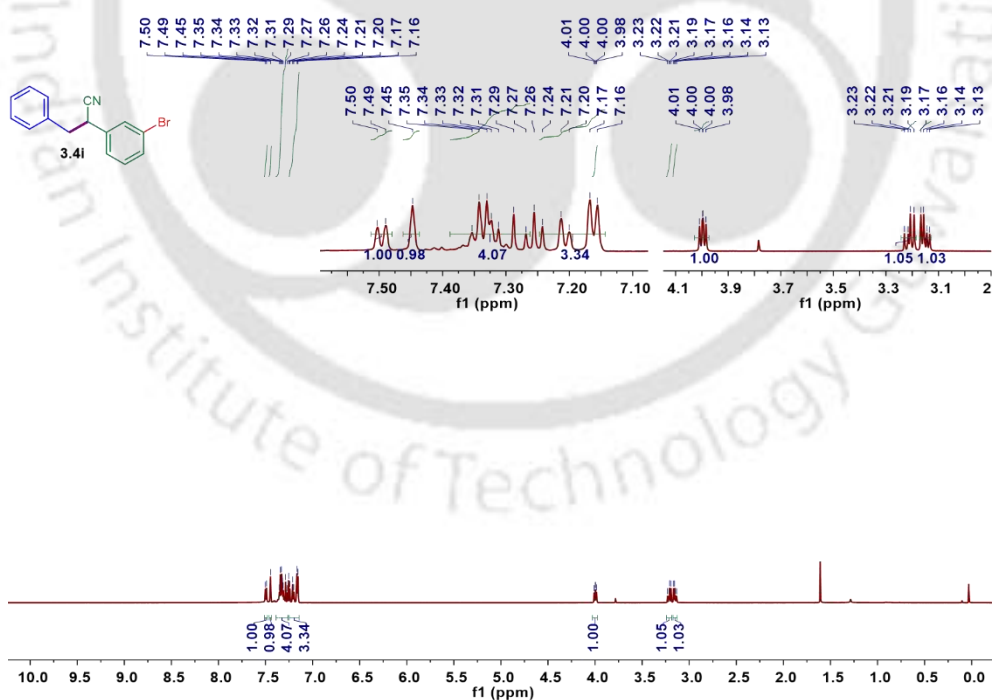
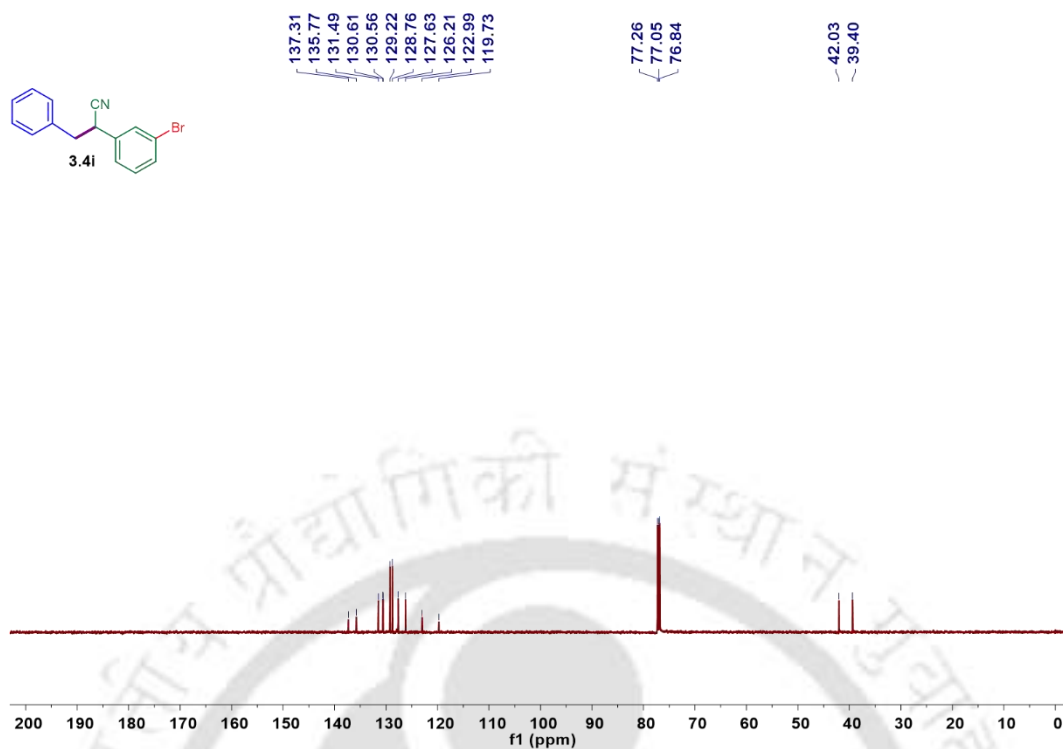
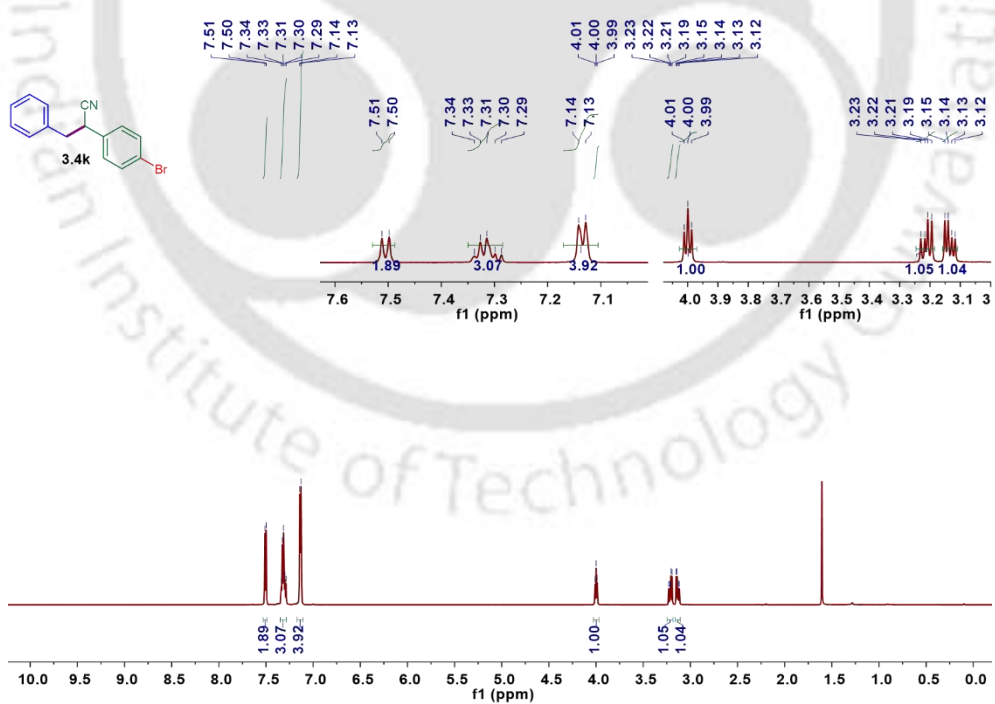


Figure B15. ^1H NMR of **3.4h** in CDCl_3 .

**Figure B16.** $^{13}\text{C}\{\text{H}\}$ NMR of **3.4h** in CDCl_3 .**Figure B17.** ^1H NMR of **3.4i** in CDCl_3 .

**Figure B18.** $^{13}\text{C}\{^1\text{H}\}$ NMR of **3.4i** in CDCl_3 .**Figure B19.** ^1H NMR of **3.4k** in CDCl_3 .

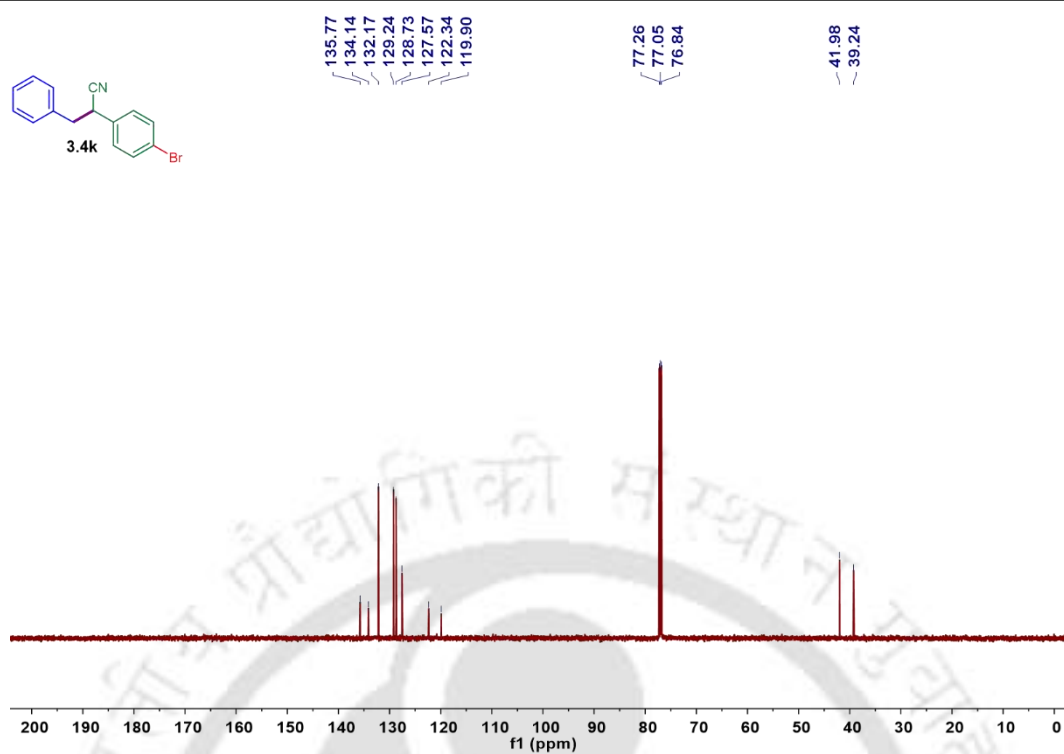


Figure B20. $^{13}\text{C}\{^1\text{H}\}$ NMR of **3.4k** in CDCl_3 .

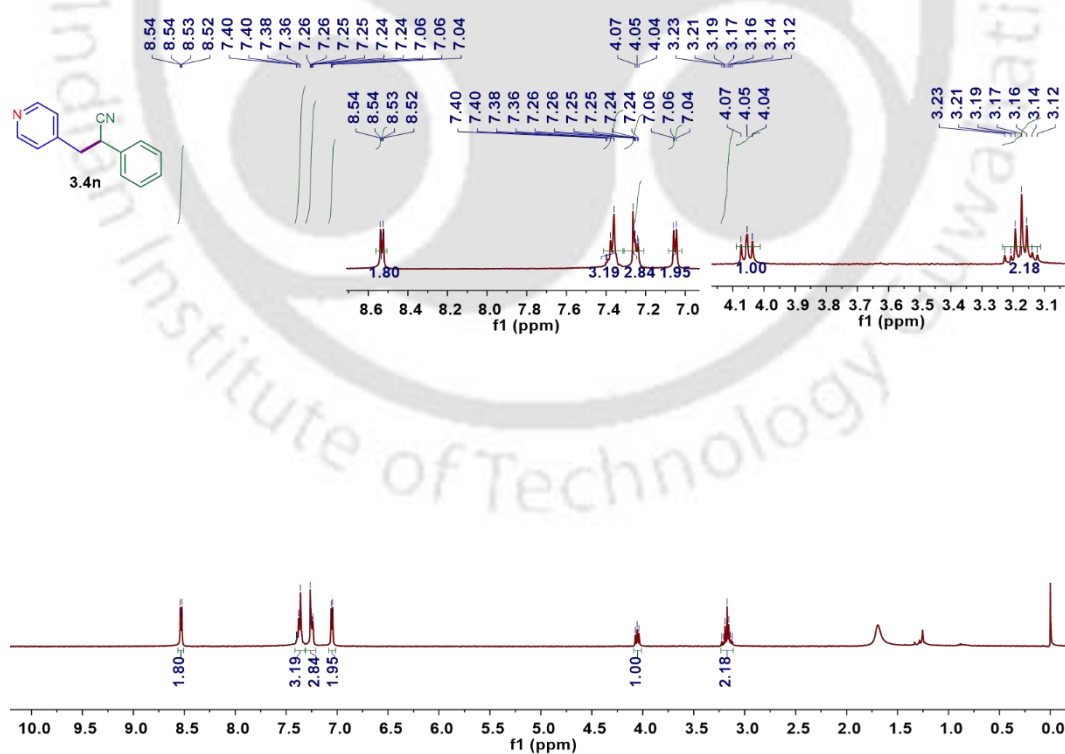
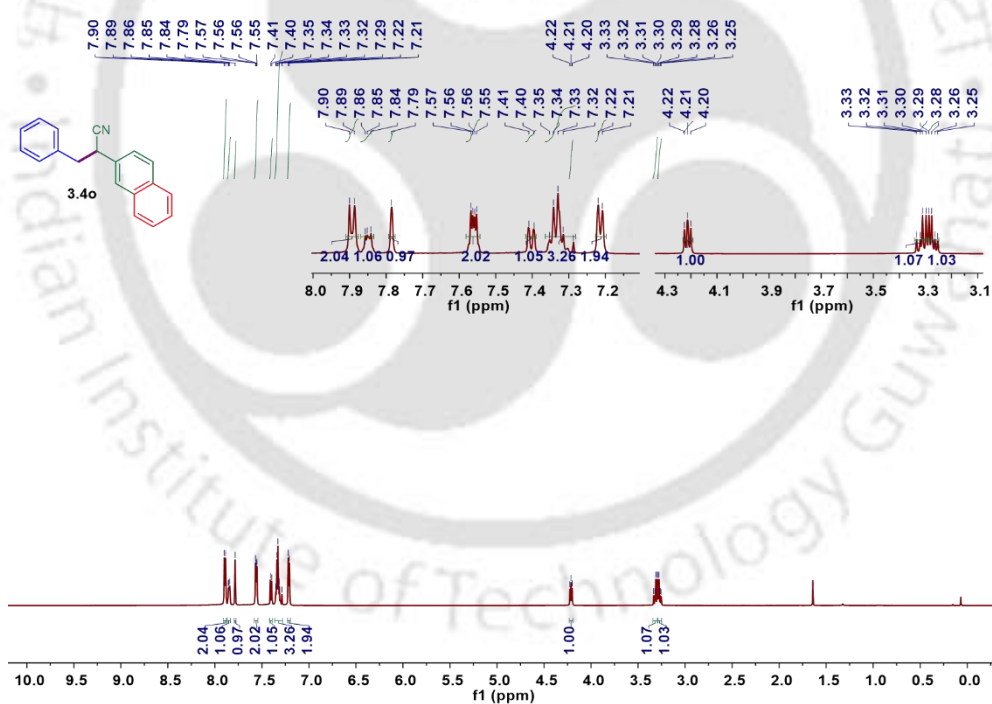
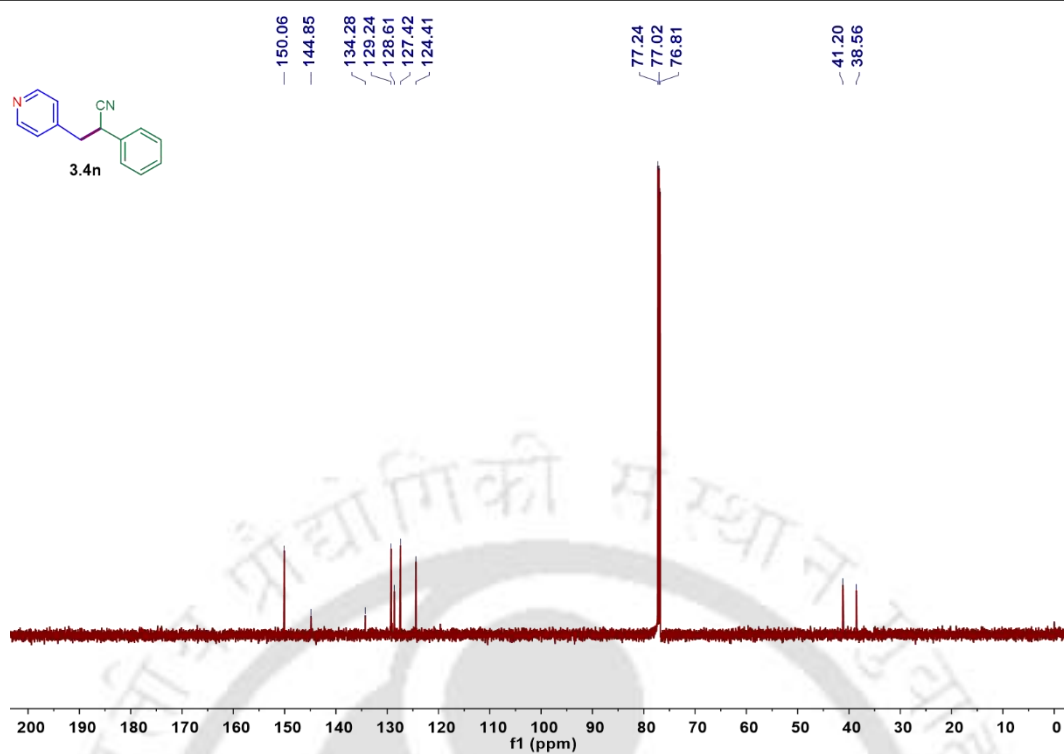


Figure B21. ^1H NMR of **3.4n** in CDCl_3 .



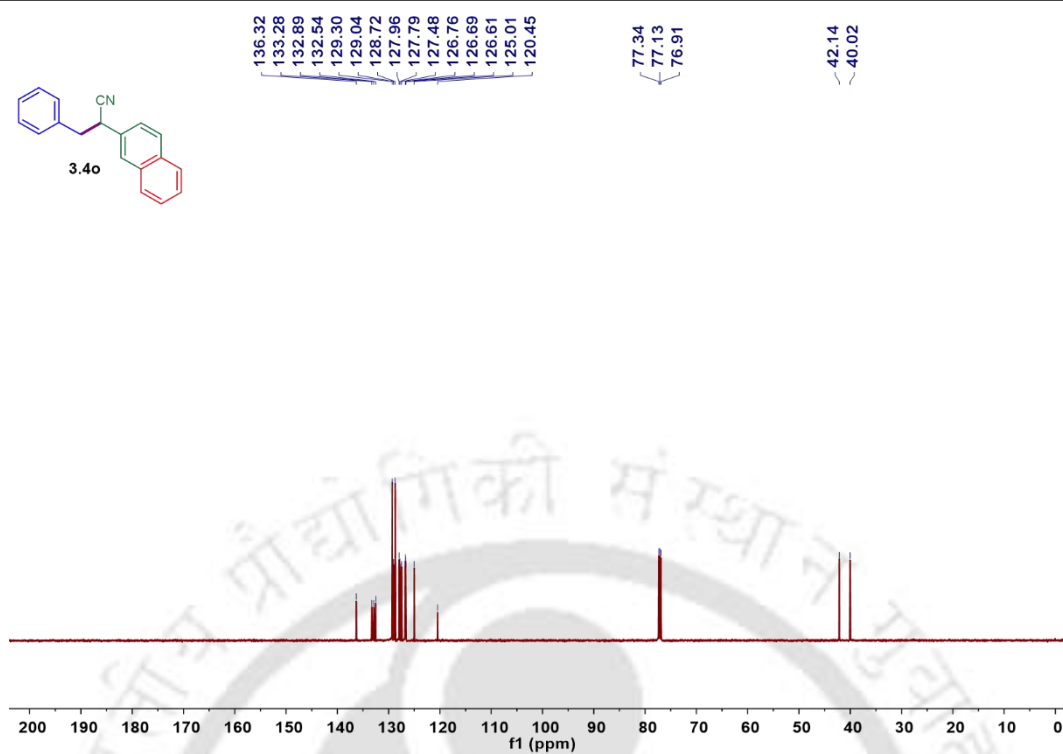


Figure B24. $^{13}\text{C}\{^1\text{H}\}$ NMR of **3.4o** in CDCl_3 .

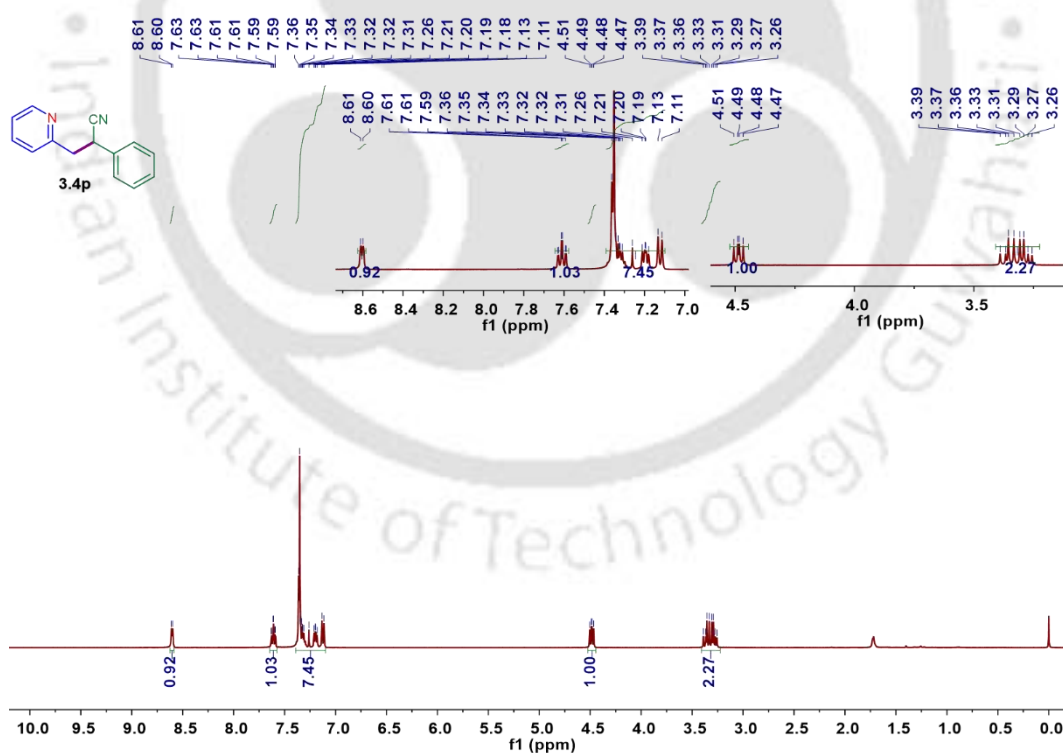


Figure B25. ^1H NMR of **3.4p** in CDCl_3 .

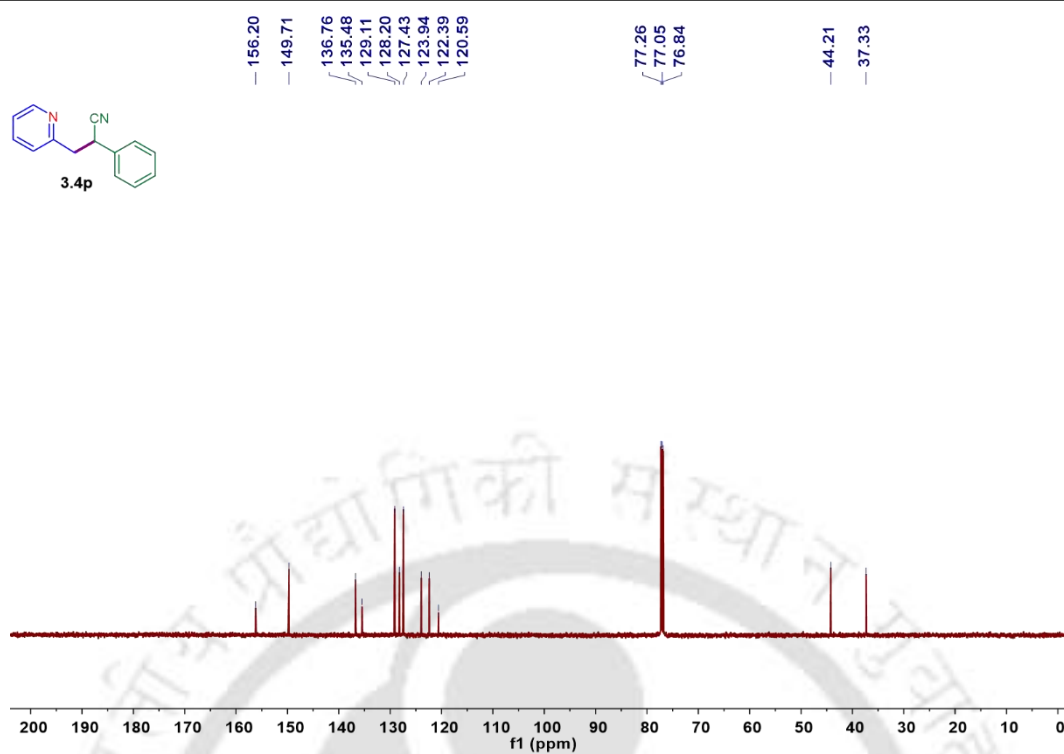


Figure B26. $^{13}\text{C}\{\text{H}\}$ NMR of **3.4p** in CDCl_3 .

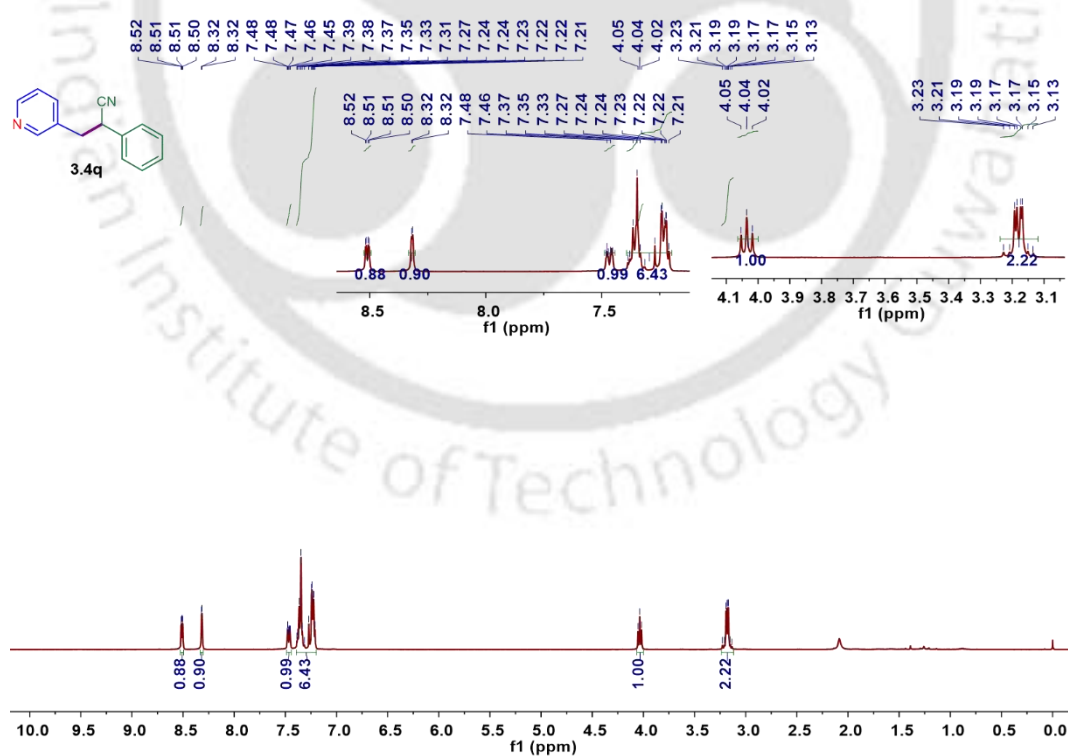
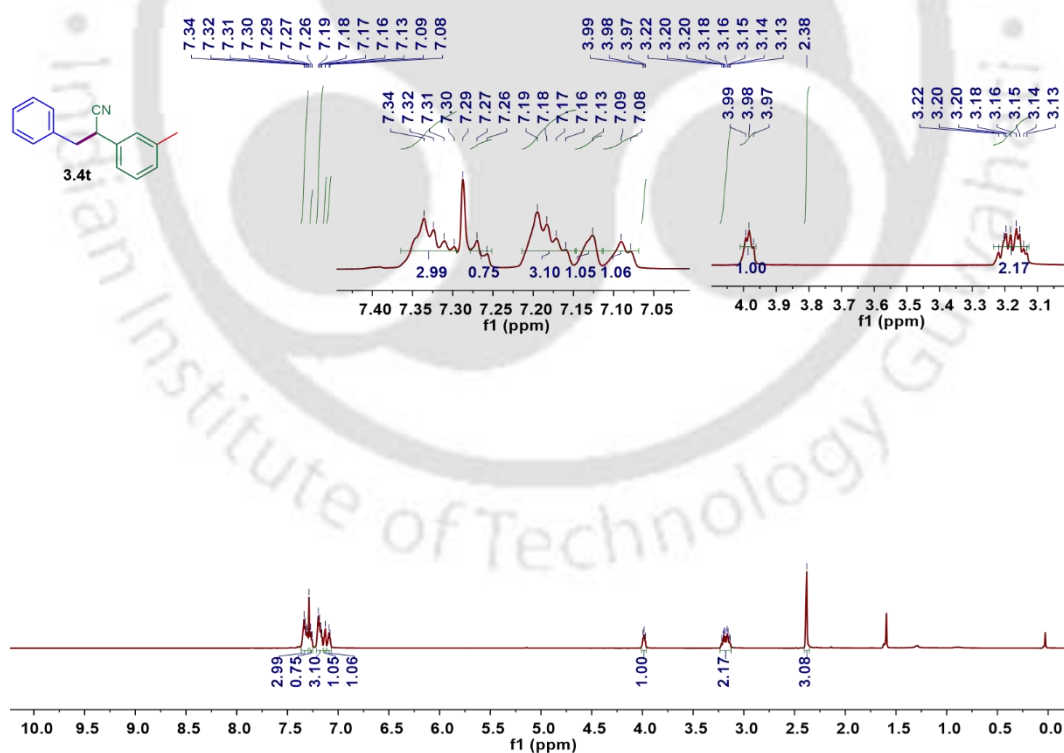
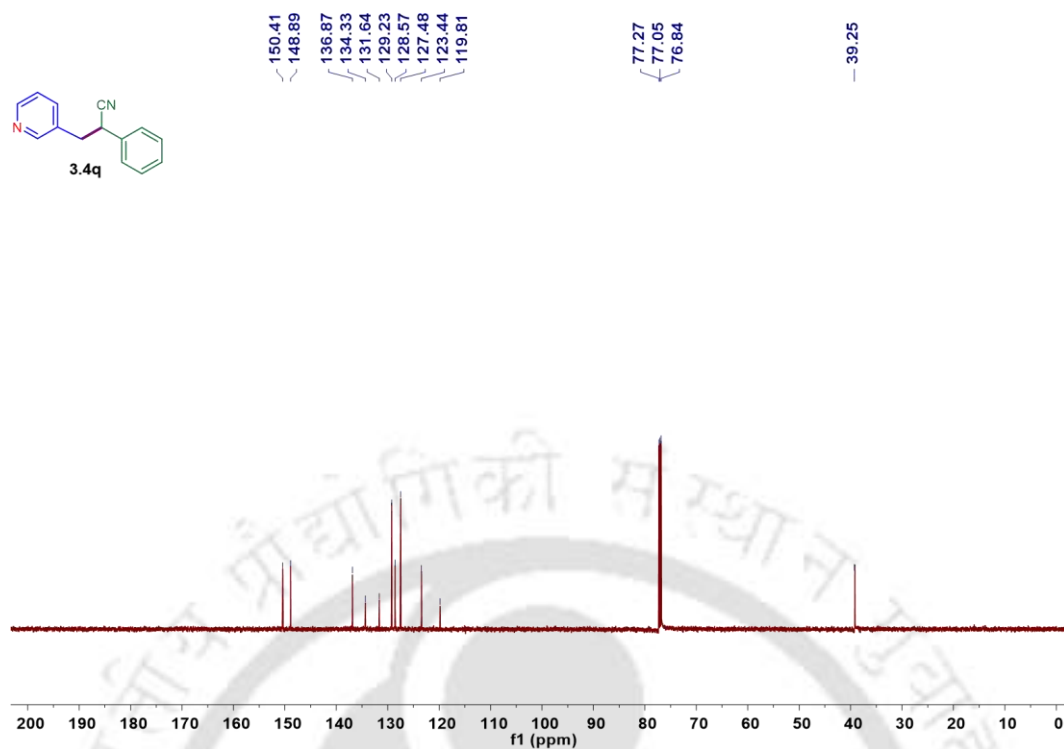


Figure B27. ^1H NMR of **3.4q** in CDCl_3 .



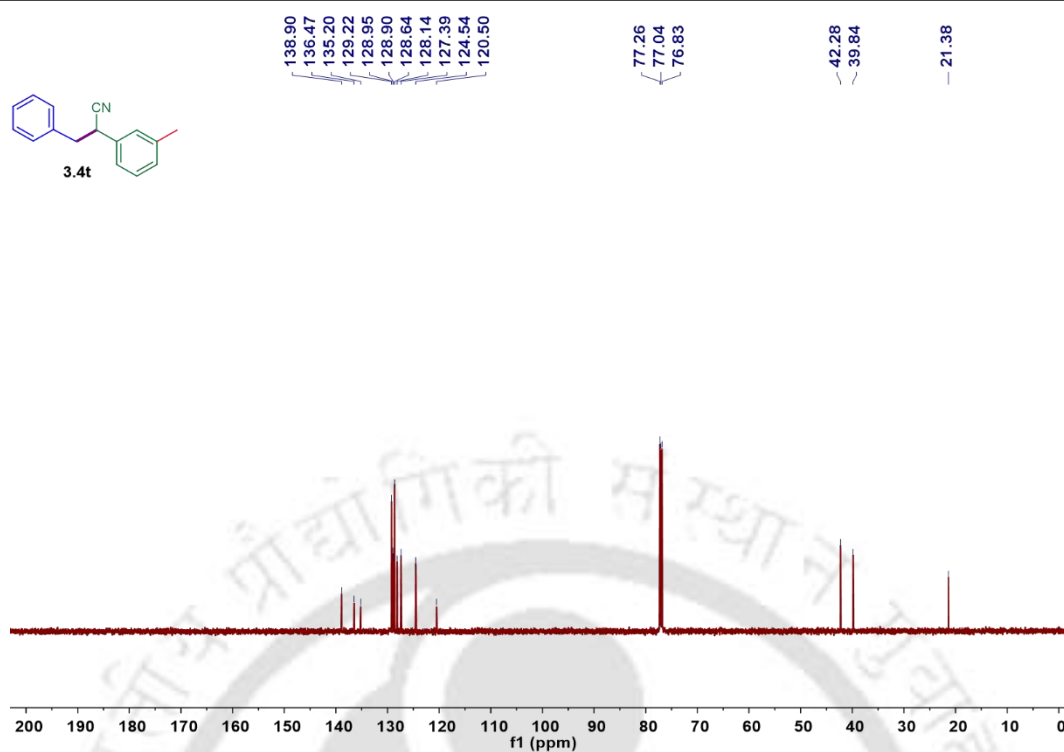


Figure B30. $^{13}\text{C}\{^1\text{H}\}$ NMR of **3.4t** in CDCl_3 .

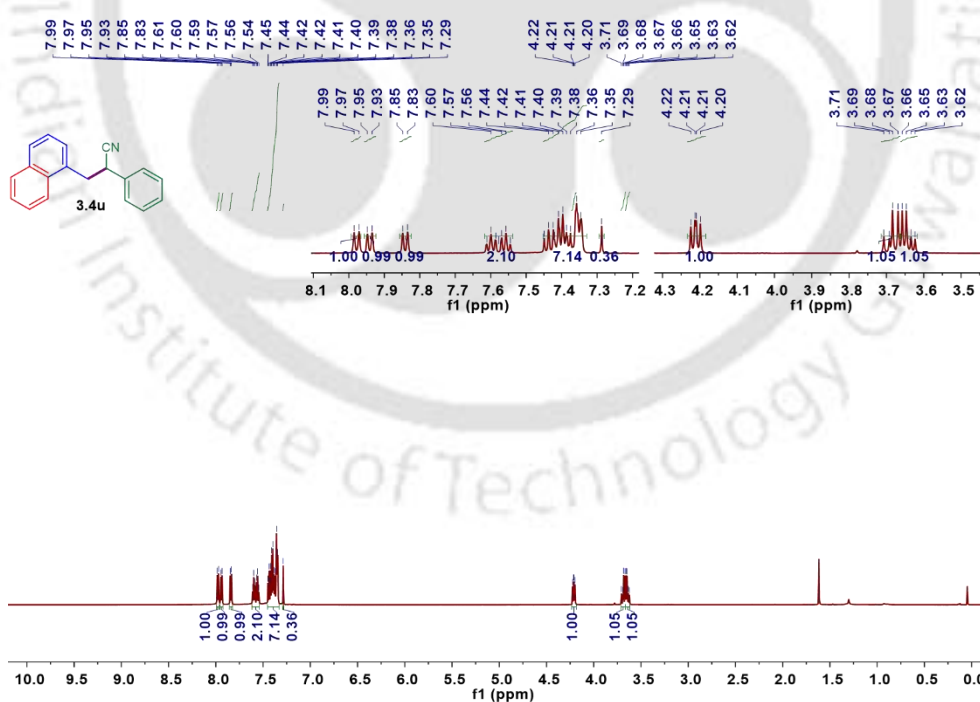


Figure B31. ^1H NMR of **3.4u** in CDCl_3 .

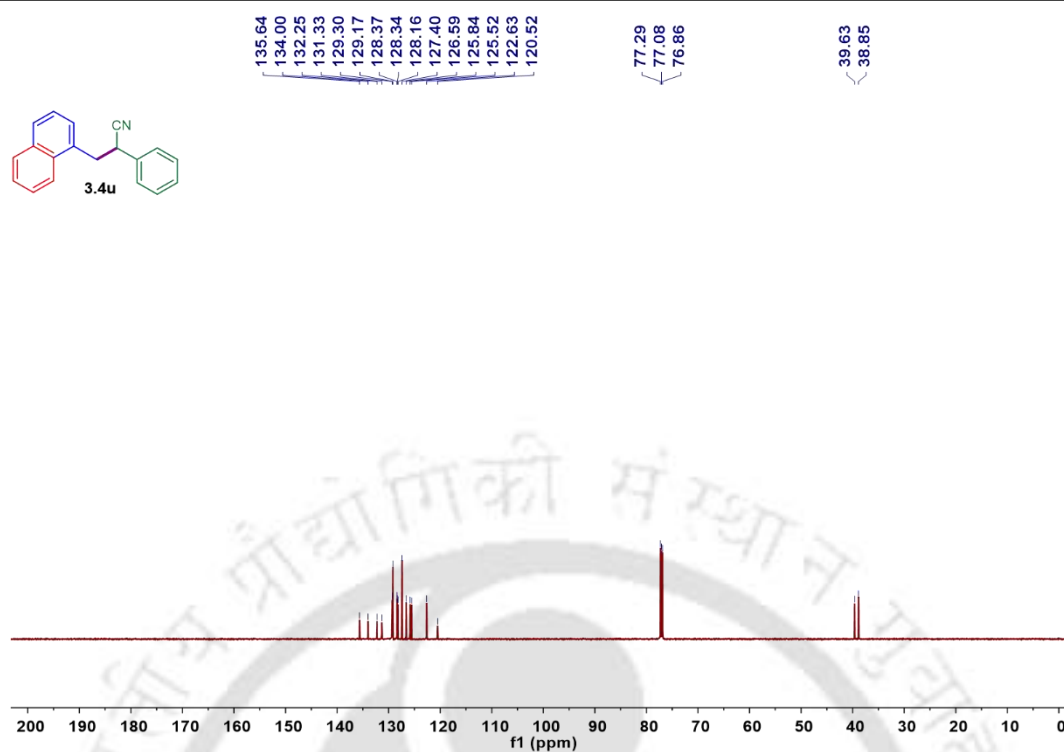


Figure B32. $^{13}\text{C}\{\text{H}\}$ NMR of **3.4u** in CDCl_3 .

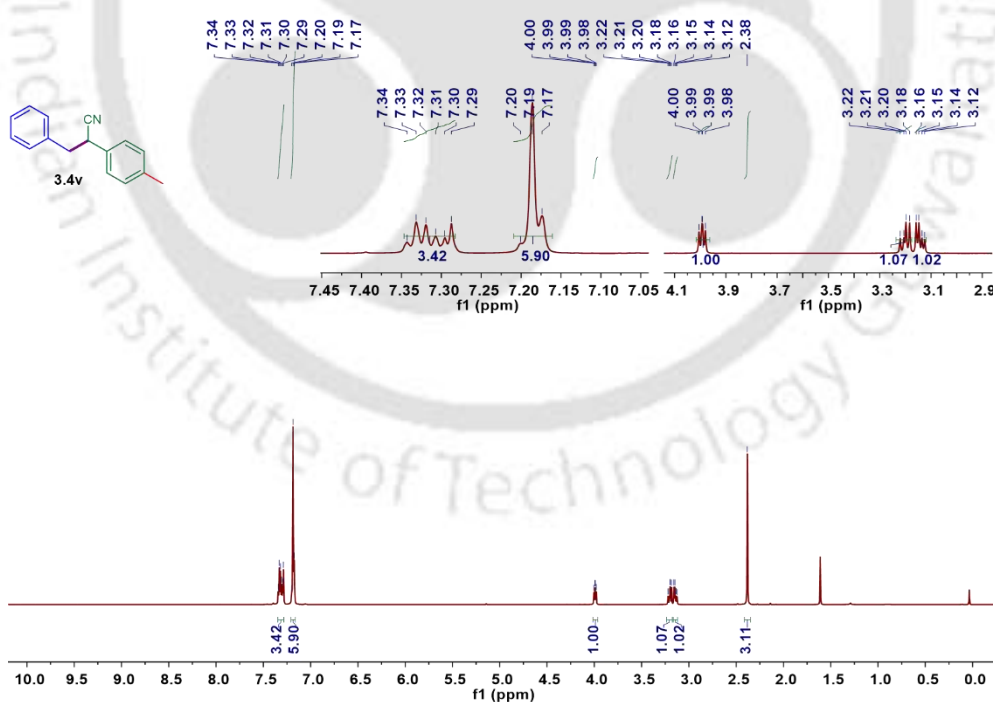


Figure B33. ^1H NMR of **3.4v** in CDCl_3 .

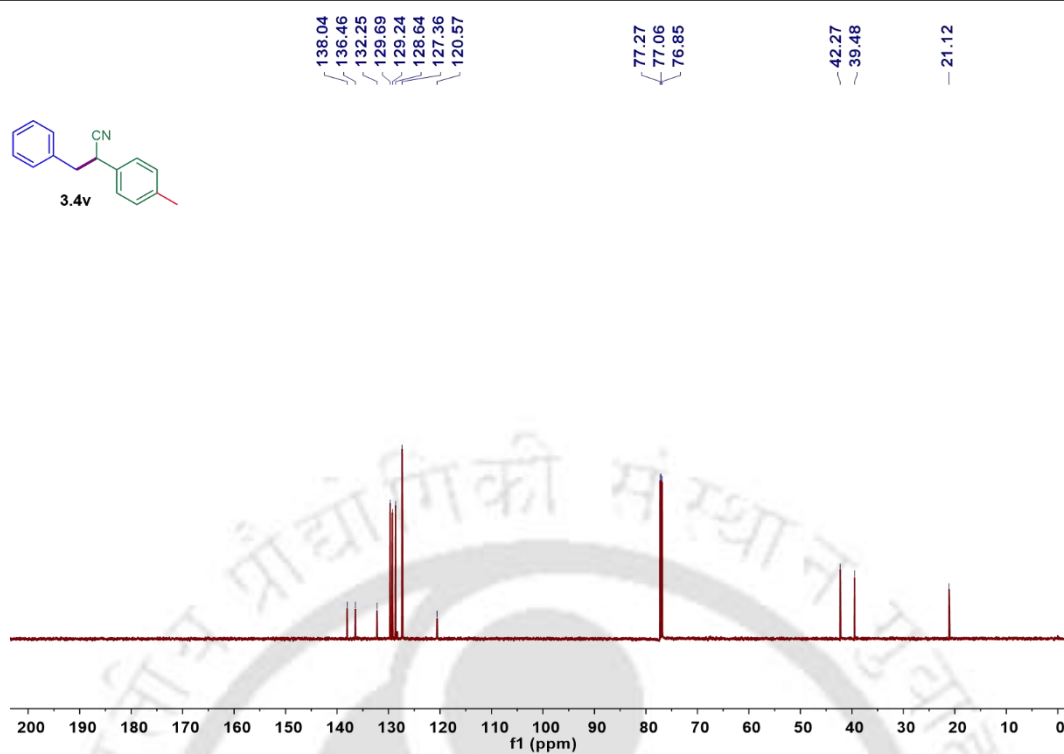


Figure B34. $^{13}\text{C}\{\text{H}\}$ NMR of **3.4v** in CDCl_3 .

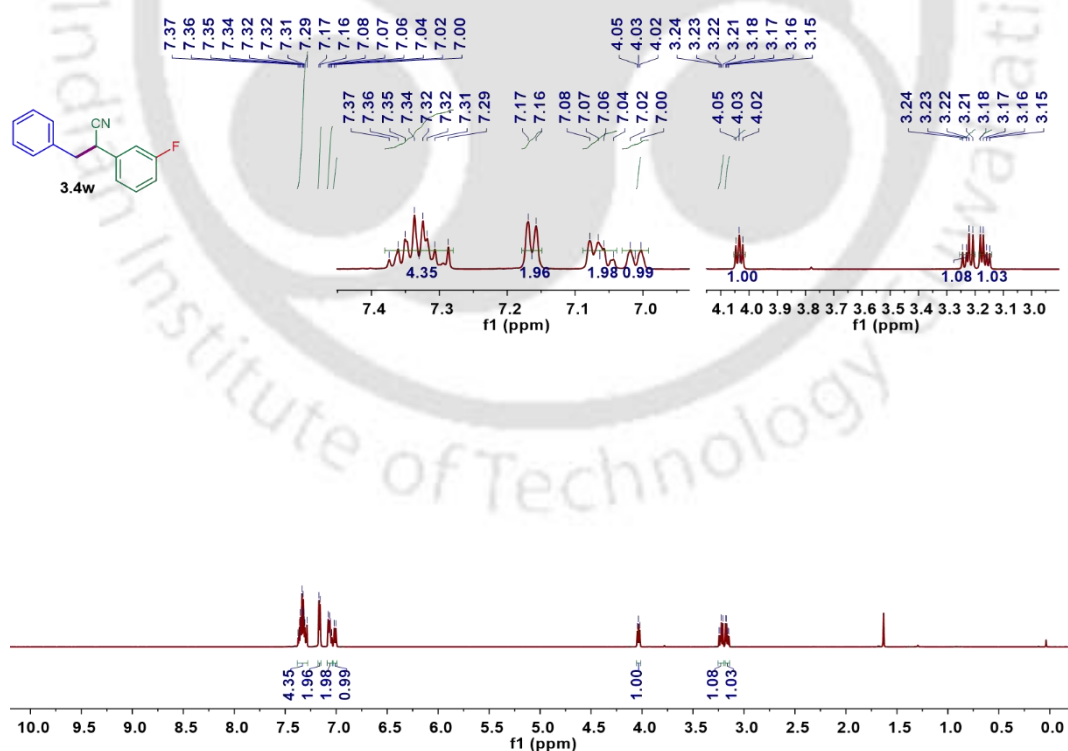


Figure B35. ^1H NMR of **3.4w** in CDCl_3 .

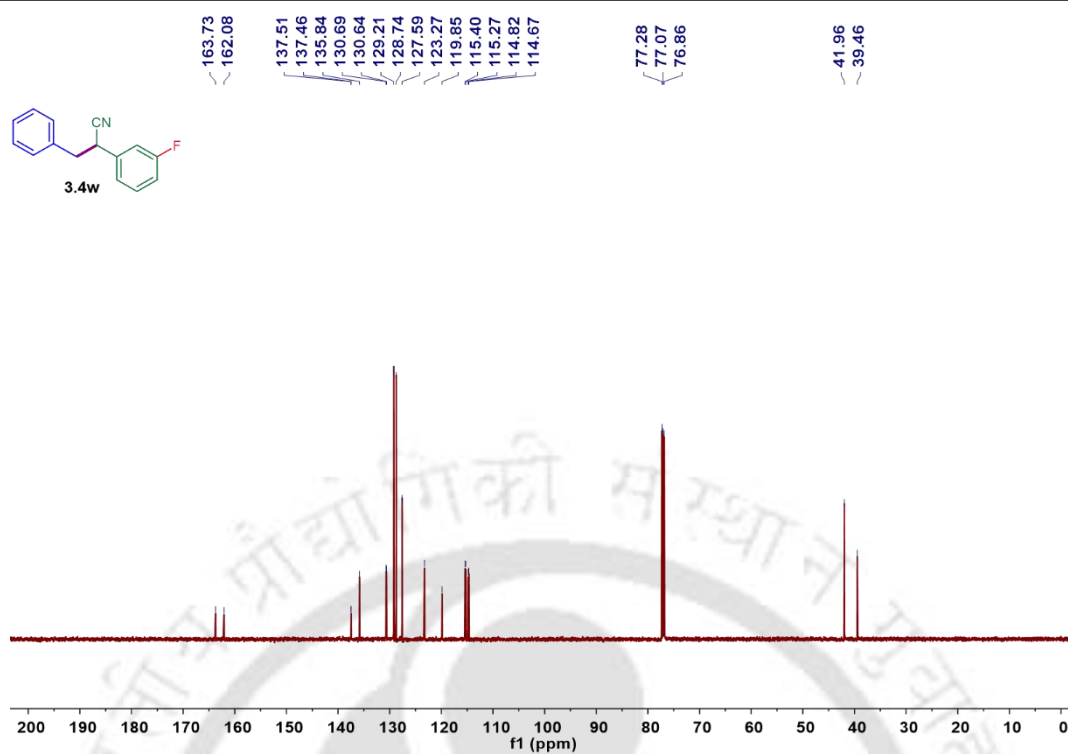


Figure B36. $^{13}\text{C}\{\text{H}\}$ NMR of 3.4w in CDCl_3 .

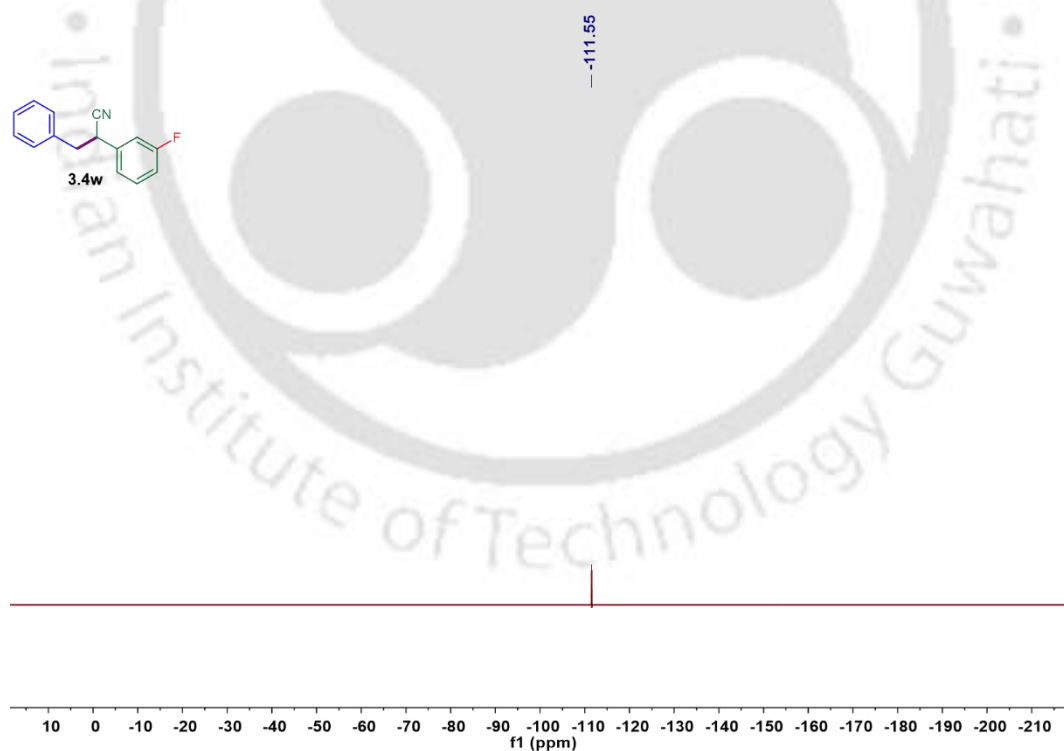


Figure B37. ^{19}F NMR of 3.4w in CDCl_3 .

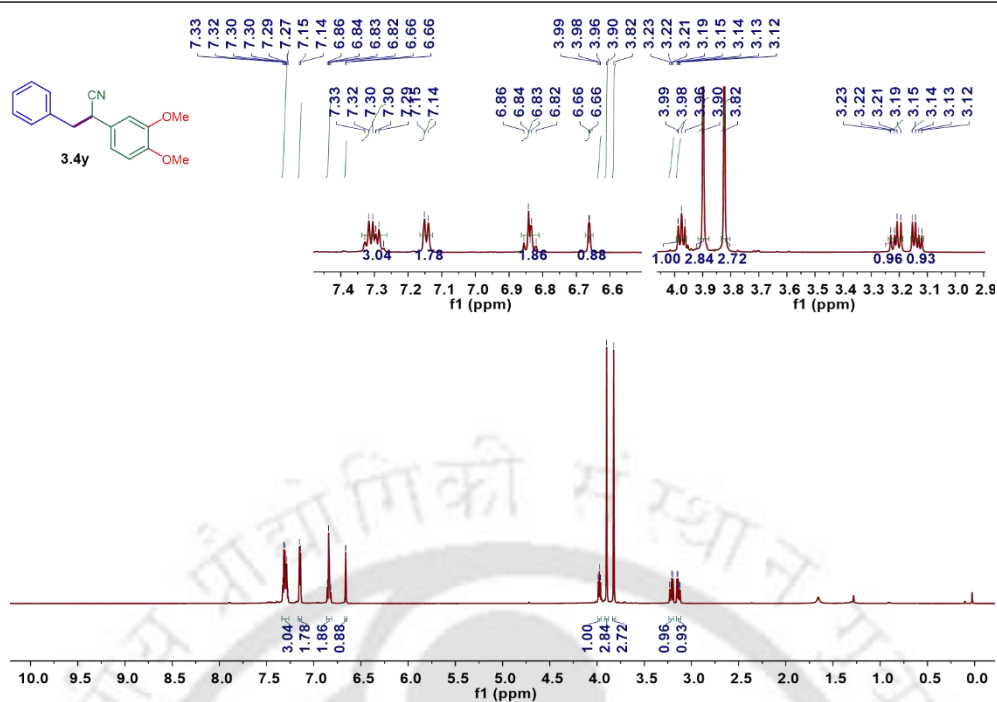


Figure B38. ¹H NMR of 3.4y in CDCl₃.

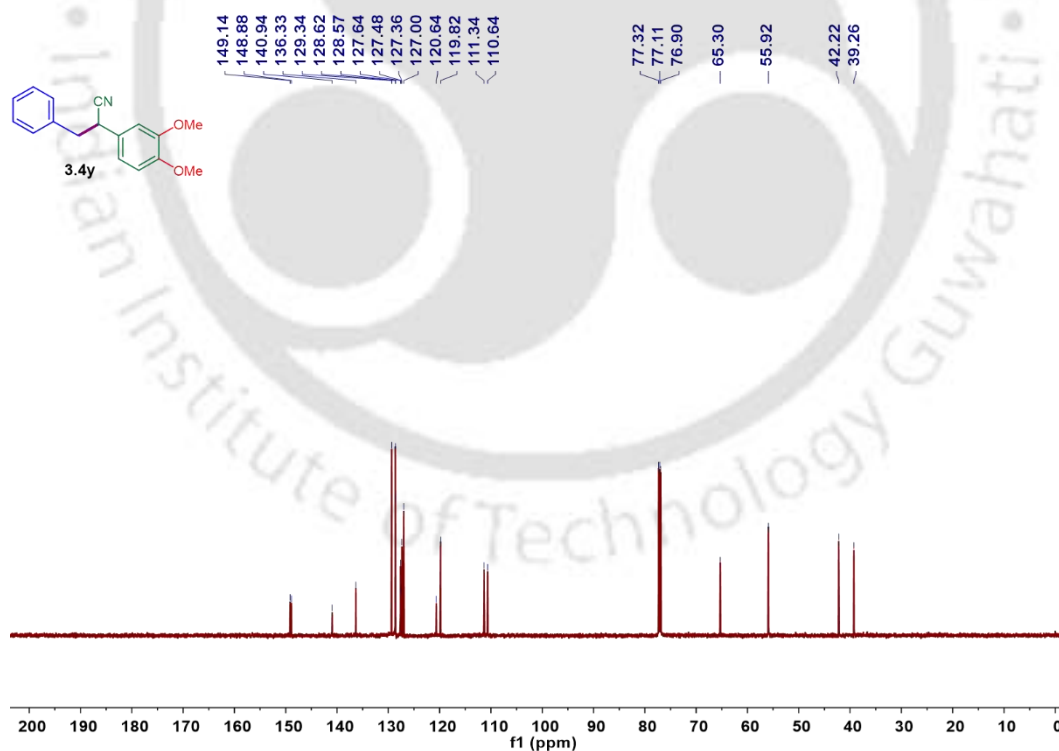


Figure B39. ¹³C{¹H} NMR of 3.4y in CDCl₃.

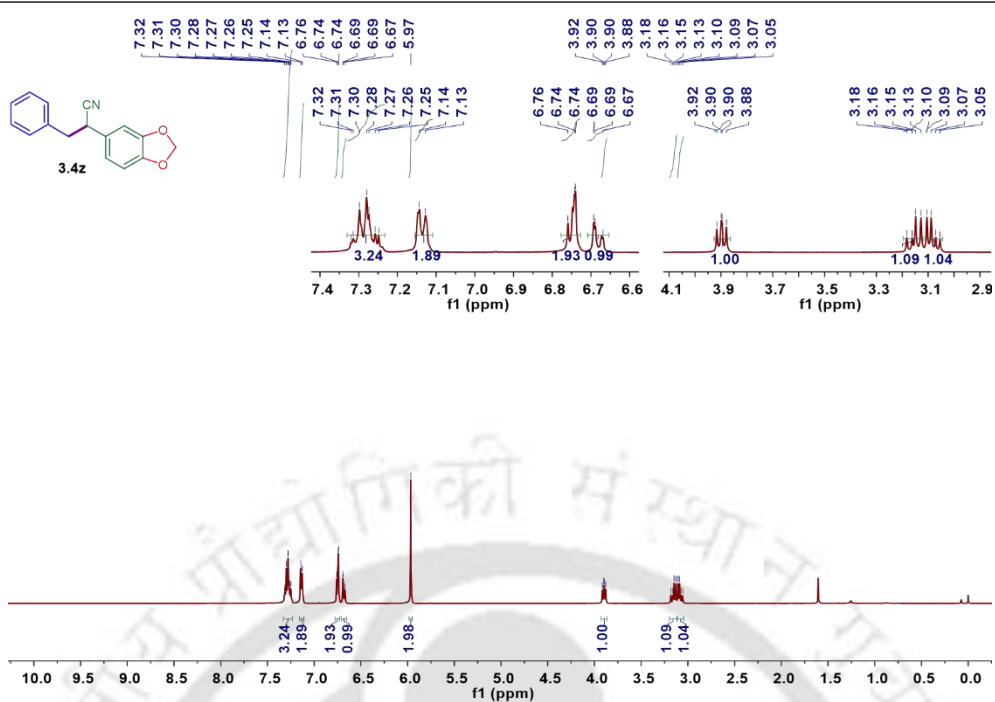


Figure B40. ¹H NMR of 3.4z in CDCl₃.

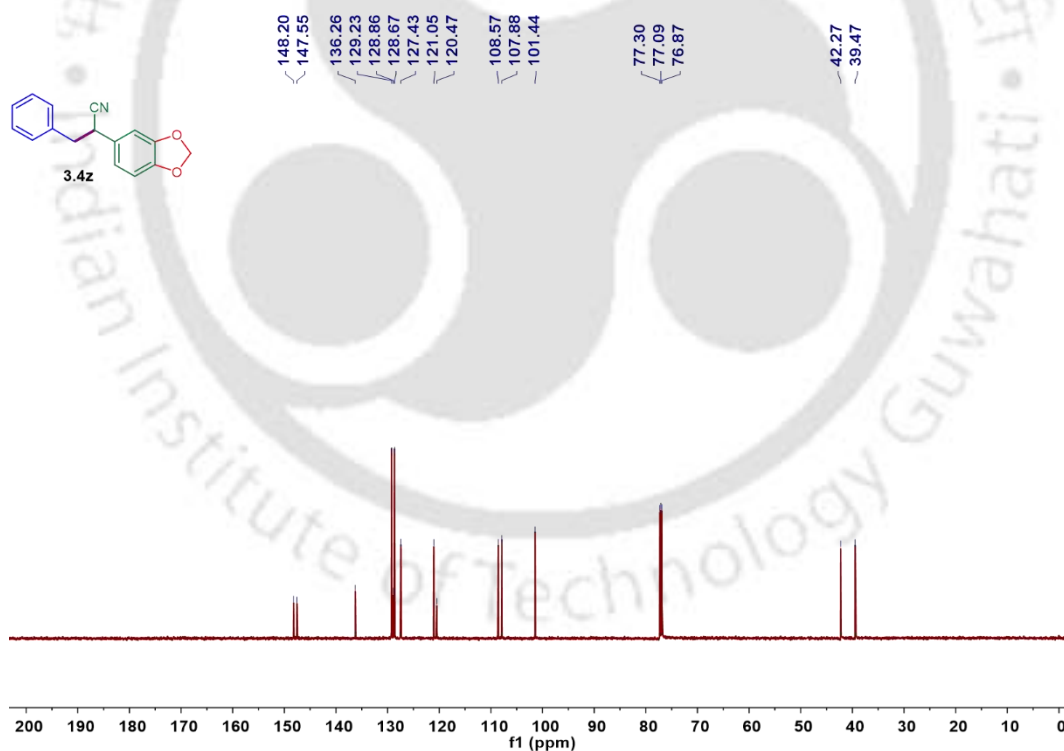


Figure B41. ¹³C{H} NMR of 3.4z in CDCl₃.

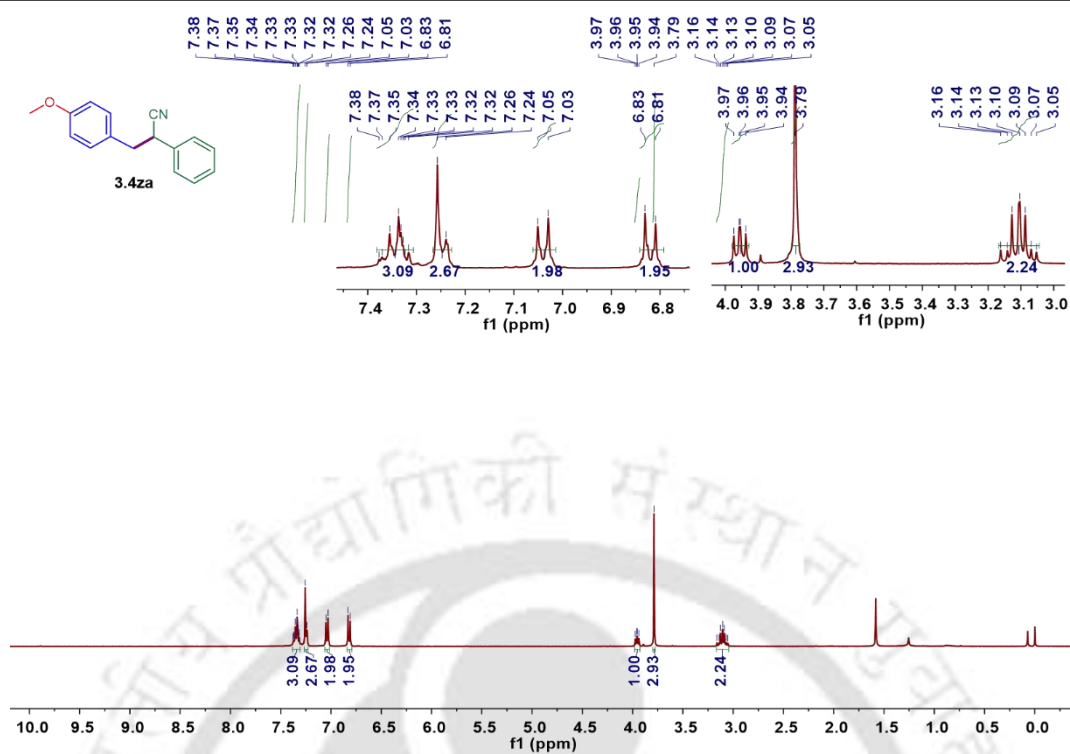


Figure B42. ¹H NMR of 3.4za in CDCl₃.

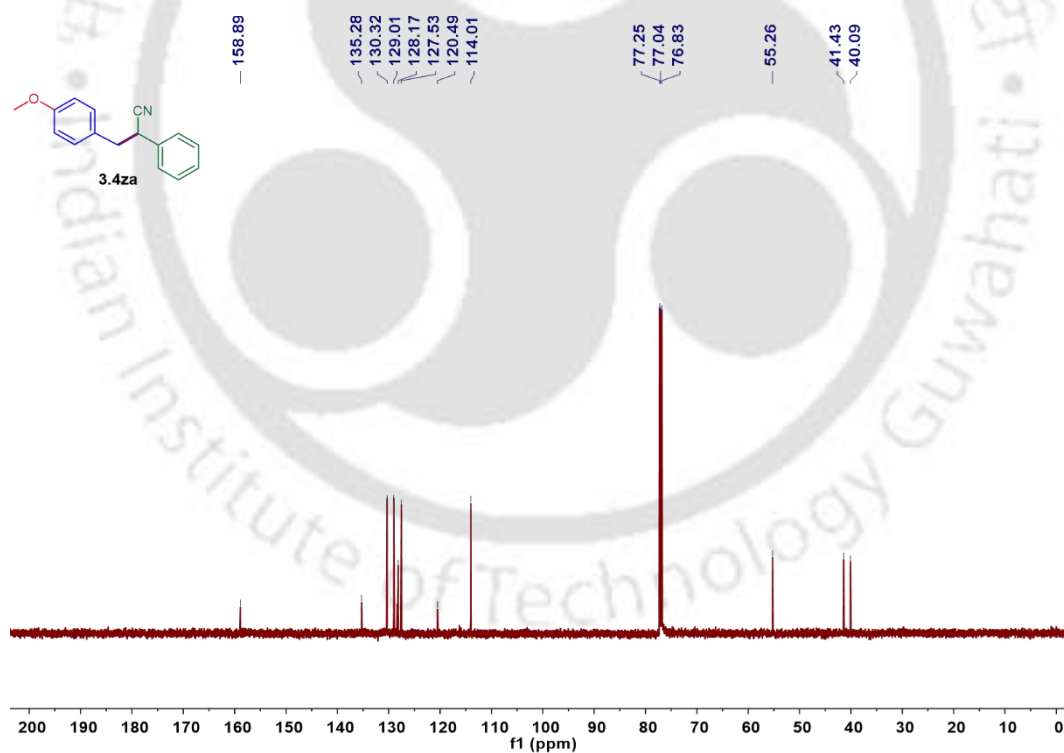


Figure B43. ¹³C{¹H} NMR of 3.4za in CDCl₃.

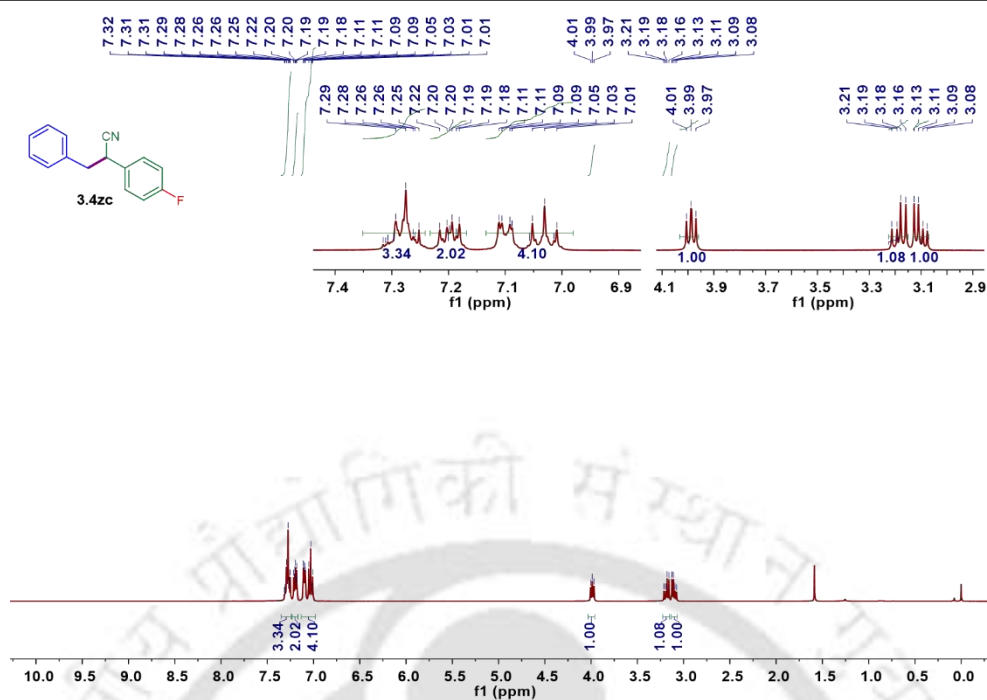


Figure B44. ¹H NMR of 3.4zc in CDCl₃.

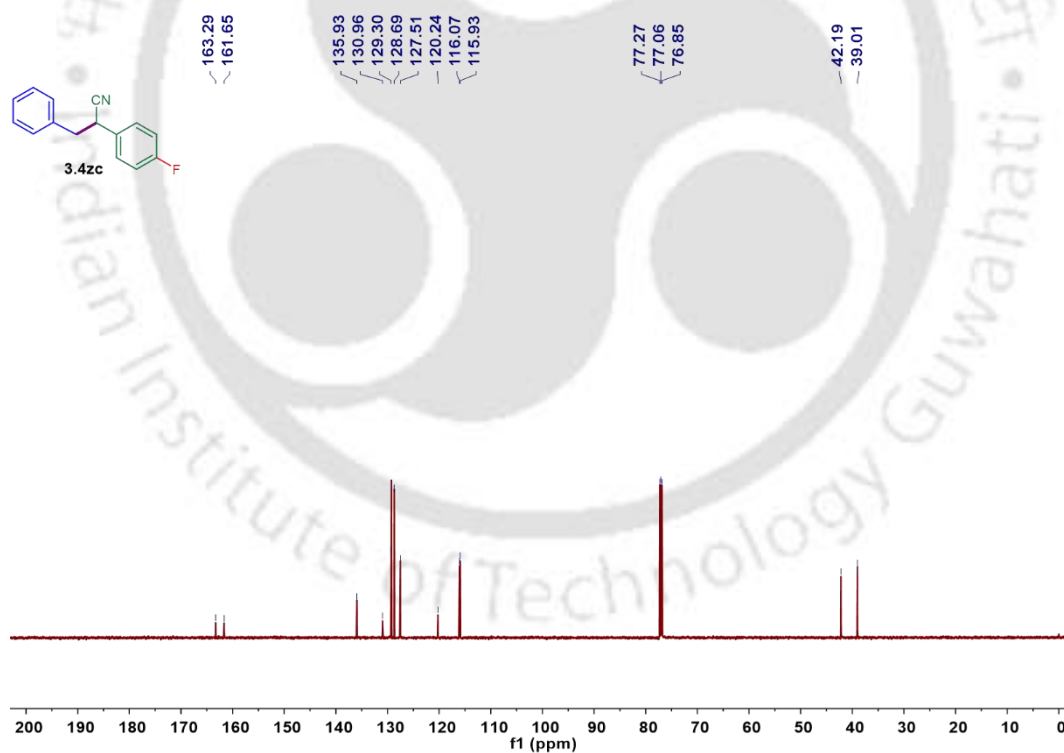


Figure B45. ¹³C{H} NMR of 3.4zc in CDCl₃.

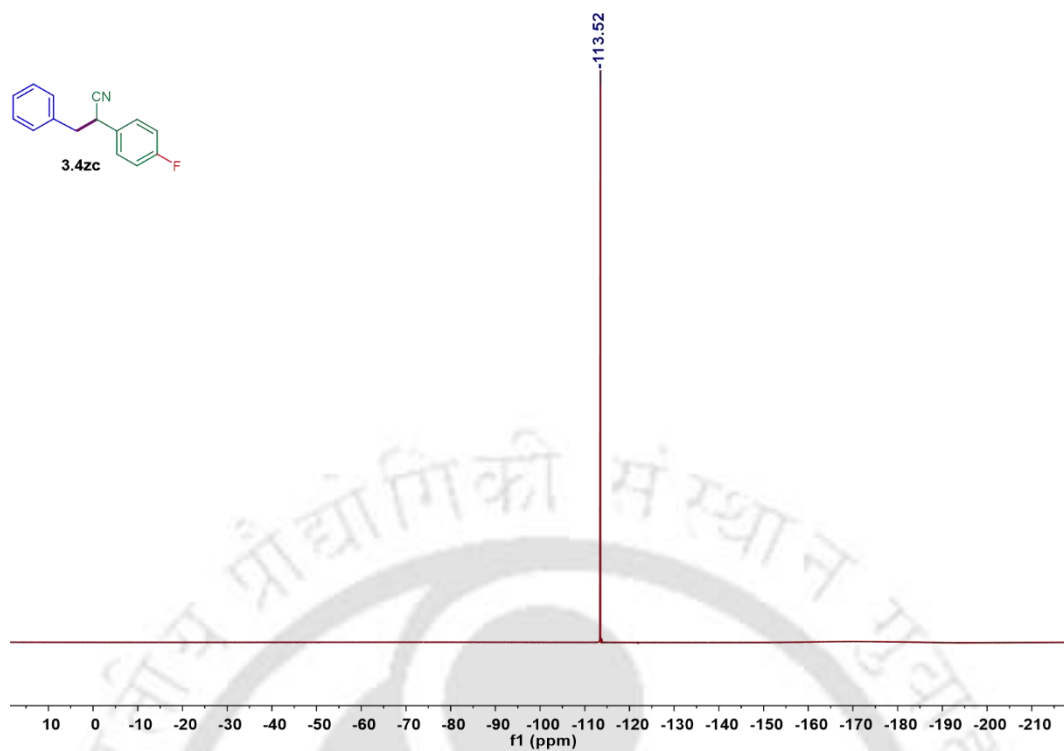


Figure B46. ^{19}F NMR of **3.4zc** in CDCl_3 .

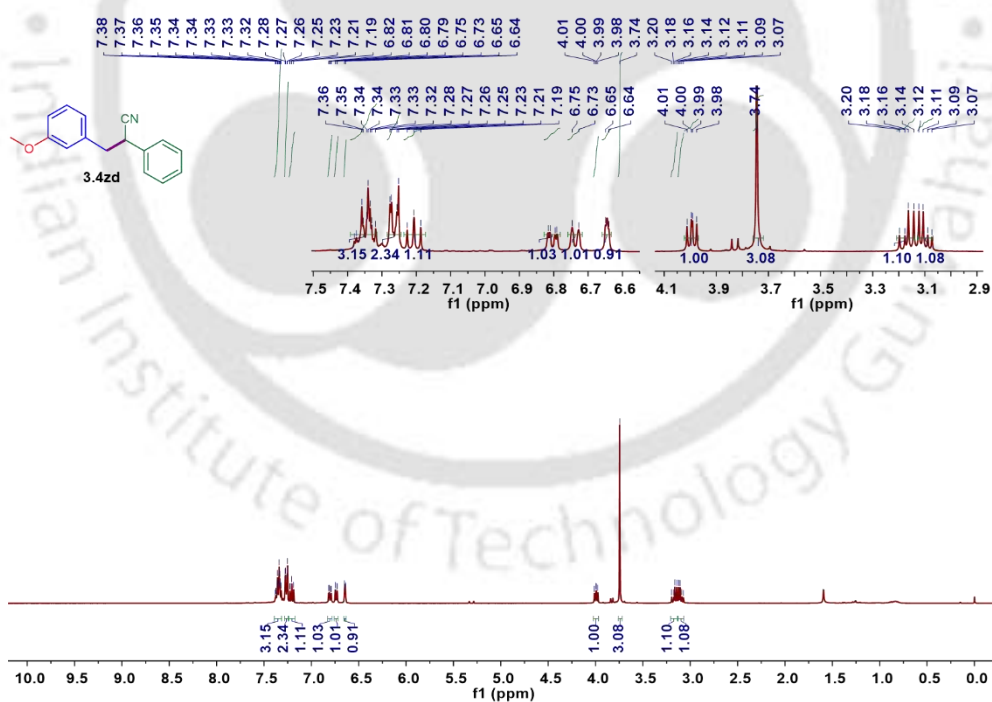
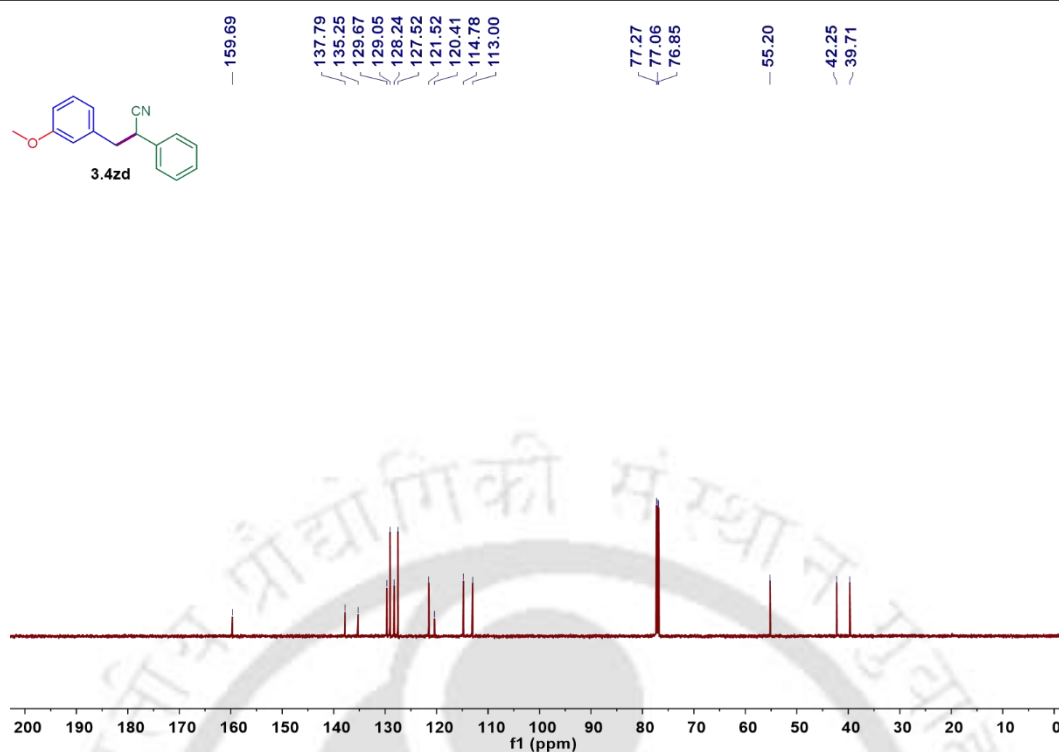
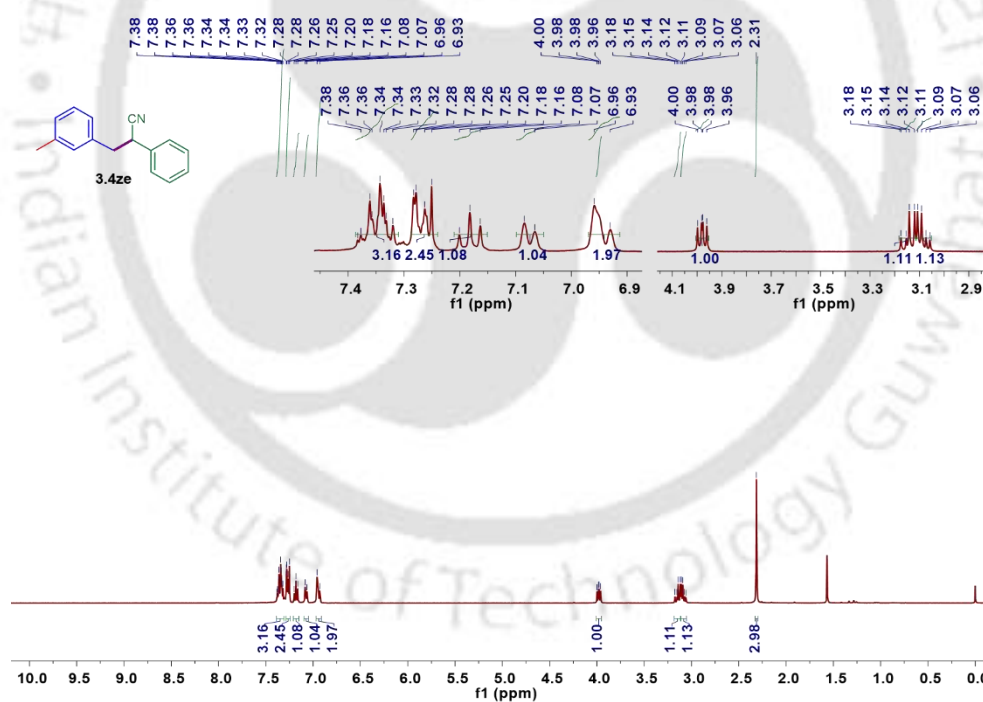


Figure B47. ^1H NMR of **3.4zd** in CDCl_3 .

**Figure B48.** $^{13}\text{C}\{\text{H}\}$ NMR of 3.4zd in CDCl_3 .**Figure B49.** ^1H NMR of 3.4ze in CDCl_3 .

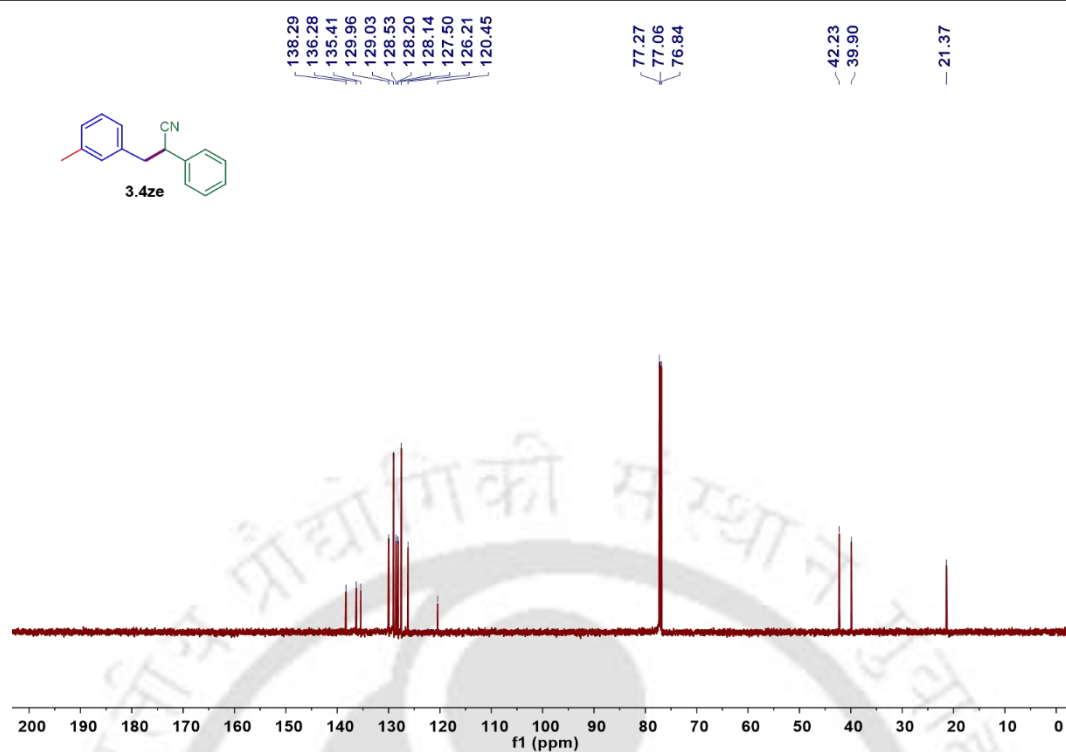


Figure B50. $^{13}\text{C}\{^1\text{H}\}$ NMR of **3.4ze** in CDCl_3 .

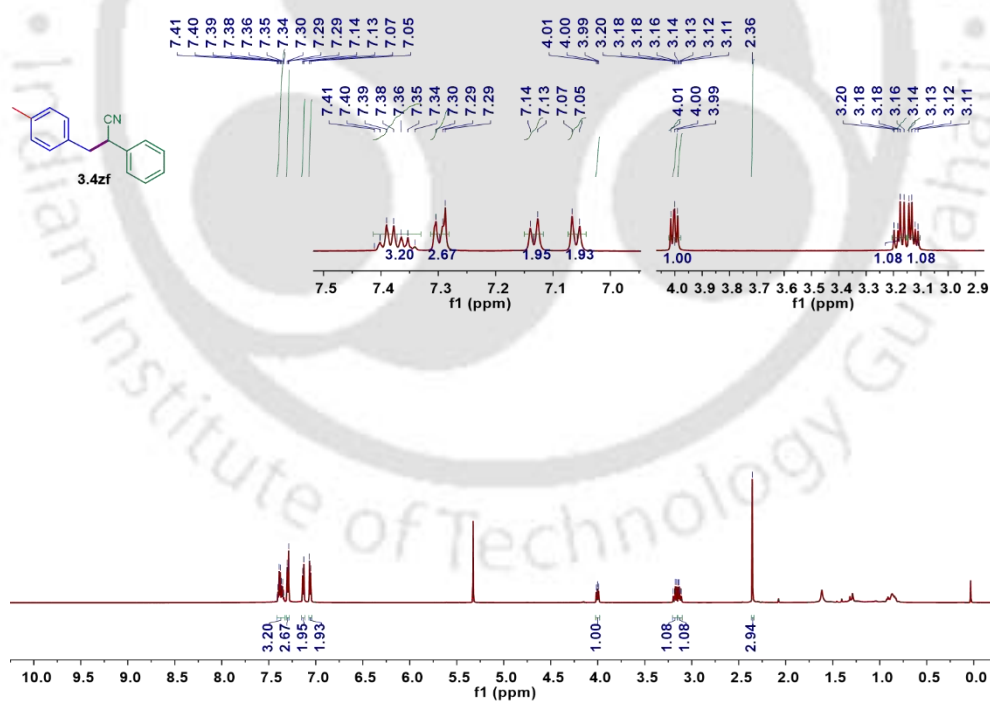


Figure B51. ^1H NMR of **3.4zf** in CDCl_3 .

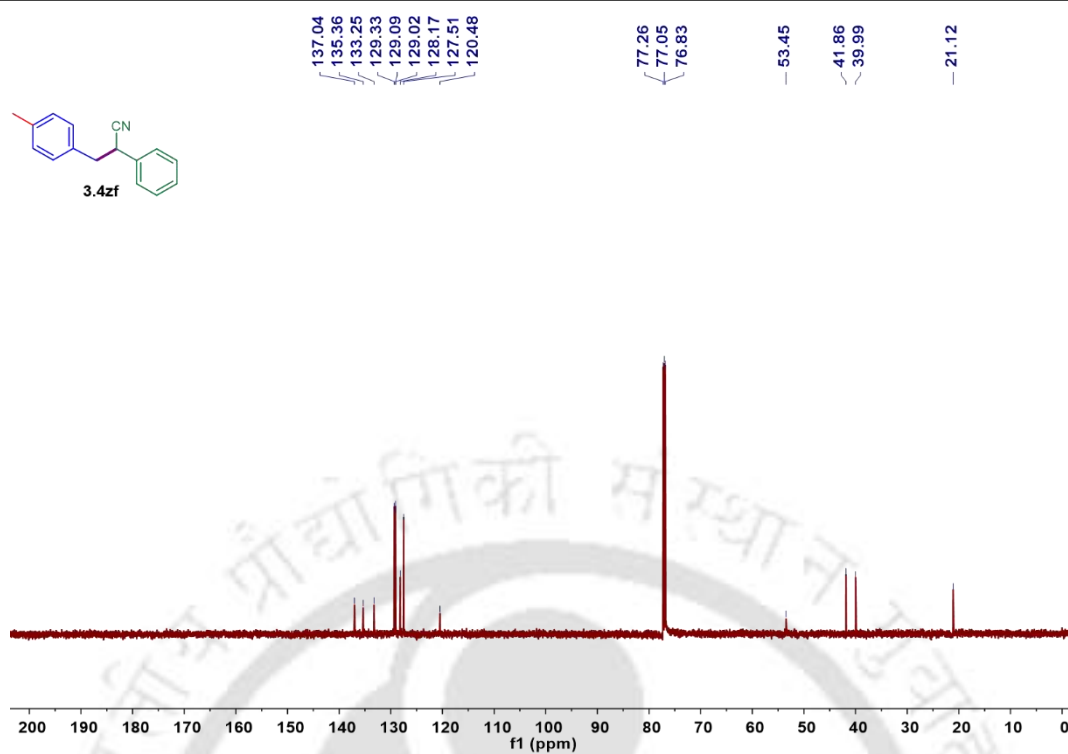


Figure B52. $^{13}\text{C}\{^1\text{H}\}$ NMR of **3.4zf** in CDCl_3 .

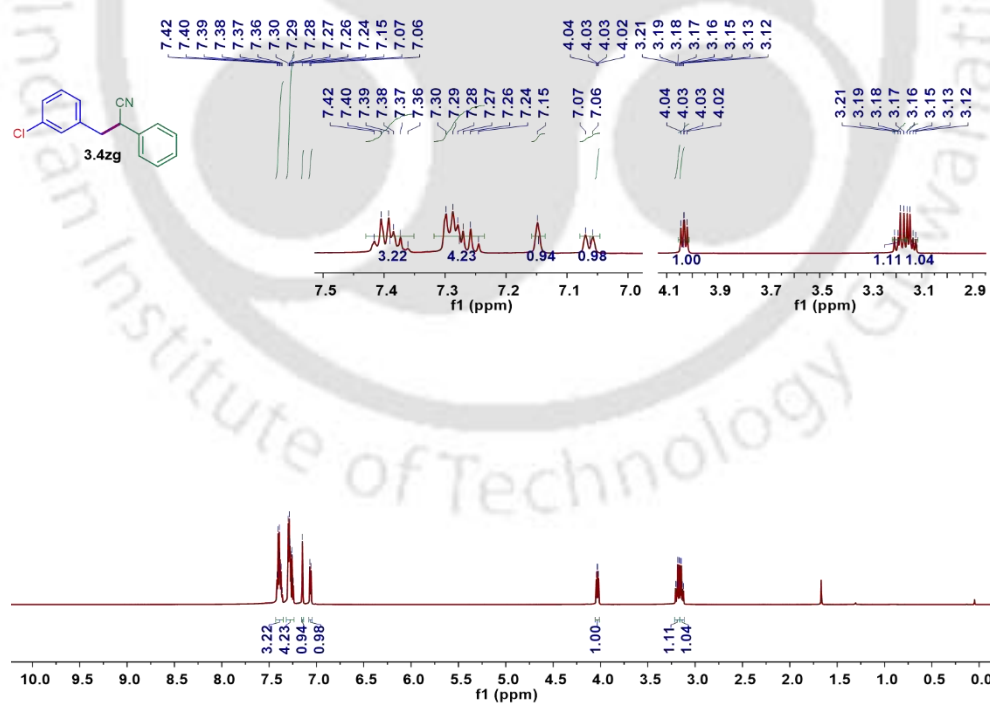


Figure B53. ^1H NMR of **3.4zg** in CDCl_3 .

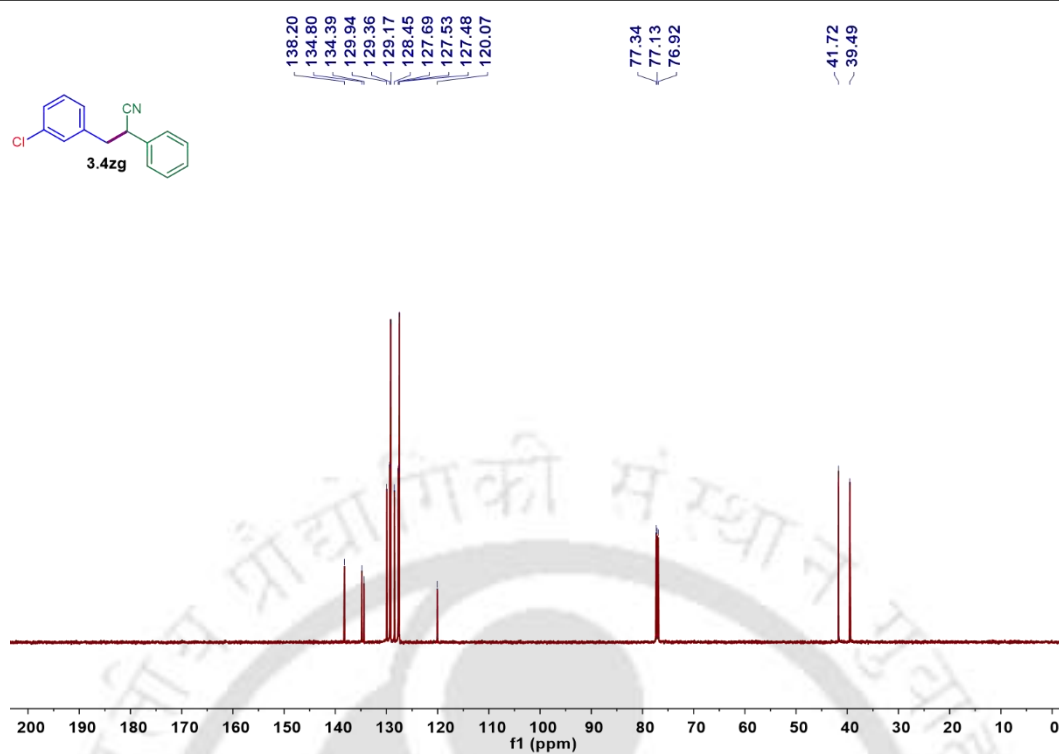


Figure B54. $^{13}\text{C}\{\text{H}\}$ NMR of **3.4zg** in CDCl_3 .

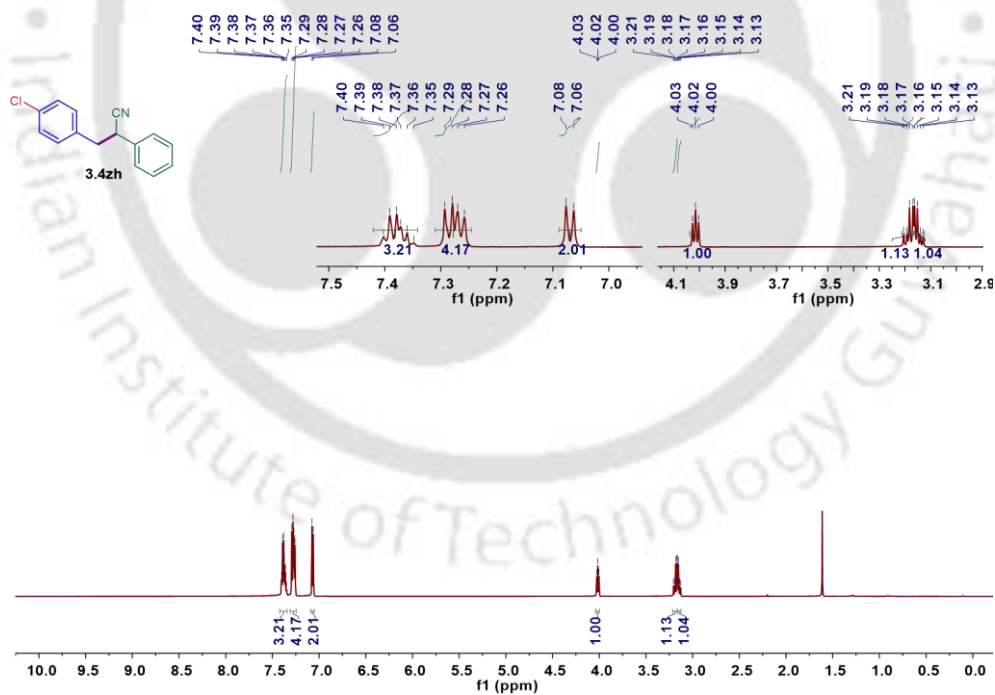


Figure B55. ^1H NMR of **3.4zh** in CDCl_3 .

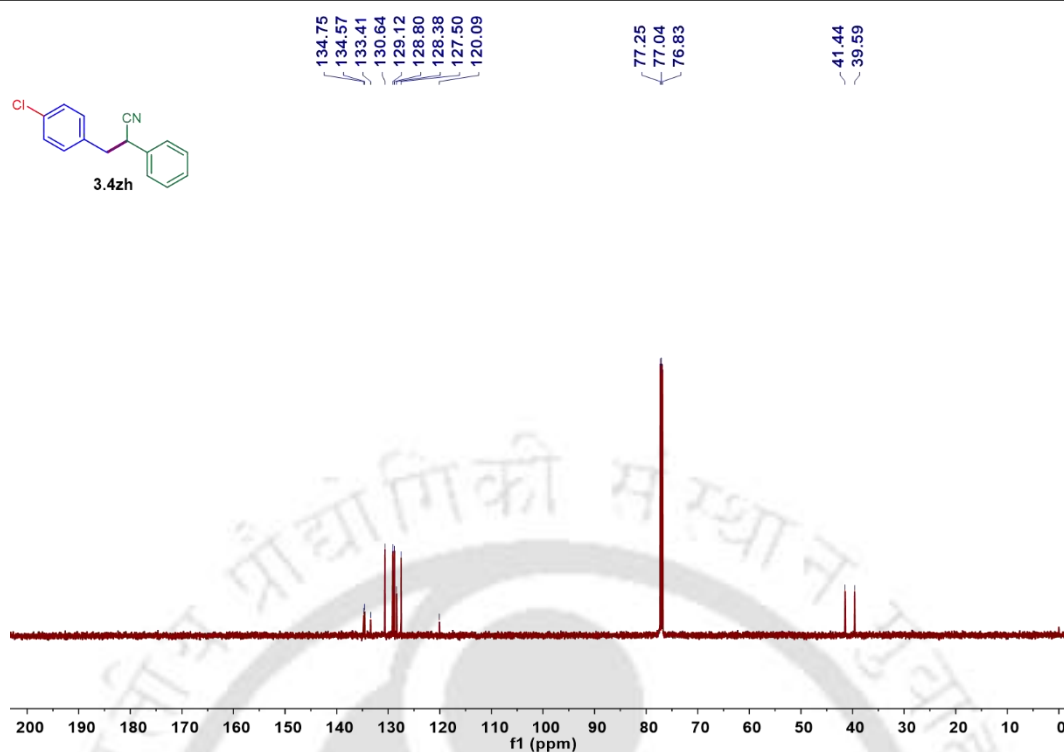


Figure B56. $^{13}\text{C}\{\text{H}\}$ NMR of **3.4zh** in CDCl_3 .

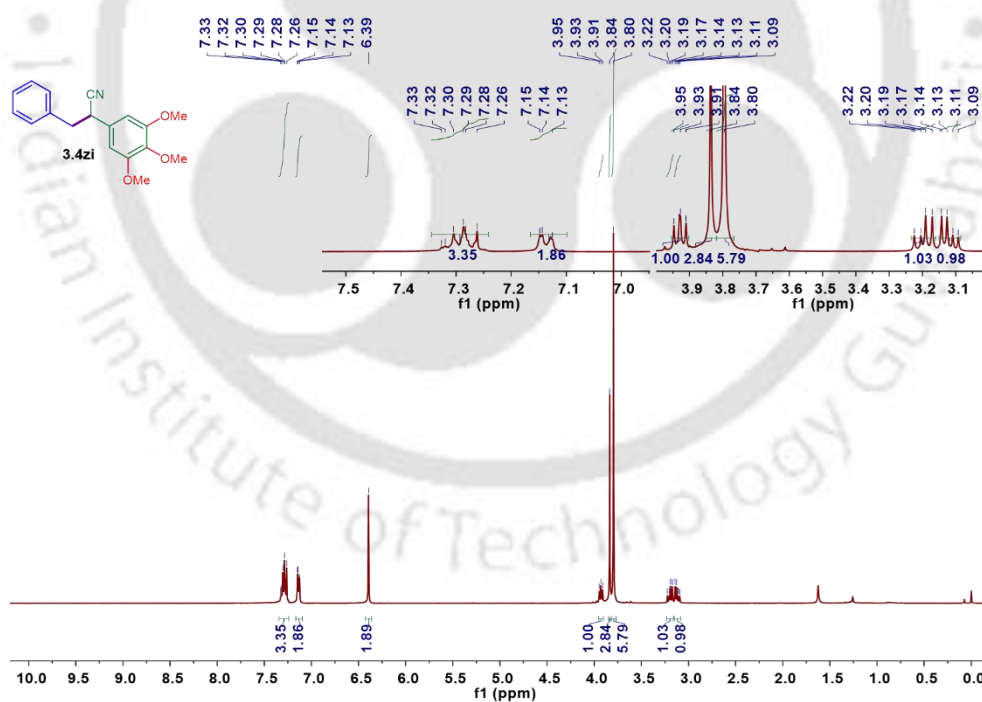


Figure B57. ^1H NMR of **3.4zi** in CDCl_3 .

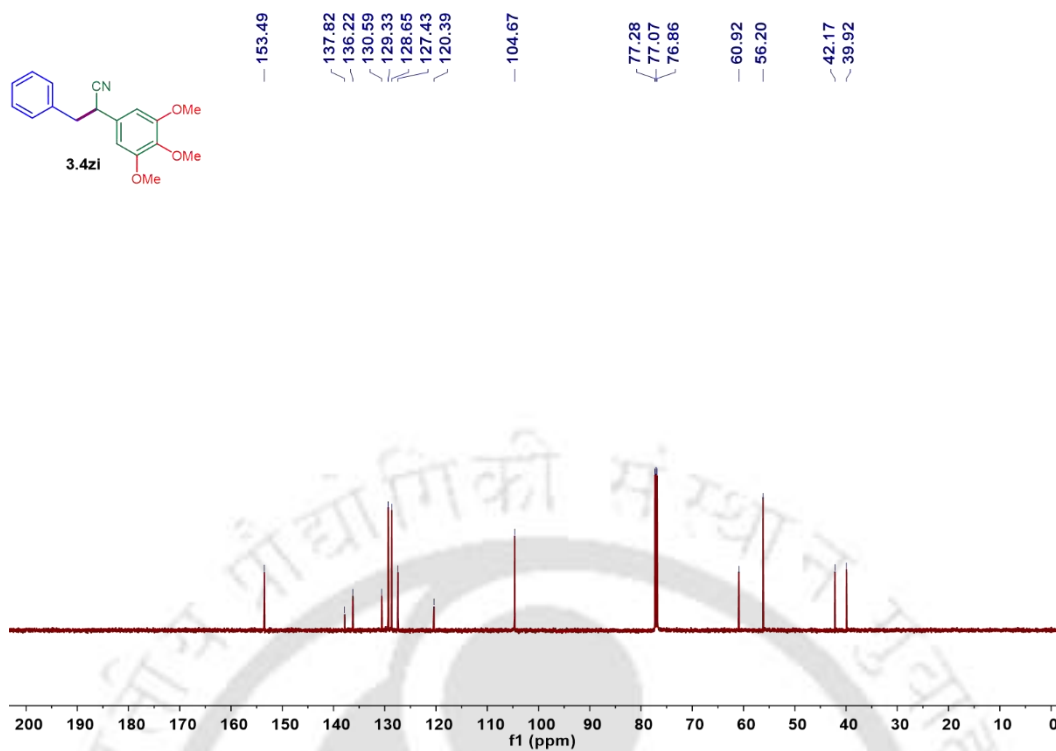


Figure B58. $^{13}\text{C}\{\text{H}\}$ NMR of **3.4zi** in CDCl_3 .

B5. FT-IR analysis of derivatives of 3.4:

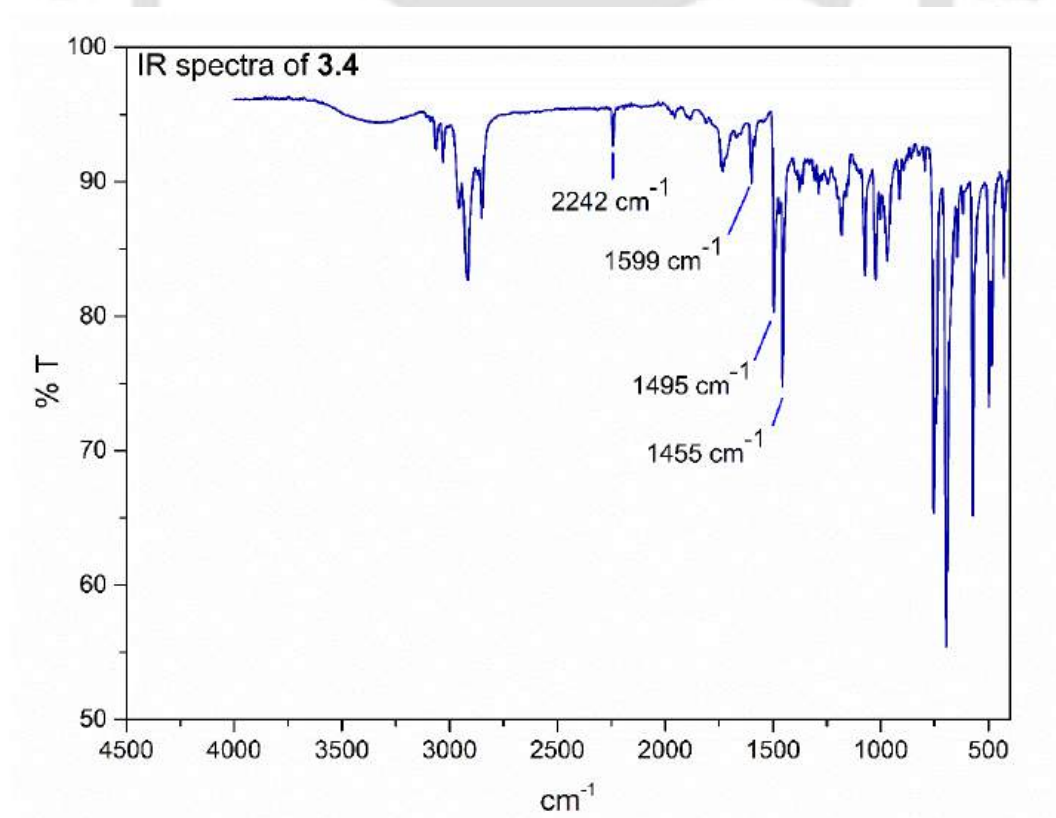


Figure B59. FT-IR spectra of **3.4**.

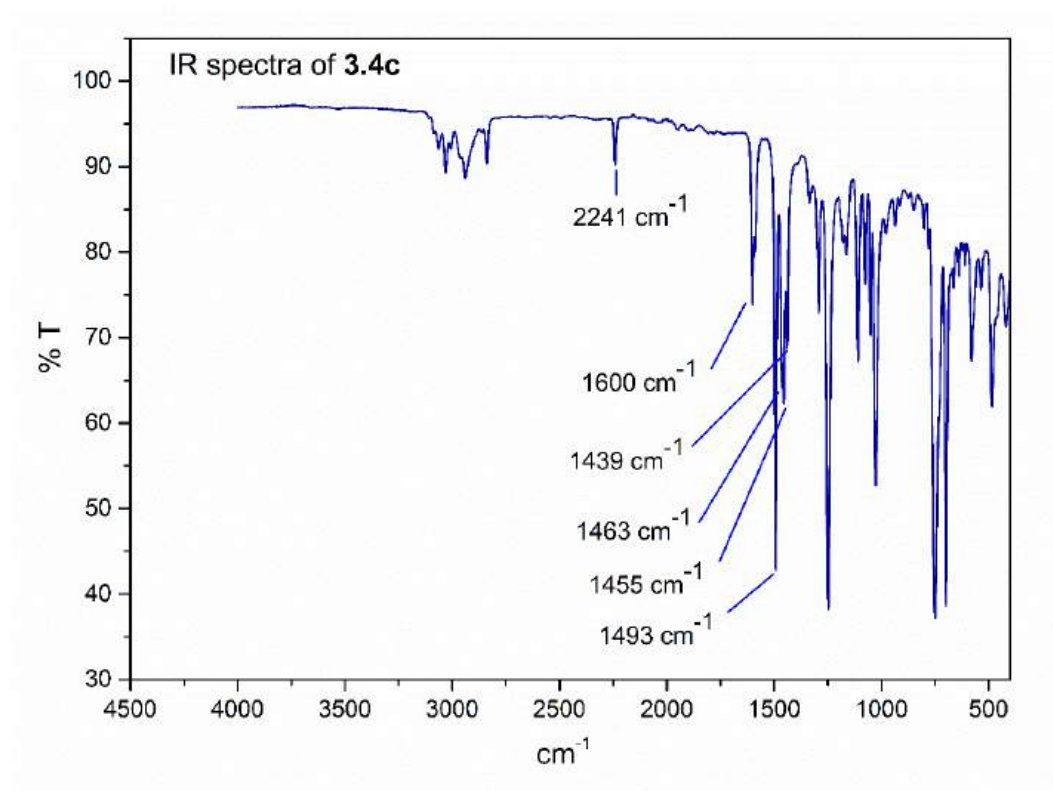


Figure B60. FT-IR spectra of **3.4c**.

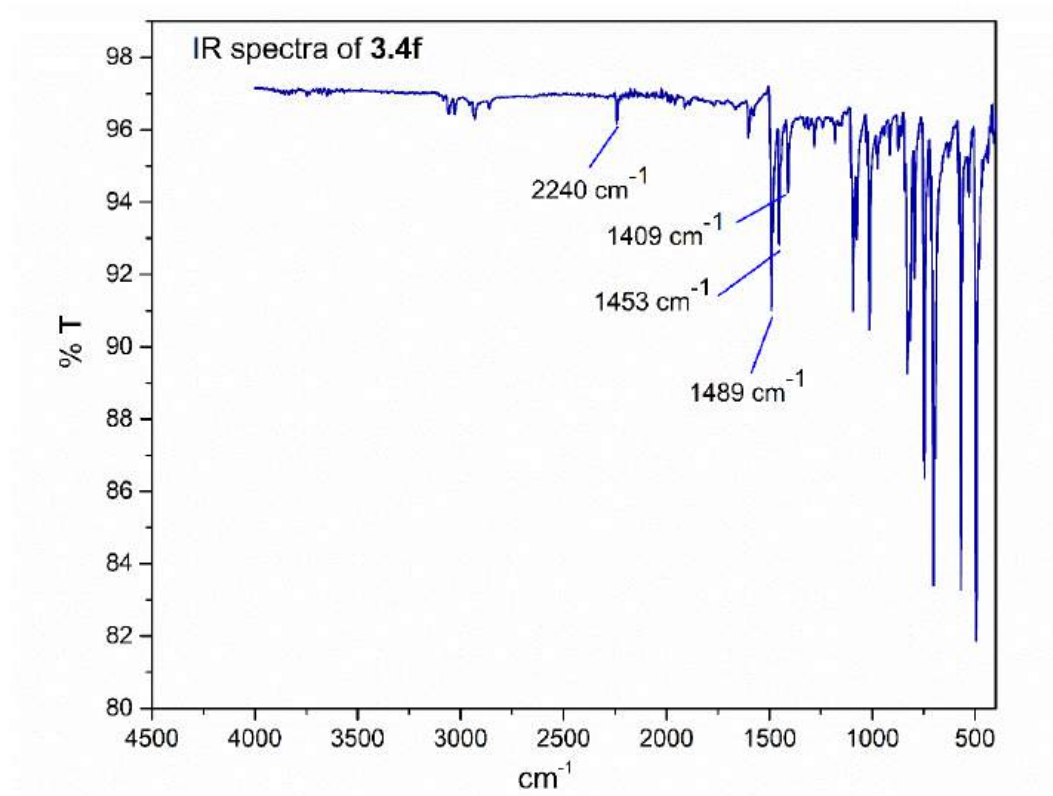


Figure B61. FT-IR spectra of **3.4f**.

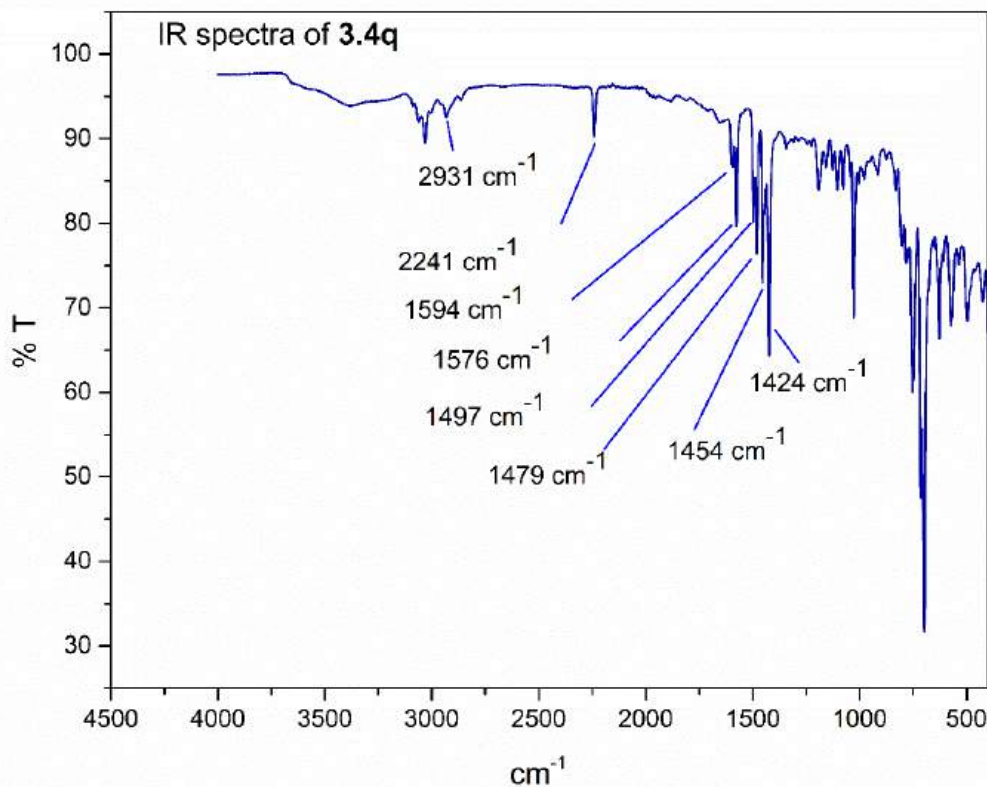


Figure B62. FT-IR spectra of **3.4q**.

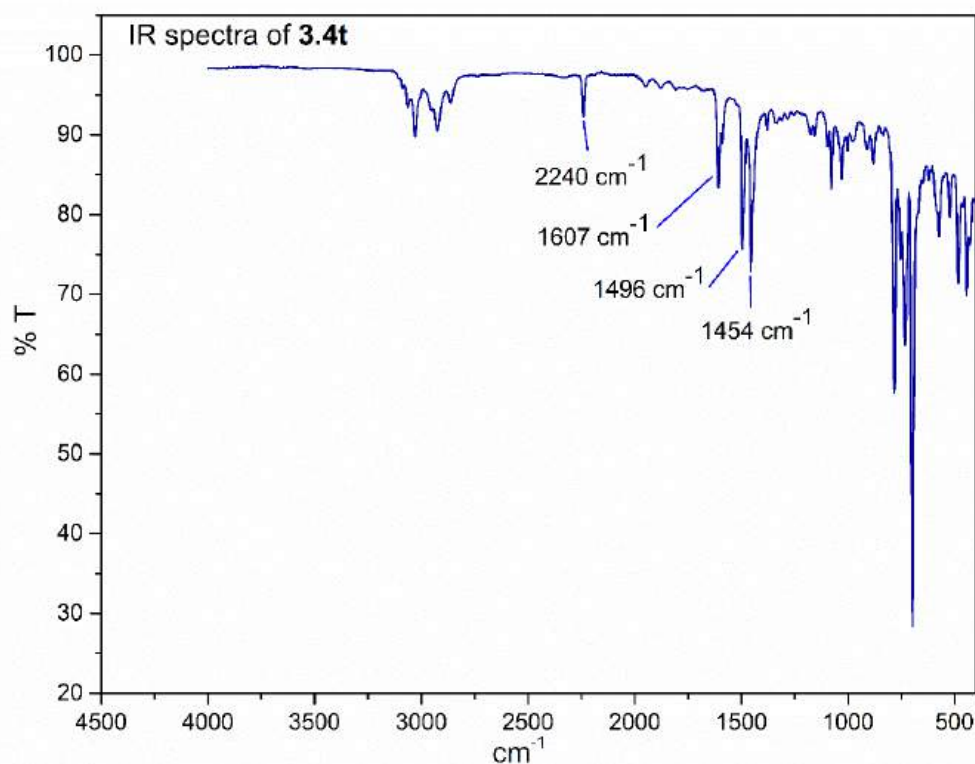


Figure B63. FT-IR spectra of **3.4t**.

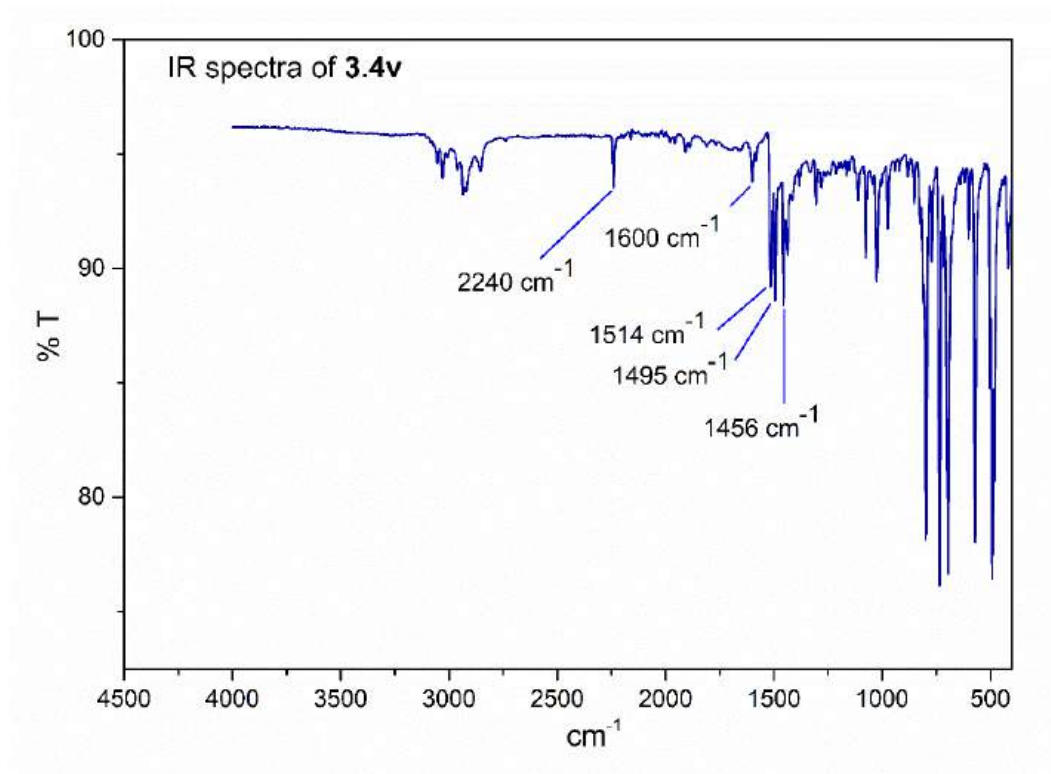


Figure B64. FT-IR spectra of **3.4v**.

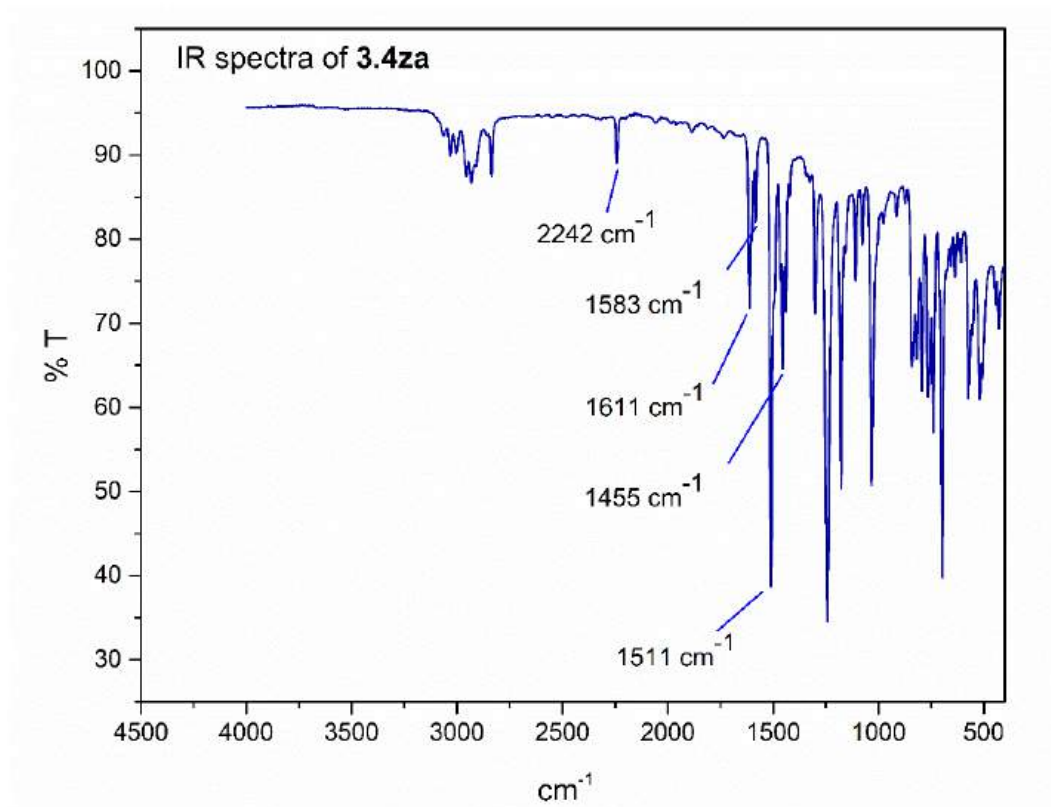


Figure B65. FT-IR spectra of **3.4za**.

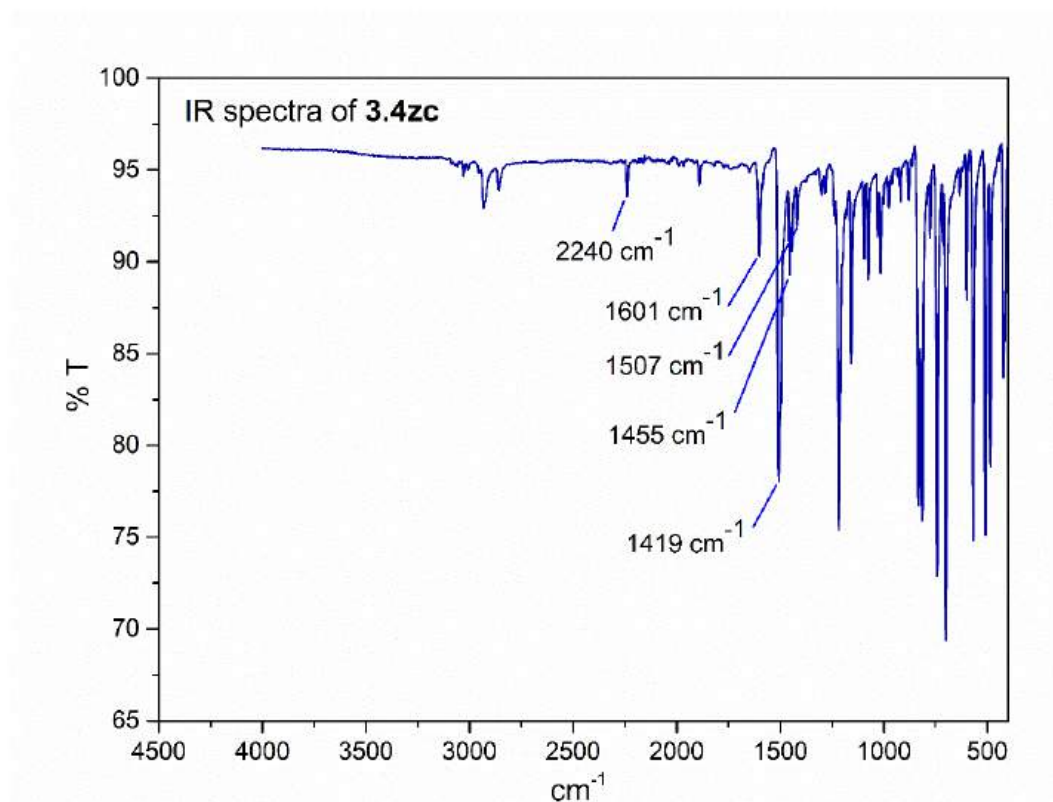


Figure B66. FT-IR spectra of **3.4zc**.

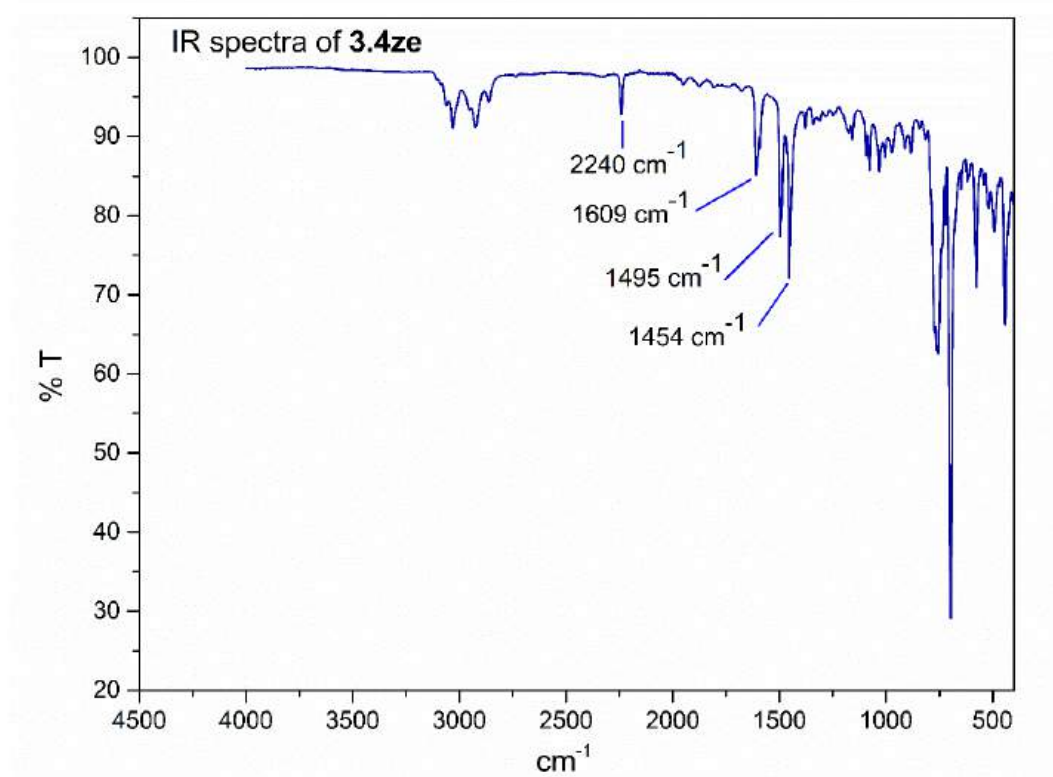


Figure B67. FT-IR spectra of **3.4ze**.

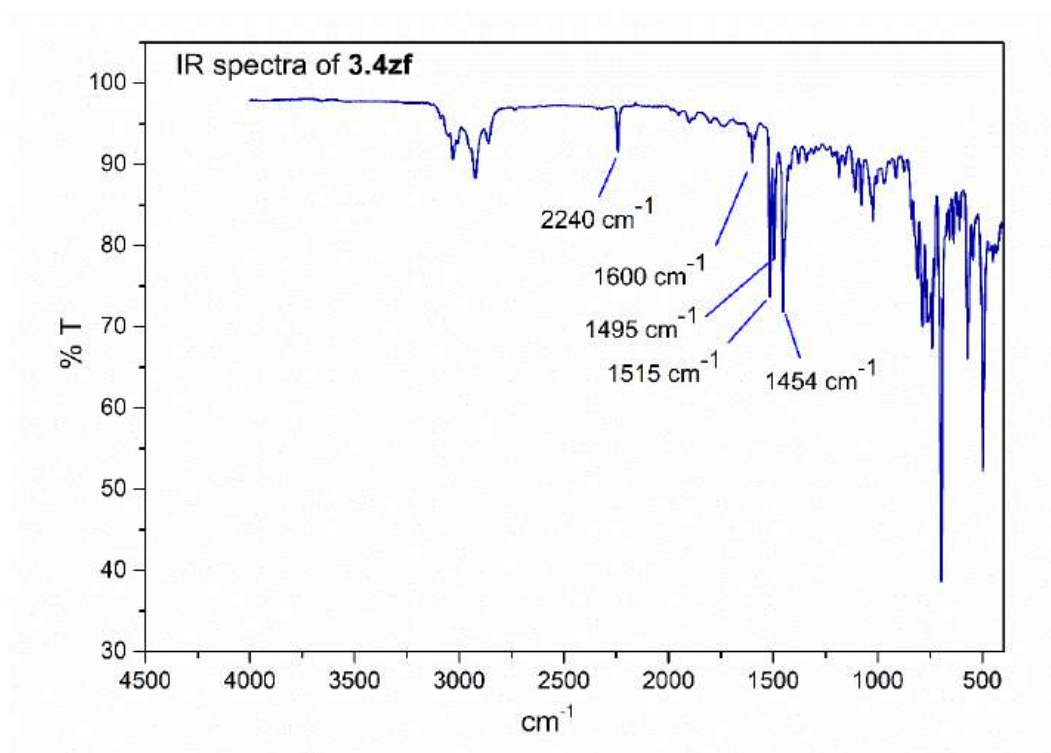


Figure B68. FT-IR spectra of **3.4zf**.

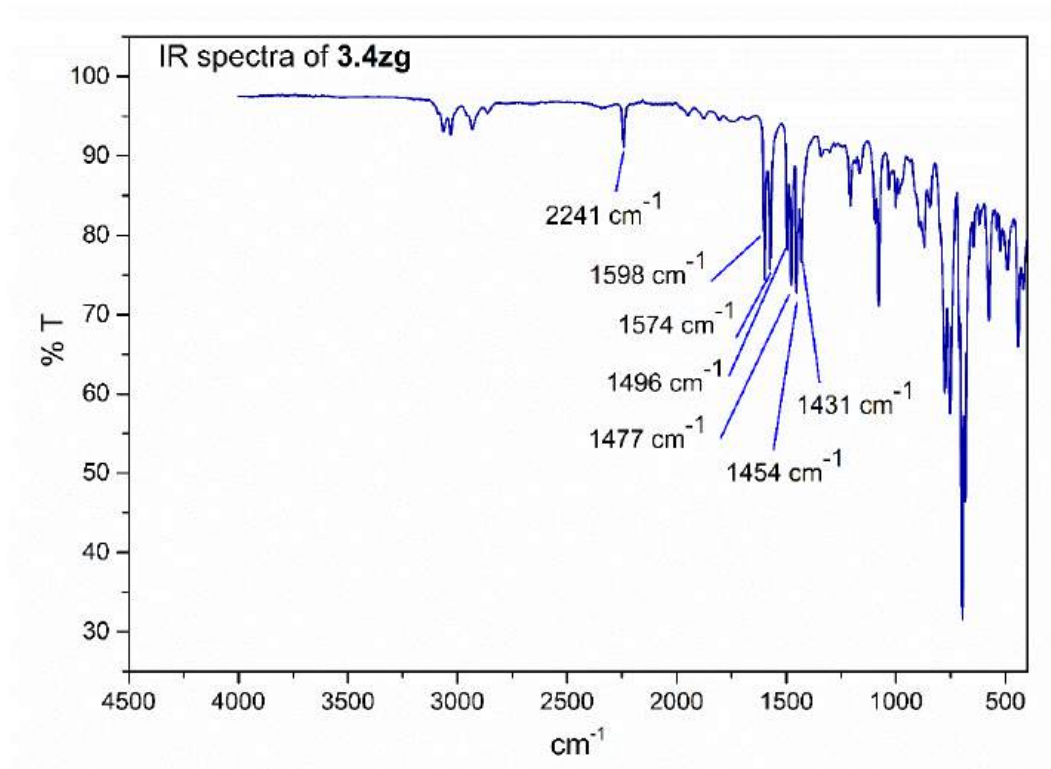


Figure B69. FT-IR spectra of **3.4zg**.

B6. The E-Factor calculations for the general procedure of preparation of 3.4:

$$\text{E-Factor} = (\text{waste mass} / \text{product mass}) = (\text{total input mass} - \text{product mass}) / \text{product mass}$$

With an intention to analyse the sustainability of our protocol, we have reported two types of E-Factors: the simple E-Factor, which excludes toluene from waste, and the complete E-Factor, which includes toluene as part of the waste.²

The E-Factors for the representative general procedure was calculated as follows:

The relevant reagent and solvent densities used in the calculations: benzyl alcohol (1.04 g/mL), benzyl cyanide (1.02 g/mL), and toluene (0.87 g/mL).

E-Factor Calculation of 2,3-Diphenylpropanenitrile (3.4):

Input Materials: CrCl₃.6H₂O (0.53 g, 0.002 mmol), benzyl alcohol (107.12 mg, 1 mmol), benzyl cyanide (58.14 mg, 0.5 mmol), KO^tBu (16.8 mg, 0.15 mmol) and toluene (870 mg, 1 mL).

Total Input Mass (excluding toluene): (107.12 + 58.14 + 0.53 + 16.8) mg = 182.59 mg

Product Mass: 97 mg

Waste Mass: 182.59 mg - 97 mg = 85.59 mg

Simple E-Factor = 85.59 mg / 97 mg = 0.88

Total Input Mass (including toluene): (107.12 + 58.14 + 0.53 + 16.8 + 870) mg = 1052.59 mg

Product Mass: 97 mg

Waste Mass: 1052.59 mg - 97 mg = 955.59 mg

Complete E-Factor = 955.59 mg / 97 mg = 9.85

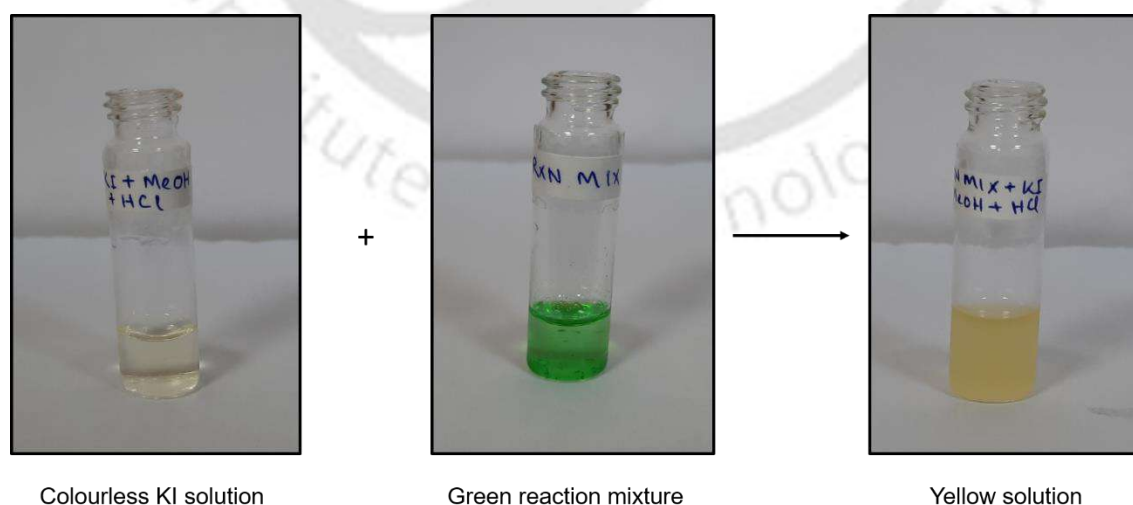
B.7. Qualitative analysis of peroxide:

Figure B70. Qualitative analysis of peroxide in the reaction mixture.

A solution of KI (8.3 mg, 0.05 mmol, 2 equivalents w.r.t. $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$) in MeOH (1 mL), was acidified with a drop of HCl. To this solution, the reaction mixture (6.7 mg, 0.025 mmol $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1 mmol **1**, 16.8 mg KO^tBu and 1 ml toluene) was added dropwise, at room temperature. A colour change from colourless (KI solution) + green (reaction mixture) → yellow (KI solution + reaction mixture) was observed indicating the presence of peroxide in the reaction mixture.

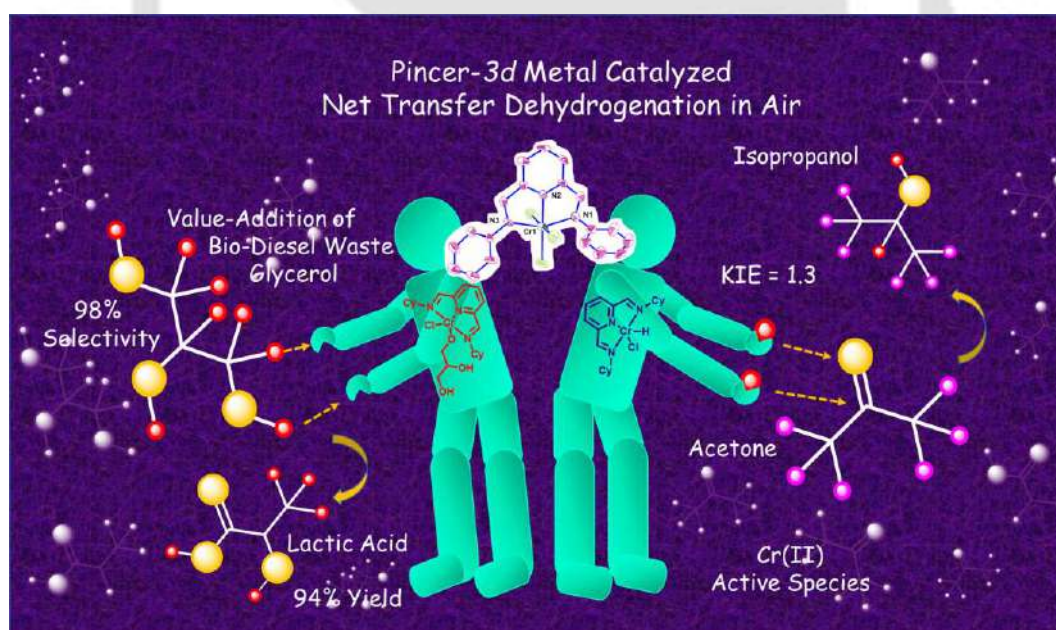
B4. References

- [1] a) A. Alanthadka, S. Bera, D. Banerjee, *J. Org. Chem.* **2019**, *84*, 11676-11686; b) J. Das, D. Banerjee, *J. Org. Chem.* **2018**, *83*, 3378-3384.
[2] Lucchesi Schio, A.; Farias Soares, M. R.; Machado, G.; Barcellos, T. *ACS Sustainable Chem. Eng.* **2021**, *9* (29), 9661–9670.



Chapter- IV

Transfer Dehydrogenative Transformation of Glycerol to Lactic Acid Catalysed by Pincer-Chromium and its Precursor Chromium (III) Chloride

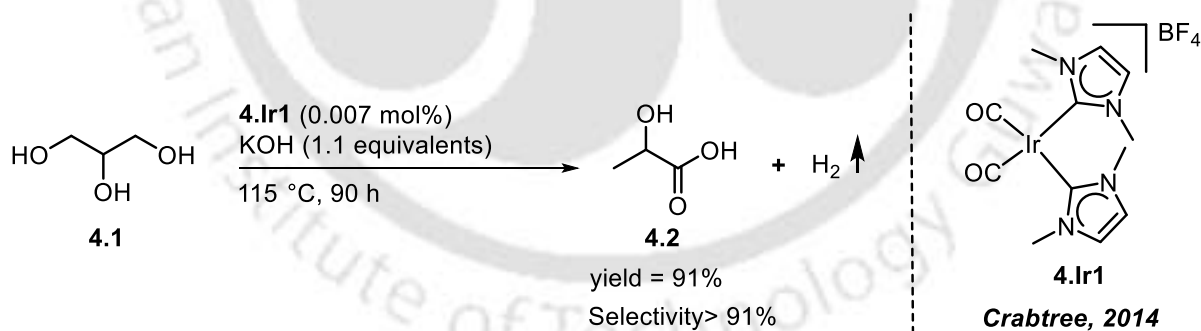


The content of this chapter has been adapted from “Catalytic Value-Addition of Glycerol to Lactic Acid by Chromium Chloride and its Corresponding Pincer Complex” by Narjinari, H.; Dhole, S.; Kumar, A. *Catal. Sci. Technol.*, 2025, Advance Article. <https://doi.org/10.1039/D5CY01041A>



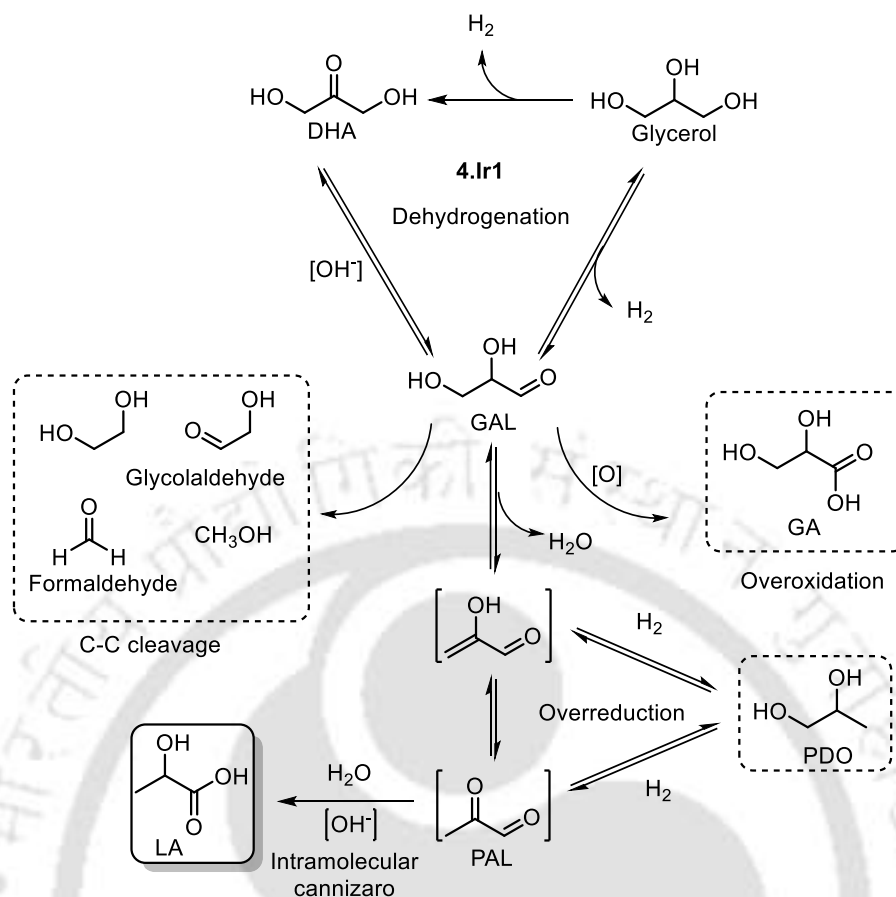
4.1. Introduction

The rapid depletion of fossil-fuel reserves has led to the increased utilization of biodiesel.¹ Biodiesel production is accompanied by a significant amount of waste generation such as glycerol (GLY).² This adds significantly to the global reservoirs already burdened by the glycerol contribution from a large number of industries involving cellulose hydrogenolysis³⁻⁴ and fermentation⁵ processes. Notably, GLY can serve as a starting material for numerous forms of speciality chemicals like lactic acid (LA), dihydroxyacetone and propanediol.⁶⁻¹⁸ Glycerol can also act as a potent hydrogen source as well as solvent in various metal aided catalysis owing to the presence of three hydroxyl groups.^{2, 19-24} LA has plethora of applications in diverse industries which includes cosmetics, pharmaceutical, food, green solvent production and polylactic acid production (PLA).²⁶⁻²⁷ Traditionally, GLY to LA conversion is carried out in two pathways which includes bacterial fermentation (via bioconversion)²⁸ and heterogeneous catalysis.^{3, 17, 29-42} Special conditions required for bacterial survival apart from challenging product separation steps are the typical challenges associated with these classical routes to LA.⁴¹ Conversely, the use of homogeneous catalysts demands milder reaction conditions and hence provides better reactivity as well as selectivity.^{25,32,42-54} Homogeneous catalysts are more advantageous than that of heterogeneous catalysts, because to get higher activity and selectivity, the homogeneous catalysts can be tuned by modifying the ligand.²⁵



Scheme 4.1. The transformation of glycerol to LA catalysed by NHC-iridium complex reported by Crabtree.⁴⁴

The Ir(I)-NHC **4.Ir1** catalysed glycerol dehydrogenation in acceptorless fashion was first demonstrated by Crabtree, where an impressive yield of LA (90%) along with hydrogen was obtained at a very high selectivity (95%) with a high turnover number of 30100 (Scheme 4.1). This protocol was similarly active to transform crude glycerol to lactic acid with slightly lower

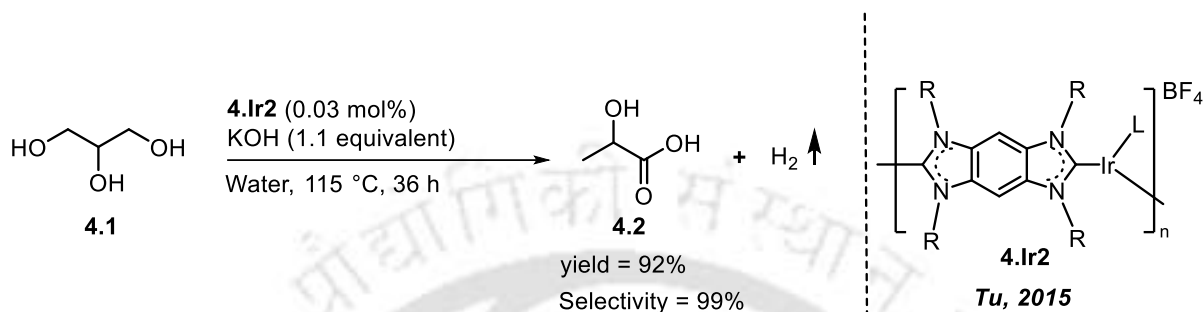


Scheme 4.2. Plausible mechanism for the **4.Ir1** catalysed acceptorless dehydrogenation of glycerol to LA reported by Crabtree.⁴⁴

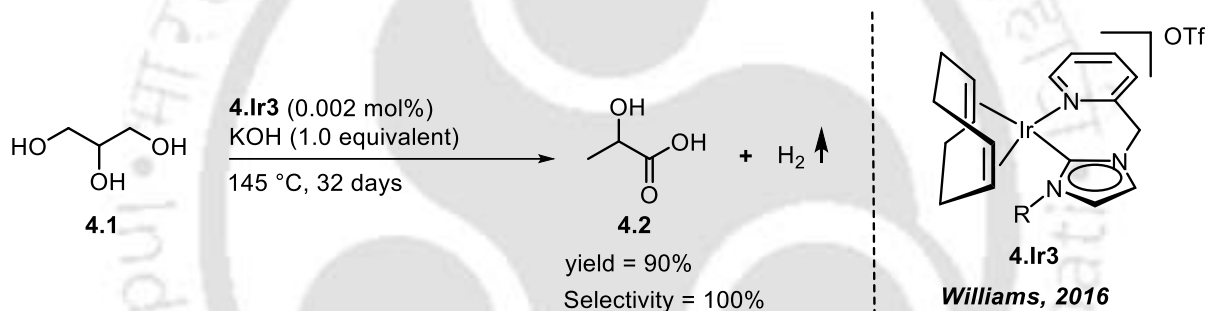
activity but maintained high selectivity towards lactic acid. In the scheme 4.2, it is nicely depicted that what other parallel reactions can lead to the formation of different side products like glycolic acid,^{18b} ethylene glycol,^{18b} glycolaldehyde,^{18b} formaldehyde,^{18b} methanol^{18b} and propanediol (PDO).^{18b} This protocol is selective towards lactic acid and it follows an inner sphere mechanism which involves dehydrogenation of glycerol to glyceraldehyde. This is followed by a catalyst independent dehydration, tautomerism and intramolecular Cannizzaro reaction that leads to lactic acid (Scheme 4.2).⁴⁴

Tu and co-workers then synthesised a co-polymer based Ir-NHC complex **4.Ir2** to perform the glycerol dehydrogenation to LA where a very high yield of LA (98%) was observed with 3266 turnover numbers (Scheme 4.3). In contrast to heterogeneous catalysts which exhibit lower selectivity, these catalysts owned the nature of homogeneous catalysts in terms of selectivity, in addition to the fact that they were active up to 31 cycles and could be easily retrieved by simple filtration process.⁴³ Williams obtained very high turnovers of 1057172 with a good yield

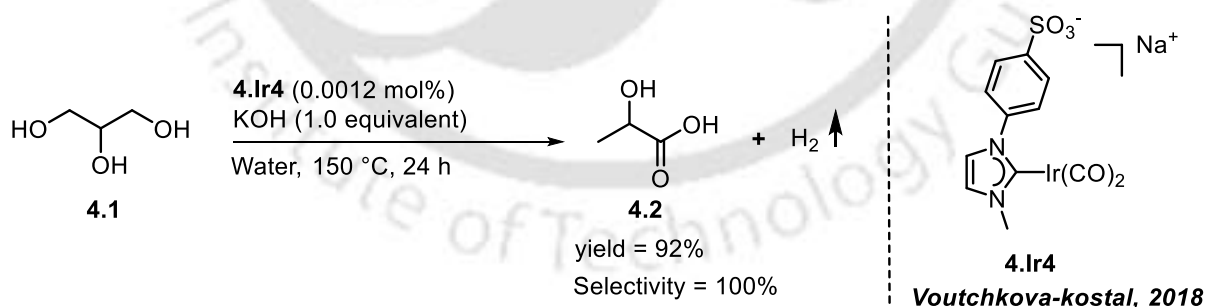
of LA when glycerol was treated with an Ir(I) complex **4.Ir3** based on bidentate(pyridylmethyl)imidazolium carbene ligand (Scheme 4.4). According to the proposed mechanism, the transformation of glycerol to lactate proceeded via oxidation of glycerol to dihydroxyacetone (dehydrogenation product of glycerol) through β -H elimination which was found to be the RDS from the results of the mechanistic studies.⁴⁵



Scheme 4.3. The transformation of glycerol to LA catalysed by an iridium NHC copolymer reported by Tu.⁴³

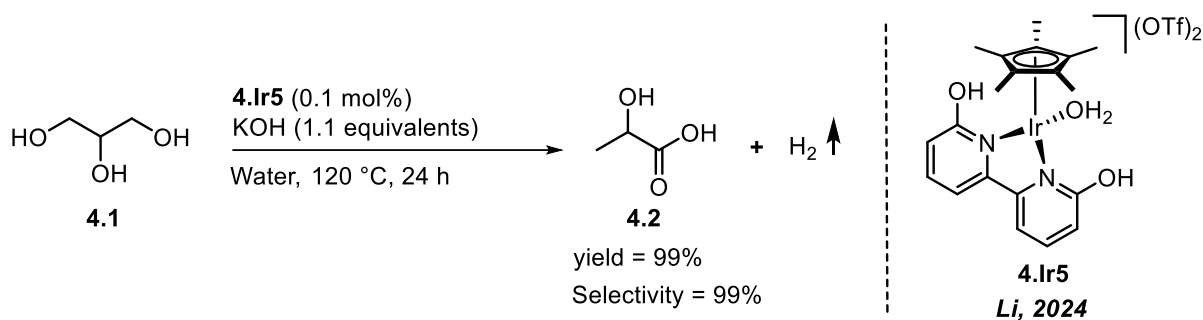


Scheme 4.4. The transformation of glycerol to LA catalysed by an iridium complex reported by Williams.⁴⁵



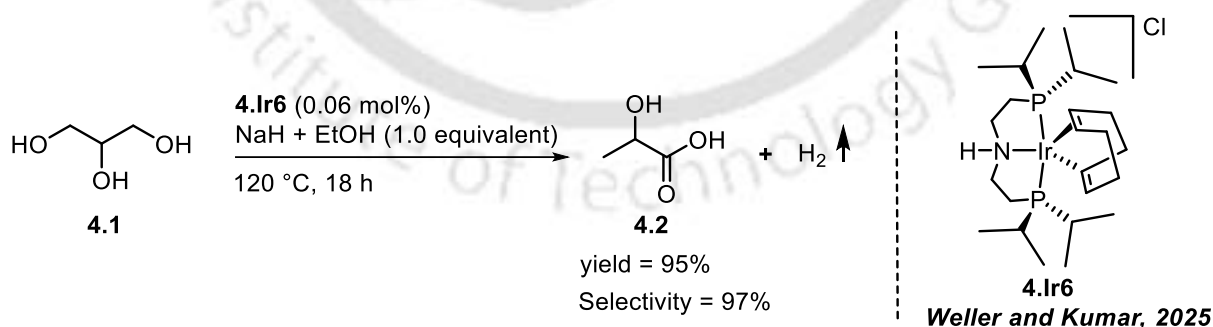
Scheme 4.5. The transformation of glycerol to LA catalysed by an NHC complex based on iridium reported by Voutchkova-Kostal.⁴⁶

Voutchkova-Kostal introduced highly charged sulfonate functionalizations to Ir(I), Ir(III) and Ru(II) NHC complexes which made it a good candidate suitable for microwave reactions alongside conventional heating reactions. They have achieved LA with 45592 turnover



Scheme 4.6. The transformation of glycerol to LA catalysed by a half-sandwich iridium complex reported by Li.⁵²

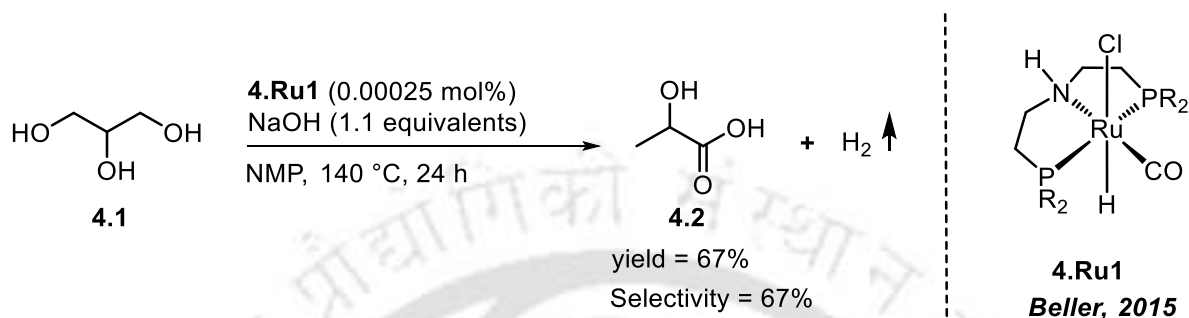
numbers under microwave conditions, whereas conventional heating provided a very low turnover of 3477 was observed under the similar reaction conditions (Scheme 4.5). This may be attributed to the fact that, microwave radiation interacts with the glycerol molecule and the GLY molecule undergoes rotation and oscillation, which leads to the conversion of electrical energy to kinetic energy resulting in efficient heating.⁴⁶ Very recently, Li studied the conversion of glycerol to LA in water in high yields (ca. 99%) and with excellent selectivity (ca. 99%) that was catalysed by a water-soluble piano-stool iridium complex **4.Ir5** (Scheme 4.6). The O-H functionality present in the ligand moiety actively participated in the mechanistic cycle. Based on the results of theoretical as well as experimental studies, they have proposed two possible mechanisms. On one hand, the complex **4.Ir5** can undergo outer sphere mechanism, where the metal centre and the oxygen present on the ligand shows metal-ligand cooperation with a barrier of 13.7 kcal/mol. On the other hand, the complex **4.Ir5** can also undergo inner-sphere mechanism with an activation barrier of 37.0 kcal/mol.⁵²



Scheme 4.7. The transformation of glycerol to LA catalysed by an iridium complex reported by Weller and Kumar.⁵³

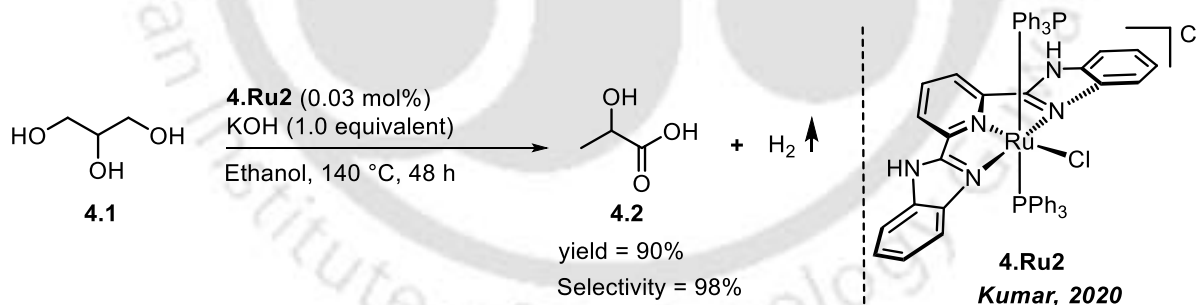
Very recently, Kumar along with Weller have reported PNP-Ir **4.Ir6** catalysed glycerol to LA transformation, where 96% yield of LA was achieved at a high selectivity of 99% with a TON

of 65000 (Scheme 4.7). A KIE value of 2.7 showed that O-H bond activation contributes to the rate determining step. Thorough computational studies have shown that the energy barrier is quite lower (27.01 kcal/mol) when there is hydrogen bonding interaction between N-H bond of the ligand and one of the terminal O-H bond of glycerol than the energy barrier (31.96 kcal/mol) where there is no presence of such interactions.⁵³



Scheme 4.8. The transformation of glycerol to LA catalysed by a PNP pincer-ruthenium complex reported by Beller.⁴⁷

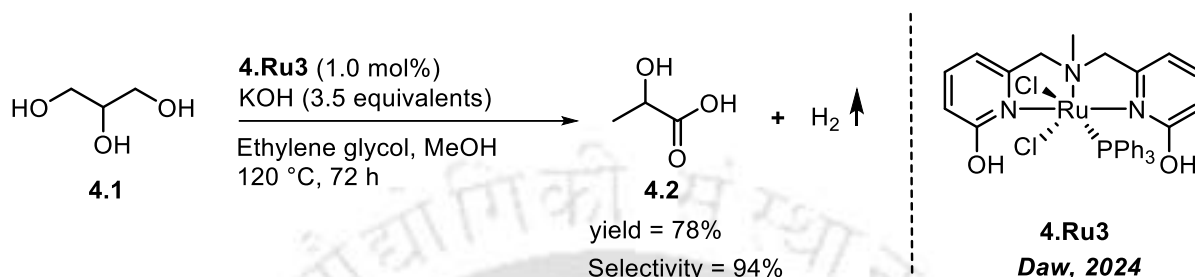
In a first report with catalytic systems based on Ru, Beller reported PNP pincer-Ru **4.Ru1** catalysed glycerol to LA acid transformation with LA yield of 67% with 67% selectivity with a high turnover number of 270000 (Scheme 4.8). It is noteworthy that, in addition to the formation of LA, they could generate molecular hydrogen from both pure glycerol (H₂ = 715.0 mL, TON = 84 000) as well as industrial glycerol (H₂ = 1334.0 mL, TON = 157 000).⁴⁷



Scheme 4.9. The transformation of glycerol to LA catalysed by a NNN pincer-Ru complex reported by Kumar.⁴⁸

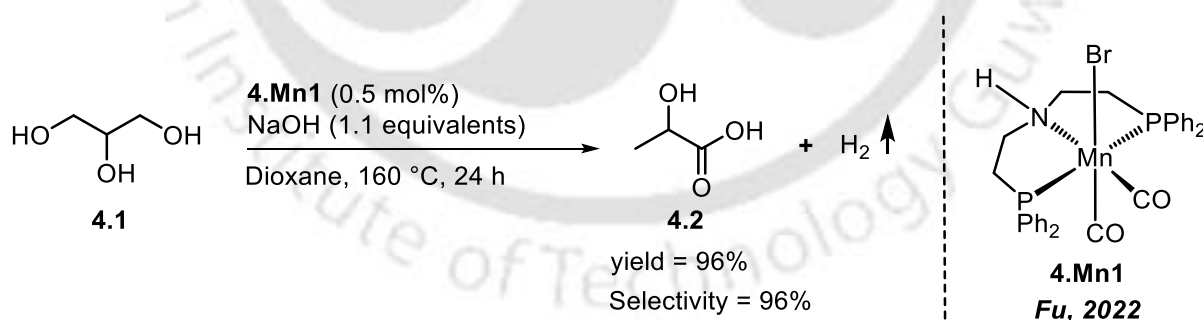
Kumar demonstrated the activity of 2,6-bis(benzimidazole-2-yl)pyridine based pincer-Ru complex **4.Ru2** towards dehydrogenation of glycerol to LA. About 90% yield of LA could be obtained with 98% selectivity in presence of **4.Ru2** (0.03 mol%), 1 equivalent KOH, at 140 °C in 48 h (Scheme 4.9). The thorough computational studies revealed that the complex **4.Ru2** had the least Ru-P interaction energy (39 kcalmol⁻¹) among the complexes that were

investigated in their report, making it the most active catalyst. The reaction initiated with Ru catalysed dehydrogenation of glycerol to glyceraldehyde, which underwent through a series of base mediated organic transformations like dehydration followed by tautomerism and Cannizzaro reactions to generate lactic acid.⁴⁸



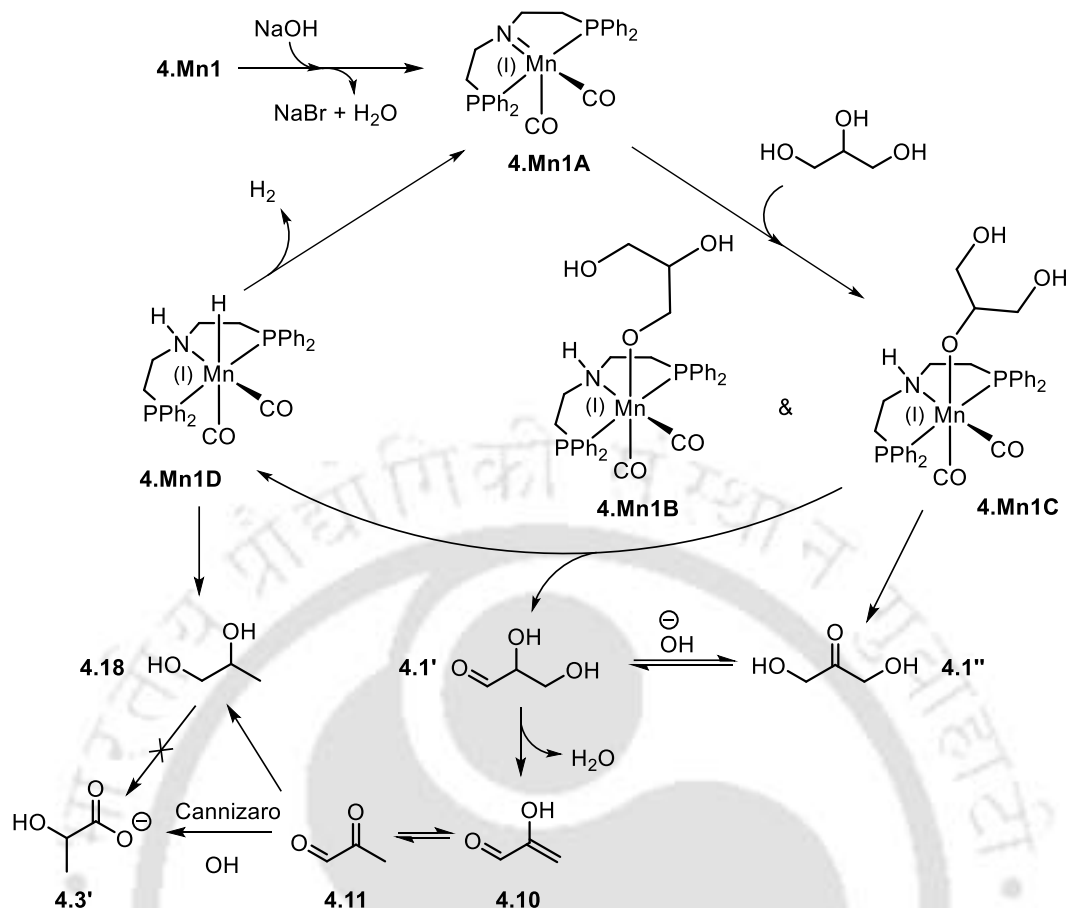
Scheme 4.10. The transformation of glycerol to LA catalysed by NNN pincer-Ru complex reported by Daw.⁵⁴

Recently, the research group of Daw have demonstrated that 78% yield of lactate was obtained from a mixture of glycerol, ethylene glycol and methanol (1:1:5) in presence of NNN pincer-Ru complex **4.Ru3** (1 mol%), KOH (3.5 equivalents) in *t*-BuOH (1 mL) at 120 °C in 72 h (Scheme 4.10).⁵⁴ Thus, it is evident that the catalytic systems based on Ir and Ru have enjoyed great success in accomplishing the dehydrogenative transformation of glycerol to lactic acid. However, in recent times significant emphasis has been laid to accomplishing these transformations using earth-abundant first row transition elements.



Scheme 4.11. The transformation of glycerol to LA catalysed by a PNP pincer-Mn complex reported by Fu.⁴⁹

The first report on the use of a 3d-metal for the GLY to LA transformation again came from Crabtree who along with Hazari performed this reaction utilizing PNP pincer-Fe complex **4.Fe1** which afforded turnover numbers of 880 at 20% conversion of glycerol and 80% selectivity towards lactic acid (Scheme 4.14). Furthermore, the same catalyst (2.5 mol%) was

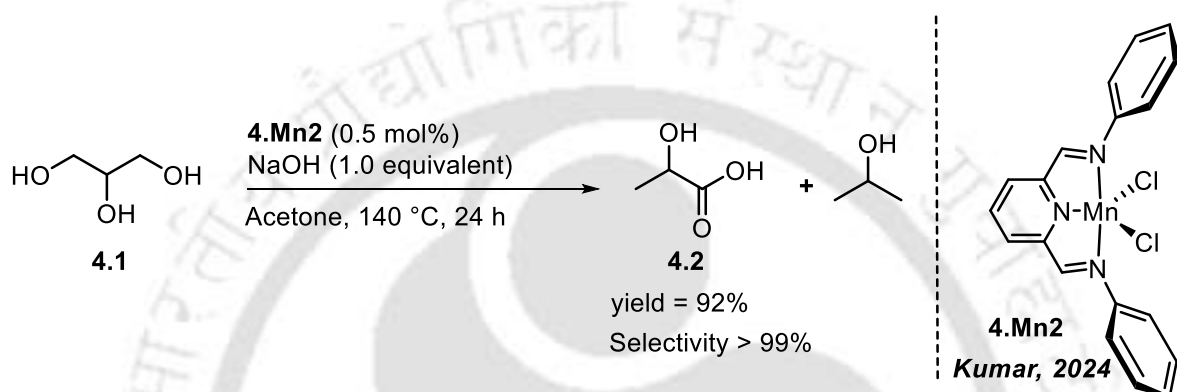


Scheme 4.12. Plausible mechanism for the PNP-Mn complex catalysed acceptorless dehydrogenation of glycerol to LA reported by Fu.⁴⁹

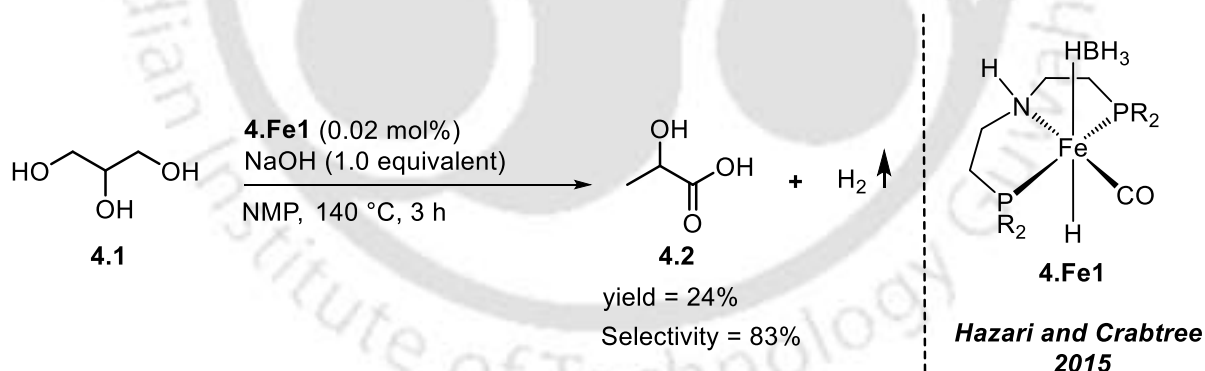
used to execute the transfer dehydrogenation of glycerol to LA in presence of an acceptor (acetophenone) at 120 °C, which afforded LA (80% yield) and 1-phenyl ethanol (the reduced product of acetophenone) in presence of very high loading of base (5-10 equivalents).²⁵ Fu have reported highly reactive pincer-Mn complex **4.Mn1** (Scheme 4.11) which afforded high yield of LA (96%) with high selectivity (96%). Based on the results of the control experiments, they have proposed a plausible mechanism (Scheme 4.12) where the very first step is the deprotonation of **4.Mn1** to the active species in the presence of base, then glycerol reacts with the active species and leads to the generation of the alkoxide species. It is followed by β-hydride elimination giving rise to glyceraldehyde which undergoes dehydration, tautomerism and base mediated Cannizzaro reaction to form lactic acid (Scheme 4.12).⁴⁹

Apart from the report on the catalytic systems based on pincer-Mn by Fu⁴⁹ and pincer-Fe by Crabtree and Hazari²⁵ there are no other report on acceptorless dehydrogenation of glycerol to lactic acid. Kumar in his recent report, demonstrated (^{Ph}₂NNN)MnCl₂ **4.Mn2** (0.5 mol%)

catalysed transfer dehydrogenation of glycerol in presence of acetone, where they achieved 92% yield of LA with 99% selectivity in presence of 1 equivalent NaOH at 140 °C (Scheme 4.13). The secondary KIE of 1.25 gave an indication of the participation of C-H bond breaking/making in the catalytic cycle but it is not the RDS.⁵⁰ Kumar have also accomplished this reaction using pincer NNN-Fe complex **4.Fe2** based on the same *bis*(imino)pyridine ligand where excellent yield of LA (91%) at 99% selectivity was afforded in presence of 1.2 equivalents NaOH at 140 °C (Scheme 4.15).⁵¹ They have reported a KIE of 1.58 which indicated that C-H bond breaking or making may not be a part of the RDS.

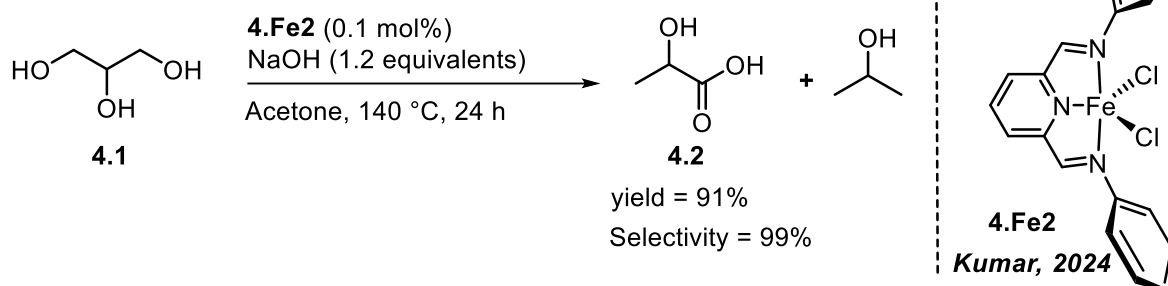


Scheme 4.13. The transformation of glycerol to LA catalysed by NNN pincer-Mn complex reported by Kumar.⁵⁰

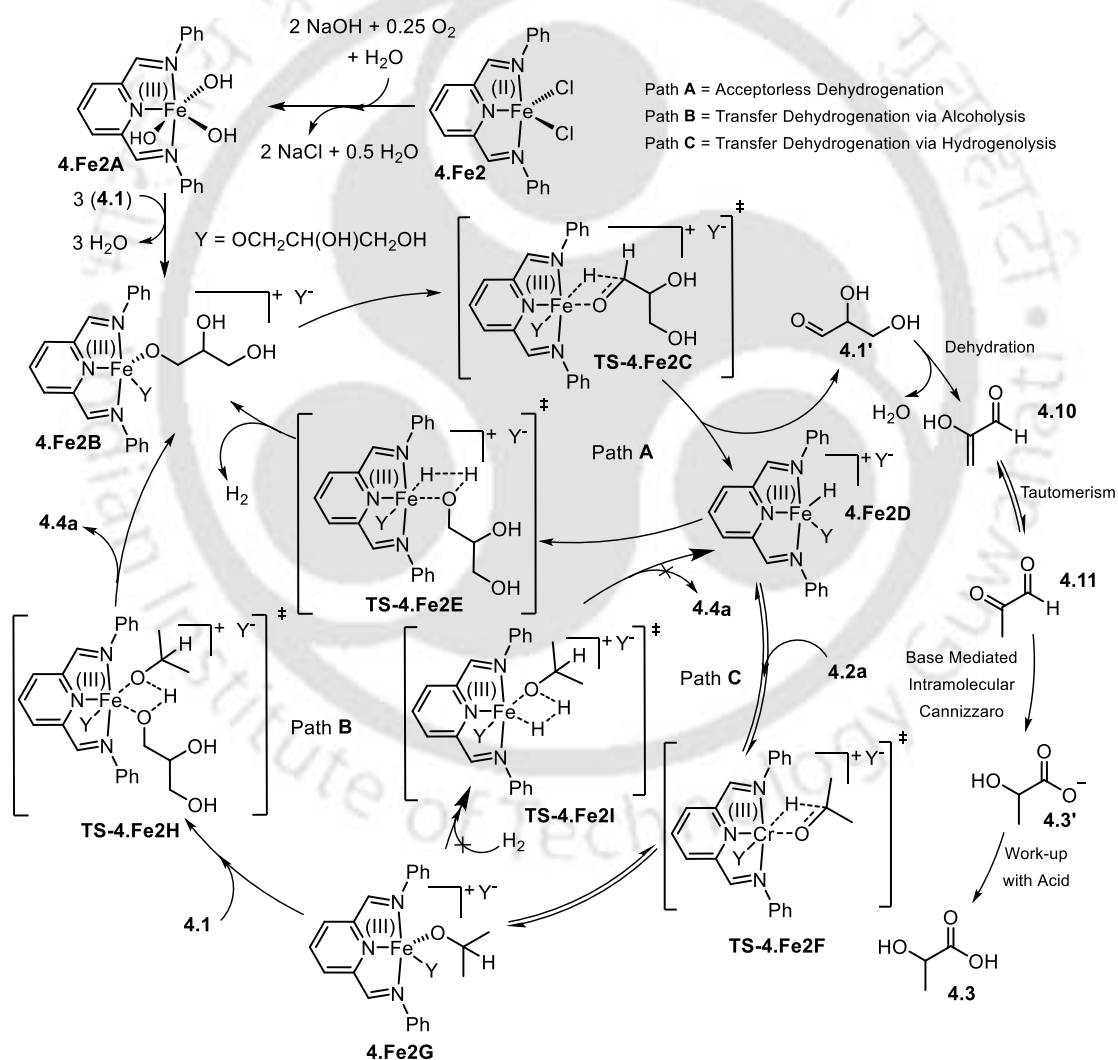


Scheme 4.14. The transformation of glycerol to LA catalysed by PNP pincer-Fe complex reported by Hazari and Crabtree.²⁵

They have proposed that the reaction can undergo through acceptorless dehydrogenative pathway as well net transfer dehydrogenative pathway (Scheme 4.16). Both the pathways were initiated with the conversion of Fe (II) species **4.Fe2** to Fe (III) active species **4.Fe2A** in presence of NaOH which then it underwent salt metathesis in presence of glycerol to generate



Scheme 4.15. The transformation of glycerol to LA catalysed by NNN pincer-Fe complex reported by Kumar.⁵¹



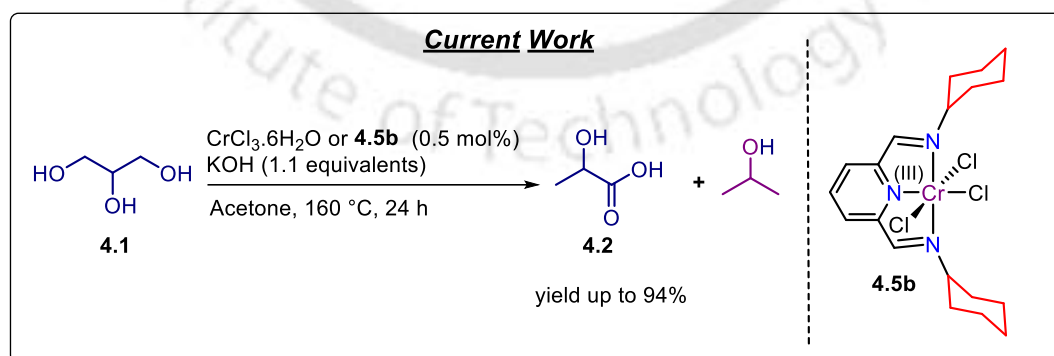
Scheme 4.16. Plausible mechanism for the pincer-Fe complex catalysed acceptorless and transfer dehydrogenation of glycerol to LA reported by Kumar.⁵¹

the alkoxide species **4.Fe2B**. The β -hydride elimination from the alkoxide species **4.Fe2B** gave rise to a Fe-hydride **4.Fe2D** along with an extrusion of glyceraldehyde which undergoes a series of base mediated organic transformations including dehydration, tautomerism and Cannizzaro reactions to form the final product, lactic acid.⁵¹

In the acceptorless dehydrogenative mechanism (Scheme 4.16), the Fe-H bond of the Fe-hydride species **4.Fe2D** undergoes a σ -bond metathesis with the O-H bond of glycerol to regenerate the Fe-alkoxide species **4.Fe2B** with release of H₂. On the other hand, in case of net transfer dehydrogenation (Scheme 4.16), insertion of C-O bond of acetone takes place into the Fe-H bond of the hydride species **4.Fe2D** giving rise to an isopropoxide species **4.Fe2G** which undergoes hydrogenolysis or alcoholysis in presence of hydrogen or glycerol and gives back the alkoxide species **4.Fe2B**. The trace amounts of hydrogen detected in GC might be the contribution from acceptorless dehydrogenation of GLY or dehydrogenation of isopropanol.⁵¹

4.2. Objectives of the current work

A comprehensive literature study reveals that the dehydrogenation of glycerol to lactic acid has been accomplished using various organometallic complexes based on precious metals like Ru,^{47,48,54} Ir,^{44-46,52-53} and also based on 3d-metals like Mn^{49,50} and Fe.^{25,51} To the best of our knowledge, there are no other reports on homogeneous 3d-metal GLY dehydrogenation catalytic systems reported for the production of LA. Taking a cue from the previous success on achieving alcohol dehydrogenation⁵⁶⁻⁶⁰ using commercially available chromium (III) chloride⁶⁰ and its corresponding pincer complexes⁶⁰⁻⁶¹, the current work attempts to address the following questions :



Scheme 4.17. Current work based on chromium (III) chloride and its corresponding pincer complexes catalysed transformation of glycerol to lactic acid.

- Can one use commercially available 3d metal salt chromium (III) chloride ($\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$) for the synthetically valuable conversion of GLY to LA in air without any compromise on the overall performance?
- Can one utilize easy to synthesize NNN pincer-Cr (III) complexes to carry out the transfer dehydrogenative transformation of glycerol to LA in air, without any compromise on the overall performance?

4.3. Results and Discussions

4.3.1. Studies on the pincer-Cr catalysed net transfer dehydrogenation of glycerol to lactic acid using acetone

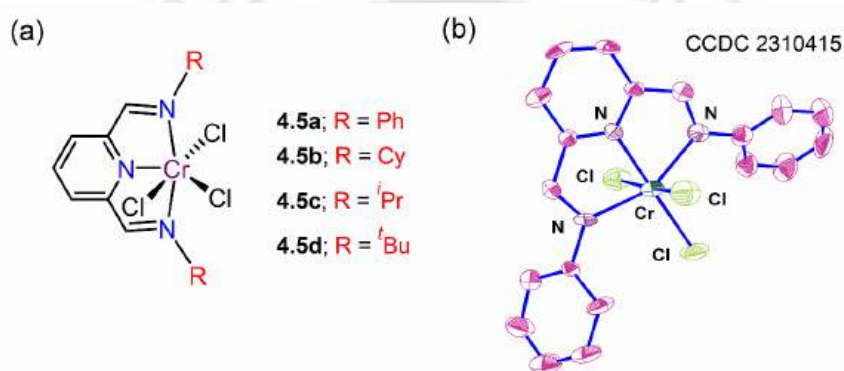


Figure 4.1. (a) The considered catalysts **4.5a-d**. (b) The molecular structure of **4.5a** is provided as ORTEP drawn at 50 % probability. All of the hydrogen atoms on **4.5a** are omitted for the sake of clarity.

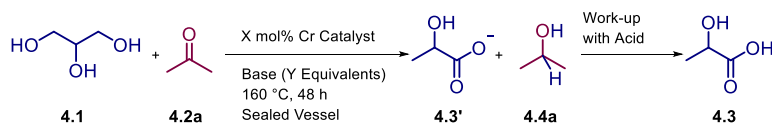
For the proposed studies on the net transfer dehydrogenation of GLY **4.1** to LA **4.3** using acetone **4.2a**, $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its corresponding NNN pincer-Cr complexes based on bis(imino)pyridine ligands,⁶¹⁻⁶² of the type ($\text{Cr}^{\text{R2}}\text{NNNCrCl}_3$ **4.5a**; R = Ph, **4.5b**; R = Cy, **4.5c**; R = *i*Pr, **4.5d**; R = *t*Bu) were used as potential catalysts. During the course of the synthesis of the considered pincer-Cr complexes using our previously reported protocol (Chapter II), we were able to obtain crystals of **4.5a**, which were suitable for single crystal XRD analysis (Table **4.1**). Green crystals were obtained for the complex **4.5a** in a solution of MeOH and water via slow evaporation. SC-XRD analysis of **4.5a** revealed that Cr in octahedral environment, to which a pincer ligand is bound in meridional geometry with one chloride *trans* to pyridyl-N and the other two chlorides are *trans* to each other. The complex **4.5a** has crystallised in $\text{P2}_1/\text{n}$ space group. The Cr-N(pyridyl) bond distance is 1.994(8) Å (Table **4.1**). Both the Cr-N(imine) bonds are comparable (2.108(9) Å and 2.099(8) Å) in length with the pyridyl(N)-Cr-N(imine) bond angles of 77.0(4) and 77.4(4) respectively.

Table 4.1. Crystal structure and refinement parameters of 4.5a

Empirical formula	C ₁₉ H ₁₅ Cl ₃ CrN ₃
Formula weight	443.70
Temperature/K	296.00
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	15.800(6)
b/Å	8.357(3)
c/Å	16.344(6)
α /°	90
β /°	103.866(10)
γ /°	90
Volume/Å ³	2095.2(12)
Z	4
ρ_{calc} /cm ³	1.464
μ /mm ⁻¹	0.942
F(000)	940.0
Crystal size/mm ³	0.18 × 0.14 × 0.12
Radiation	MoK α (λ = 0.71073)
2 θ range for data collection/°	4.112 to 37.506
Index ranges	-14 ≤ h ≤ 14, -7 ≤ k ≤ 7, -14 ≤ l ≤ 14
Reflections collected	24605
Independent reflections	1615 [R _{int} = 0.1150, R _{sigma} = 0.0500]
Data/restraints/parameters	1615/225/235
Goodness-of-fit on F ²	1.223
Final R indexes [I >= 2 σ (I)]	R ₁ = 0.0761, wR ₂ = 0.1220
Final R indexes [all data]	R ₁ = 0.1029, wR ₂ = 0.1337
Largest diff. peak/hole / e Å ⁻³	0.36/-0.30

The catalytic investigations were initiated using 5 mmol of glycerol **4.1**, 5 mmol of acetone **4.2a**, 0.5 mol% CrCl₃.6H₂O and KOH (0.5 equivalents with respect to glycerol) where 25% glycerol conversion was observed that resulted in 23% lactate **4.3'** with 92% selectivity at 160 °C after 24 hours (entry 1, Table 4.2). A higher yield of **4.3'** (40%) was observed at a higher KOH loading of 0.75 equivalents (entry 2, Table 4.2). In the presence of one equivalent of KOH, 50% yield of lactate **4.3'** was obtained at 98% selectivity (entry 3, Table 4.2).

The yield of lactate further increased to 62±1% when 1.1 equivalents of KOH was used (entry 4, Table 4.2). On further increasing the equivalents of base, comparable yield of lactate **4.3'** was observed (entries 5 and 6, Table 4.2). Further optimizations were hence carried out using 1.1 equivalents of KOH. While increasing the loading of **4.5a** to 0.75 mol% led to comparable yield of lactate **4.3'** (68%, entry 7, Table 4.2), further lowering the catalyst loading resulted in lactate yields that were in the range of 60-50% after 24 hours of reaction (entries 8-16, Table 4.2). Notably, with a very low loading of 0.0025 mol% CrCl₃.6H₂O, 59% yield of lactate **4.3'** which corresponds to an unprecedented turnover of 23600 TON was obtained in 96 hours (entry 17, Table 4.2).

Table 4.2. Net-transfer dehydrogenative transformation of glycerol to lactic acid catalysed by $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its pincer-complexes under varying conditions^a

Entry	Catalyst (X mol%)	Base (Y Equiv.)	%Conversion ^b 4.1	%Yield ^b 4.3'	4.3'% Selectivity ^c	% Yield ^b 4.4a	C _{balance} (%)
1	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KOH (0.5)	25%	23%	92%	19%	97
2	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KOH (0.75)	40%	40%	100%	38%	93
3	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KOH (1)	51%	50%	98%	42%	90
4 ^d	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KOH (1.1)	62±2%	62±1%	>99%	55±1%	95
5 ^d	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KOH (1.2)	62±2%	61±3%	98%	57±1%	94
6 ^d	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KOH (1.3)	67±1%	66±1%	98%	60±2%	93
7	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.75)	KOH (1.1)	70%	68%	97%	68%	97
8	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.25)	KOH (1.1)	63%	62%	98%	54%	95
9	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.1)	KOH (1.1)	58%	58%	100%	51%	92
10	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.075)	KOH (1.1)	55%	53%	96%	49%	93
11	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.05)	KOH (1.1)	55%	54%	98%	40%	94
12	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.025)	KOH (1.1)	60%	58%	97%	48%	93
13	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.01)	KOH (1.1)	55%	54%	98%	54%	96
14	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.0075)	KOH (1.1)	55%	55%	100%	45%	97
15	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.005)	KOH (1.1)	51%	50%	98%	38%	97
16	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.0025)	KOH (1.1)	50%	49%	98%	31%	96
17 ^e	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.0025)	KOH (1.1)	60%	59%	98%	53%	95
18 ^d	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	NaOH (1.1)	88±2%	84±1%	95%	67±1%	95
19 ^f	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	NaOH (1.1)	82%	81%	99%	52%	97
20 ^d	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	NaO ^t Bu (1.1)	40±1%	39±1%	99%	5±1%	92
21 ^d	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KO ^t Bu (1.1)	27±1%	26±1%	99%	21±1%	93
22 ^d	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	NaOEt (1.1)	26±1%	26±1%	>99%	24±1%	95
23	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	Na_2CO_3 (1.1)	Trace	Trace	Trace	Trace	94
24	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	K_2CO_3 (1.1)	Trace	Trace	Trace	Trace	96
25	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	NaHCO_3 (1.1)	0	0	0	0	97
26	$\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ (0.5)	KHCO_3 (1.1)	0	0	0	0	97
27	4.5a (0.5)	NaOH (1.1)	92%	91%	99%	67%	96
28	4.5b (0.5)	NaOH (1.1)	96±1%	94±1%	98%	79±1%	95
29	4.5c (0.5)	NaOH (1.1)	86%	84%	98%	53%	95
30	4.5d (0.5)	NaOH (1.1)	78%	75%	96%	43%	96
31	4.5b (0.75)	NaOH (1.1)	87%	86%	99%	76%	96
32	4.5b (0.25)	NaOH (1.1)	75%	73%	95%	38%	95
33	4.5b (0.05)	NaOH (1.1)	68%	67%	98%	28%	95
34	4.5b (0.005)	NaOH (1.1)	61%	59%	91%	26%	94
35	4.5b (0.00125)	NaOH (1.1)	73%	72%	95%	47%	93
36 ^g	4.5b (0.5)	NaOH (1.1)	63%	61%	99%	48%	96
37 ^h	4.5b (0.5)	NaOH (1.1)	26%	24%	97%	20%	93
38 ⁱ	4.5b (0.5)	NaOH (1.1)	26%	24%	92%	20%	92
39	No catalyst	NaOH (1.1)	21%	19%	90%	Trace	96

^aReaction conditions: 5 mmol glycerol, X mol% catalyst, Base (Y equivalents with respect to glycerol), 5 mmol 4.2a, at 160 °C, in a 15 mL pressure tube, under air. ^bDetermined from ¹H NMR analysis using sodium acetate as an internal standard. ^cSelectivity of lactic acid = (yield of lactic acid / conversion of glycerol)100.

^dAverage of two runs. ^eReaction was done for 96 h. ^f0.555 mL acetone was used (1.5 equivalents with respect to glycerol). ^gReaction was done at 140 °C. ^hReaction was done at 120 °C. ⁱReaction was done at 100 °C.

To investigate the effect of various bases, the GLY to LA transformation was done using 5 mmol glycerol, 5 mmol acetone, 0.5 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents of base at 160 °C for 24 hours (entries 18-26, Table 4.2). A very good yield of lactate **4.3'** (ca. 84±1%, entry 18, Table 4.2) was obtained in presence of NaOH. Use of NaO^tBu gave lower yield of lactate **4.3'** (39±1%, entry 20, Table 4.2). Both KO^tBu and NaOEt have shown poor efficiency giving rise to similar yield of **4.3'** (26±1%, entries 21 and 22, Table 4.2). The carbonate and bicarbonate salts of neither sodium nor potassium were active (entries 23-26, Table 4.2). Increasing the amount of acetone hardly improved the productivity of **4.3'** (entry 18 Vs. 19, Table 4.2).

At the optimized condition (entry 18, Table 4.2), the transfer dehydrogenation of glycerol with acetone was repeated using pincer-Cr complexes based on *bis(imino)pyridine* ligands⁶¹⁻⁶² of the type (R^2NNN)CrCl₃ (**4.5a**; R = Ph, **4.5b**; R = Cy, **4.5c**; R = ⁱPr, **4.5d**; R = ^tBu) which were previously reported by our group.⁶¹⁻⁶² To our delight, the complexes **4.5a** and **4.5b** have shown better reactivity than the precursor $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ in terms of productivity of lactate **4.3'** (entry 18 Vs. entries 27 and 28, Table 4.2). In particular, 91% lactate **4.3'** was obtained with 99% selectivity, when glycerol (5 mmol) was treated with 0.5 mol% **4.5a** in presence of acetone (5 mmol) and NaOH (1.1 equivalents with respect to glycerol) (entry 27, Table 4.2). Under similar conditions, slightly better reactivity was demonstrated by **4.5b** compared to **4.5a** (entry 27 Vs. entry 28, Table 4.2) where 94±1% lactate **4.3'** yield was obtained with 98% selectivity along with 79±1% isopropanol. Whereas, slightly lower yield of lactate (84%, entry 29, Table 4.2) but still at higher selectivity (98%) was observed upon use of catalyst **4.5c** under identical conditions.

The optimization of the loading of **4.5b** was then investigated. On increasing the loading of **4.5b** to 0.75 mol%, 86% yield of lactate **4.3'** with 99% selectivity was obtained which is slightly lower compared to that of 0.5 mol% **4.5b** (compare entry 31 with 27, Table 4.2) which may be attributed to the lower solubility of the higher amount of catalyst. On lowering the loading of **4.5b** to 0.25 mol%, a decrement in the yield of lactate **4.3'** was observed (73% with 95% selectivity, entry 32, Table 4.2). Further sequential lowering of **4.5b** loading led to gradual decrement in lactate **4.3'** yield however with good turnovers (entries 33-35, Table 4.2).

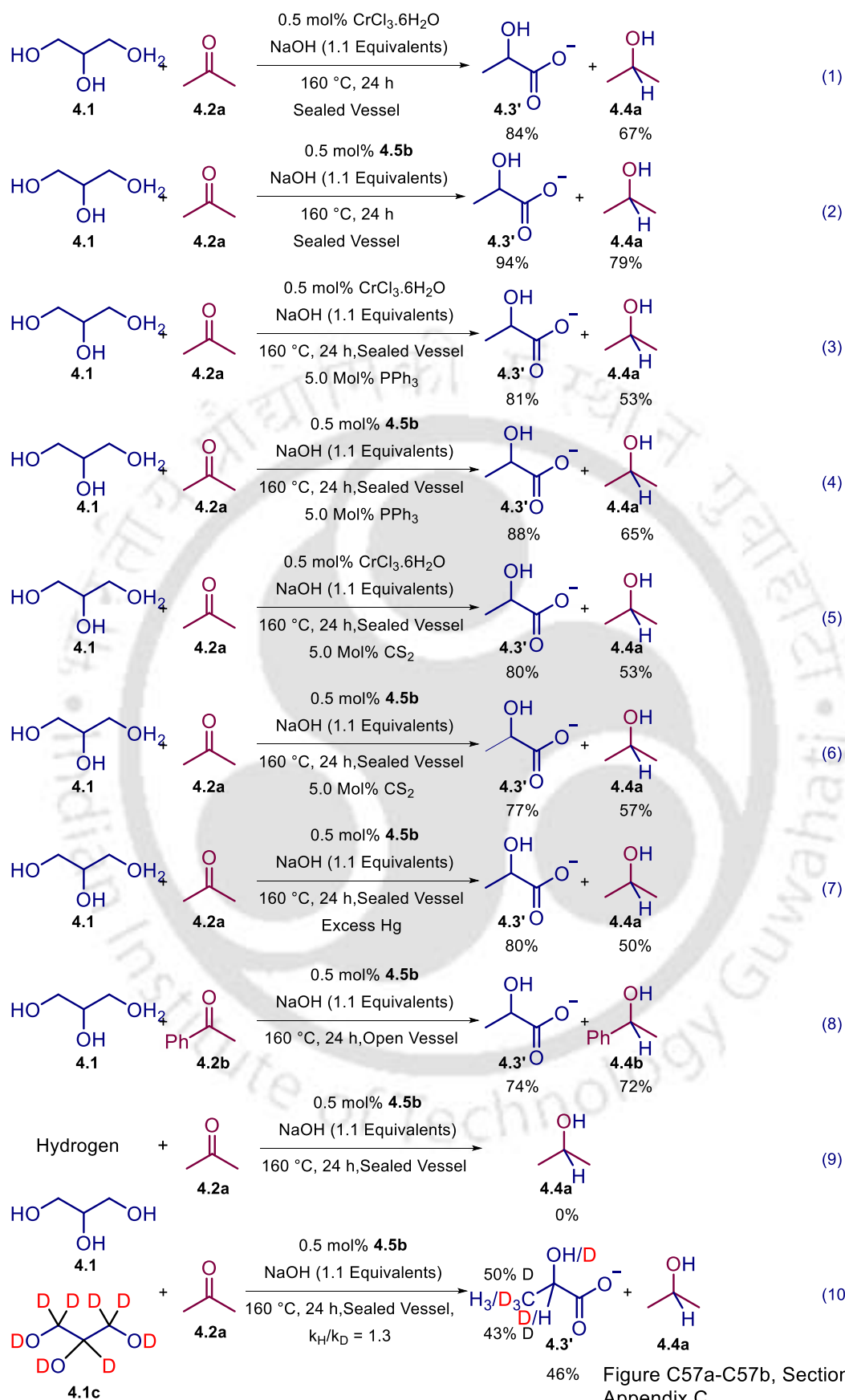
To investigate the effect of the temperature, the reaction was performed at lower temperatures also. On lowering the temperature from 160 °C to 140 °C, a lower yield of lactate **4.3'** (72%, entry 36, Table 4.2) was obtained which drops to 61% at 120 °C (entry 37, Table 4.2). The yield of lactate **4.3'** further dropped to 24% at 100 °C (entry 38, Table 4.2).

Table 4.3. The **4.5b** catalysed net transfer dehydrogenative conversion of glycerol to lactic acid using various acceptors^a

Entry	Acceptor	% Conversion ^b 4.1	% Yield ^b 4.3'	4.3' % Selectivity ^c	% Yield ^b 4.4a-4.4q	C _{balance} (%)
1	Acetone (4.2a)	96±1%	94±1%	98%	67±1%	99
2	Acetone (4.2a)	0%	0%	0%	0%	93
3	Acetone (4.2a)	18%	18%	100%	0%	98
4	Acetophenone (4.2b)	76%	70%	97%	72%	98
5	Benzaldehyde (4.2c)	31%	30%	97%	49%	97
6	4'-Chloroacetophenone (4.2d)	78%	76%	97%	32%	97
7	4'-Methylacetophenone (4.2e)	90%	89%	99%	84%	99
8	Cyclopentanone (4.2f)	74%	72%	97%	45%	99
9	4'-Nitroacetophenone (4.2g)	32%	18%	56%	Trace	98
10	Benzophenone (4.2h)	54%	50%	93%	47%	97
11	3'-Methoxyacetophenone (4.2i)	75%	73%	97%	56%	98
12	4-Acetylpyridine (4.2j)	48%	45%	94%	6%	98
13	4'-Bromoacetophenone (4.2k)	87%	84%	96%	22%	97
14	4'-Fluoroacetophenone (4.2l)	7%	6%	86%	0%	98
15	4'-CF ₃ -acetophenone (4.2m)	47%	45%	96%	15%	95
16	4'-Methoxyacetophenone (4.2n)	74%	73%	98%	51%	98
17	4'- <i>tert</i> -Butylacetophenone (4.2o)	25%	23%	92%	0%	96
18	2-Acetylthiophene (4.2p)	65%	62%	95%	49%	95
19	4'-Hydroxyacetophenone (4.2q)	15%	12%	50%	Trace	97
20	No acceptor	10%	8%	80%	0%	95

^a Reaction conditions: 5 mmol glycerol, 0.5 mol% **4.5b**, NaOH (1.1 equivalents with respect to glycerol), 5 mmol acetone (1 equivalent with respect to glycerol), at 160 °C, in a 15 mL pressure tube, under air. ^b Determined from ¹H NMR analysis using sodium acetate as an internal standard. ^c Selectivity of lactic acid = (yield of lactic acid / conversion of glycerol)100. ^d Average of two runs. ^e Reaction was done in absence of base ^f Reaction was done in absence of **4.5b**. ^gReaction was done in absence of acceptor.

Under the optimized conditions but in absence of base no reactivity was observed (entry 2, Table 4.3), while in the absence of **4.5b**, only 18% yield of **4.3'** was observed with 100% selectivity towards **4.3'** (entry 3, Table 4.3). The GLY to LA transformation was then performed in presence of various acceptors under the optimized reaction condition (entry 28, Table 4.2), to understand the effect of acceptor on the productivity of lactate **4.3'** (Table 4.3). In the presence of acetophenone **4.2b** as an acceptor, moderate yield of lactate **4.3'** (74%) was observed (entry 4, Table 4.3). In presence of benzaldehyde **4.2c**, poorer yield of lactate **4.3'** was obtained (30%, entry 5, Table 4.3). Hence, further studies were continued with various derivatives of acetophenone. A very poor yield of lactate **4.3'** (6%) was obtained when **4.2l** with electron-withdrawing *p*-fluoro group was employed as an acceptor (entry 14, Table 4.3). The yield of **4.3'** improved to 45% when the *p*-fluoro group was replaced by *p*-trifluoromethyl group in **4.2m** (entry 15, Table 4.3). In presence of **4.2d** containing relatively less electron-

Figure C57a-C57b, Section C3
Appendix C

Scheme 4.18. Control experiments.

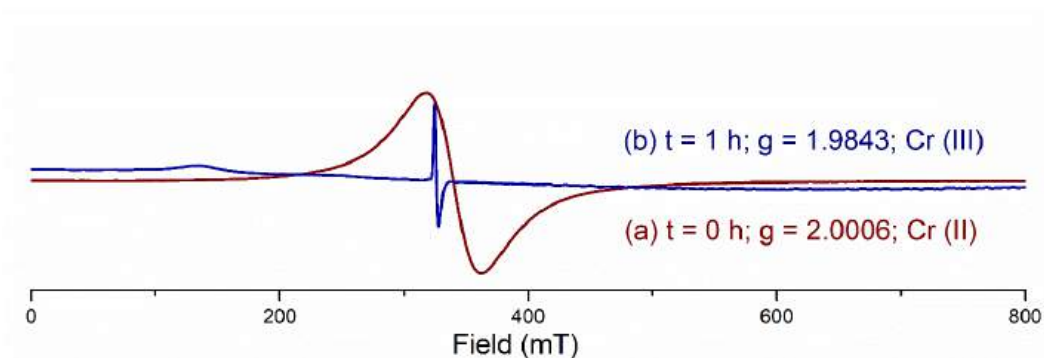


Figure 4.2. EPR analysis of the reaction mixture obtained from the optimized transfer dehydrogenation of glycerol (entry 28, Table 4.2 and equation 2, Scheme 4.18) (a) at $t = 0$ h in absence of NaOH and (b) at $t = 1$ h in presence of NaOH. The X-band EPR spectra was recorded in methanol on a JESFA200 ESR spectrometer at 78K with microwave power of 0.998 mW and microwave frequency of 9.14 GHz.

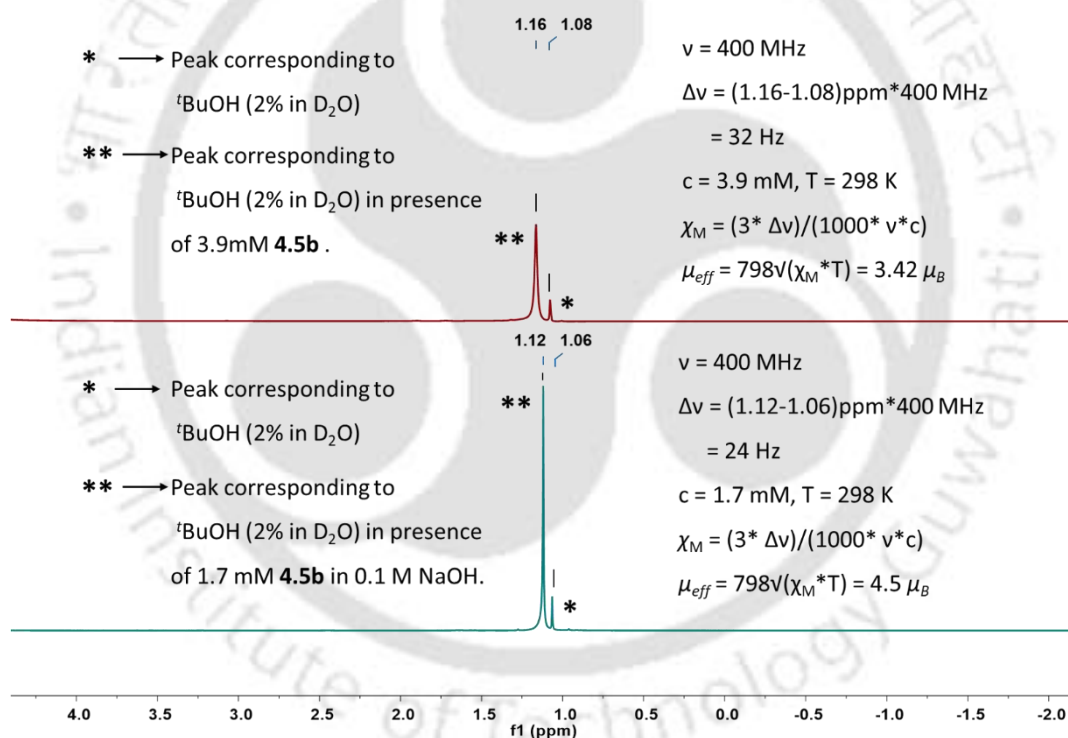


Figure 4.3. Magnetic moment determination via Evan's method of **4.5b** before addition of NaOH and **4.5b** after addition of NaOH at room temperature.

withdrawing chloro group, comparable yield of lactate **4.3'** (76% to 97% selectivity) was observed in comparison to **4.2b** that results in 70% yield of **4.3'** (entry 4 Vs. entry 6, Table 4.3). Similarly, **4.2i** containing an electron withdrawing methoxy group in the meta position shows comparable reactivity as that of **4.2b** yielding 73% of lactate (entry 4 Vs. entry 11, Table 4.3). The acceptor **4.2k** with a relatively much lower electron withdrawing *p*-bromo substituent

resulted in 84% yield of lactate **4.3'** (entry 13, Table 4.3). Based on the observance, it is evident that the yield of the lactate **4.3'** systematically decreased on increasing the electron deficiency and followed the trend $p\text{-Br} > p\text{-Cl} \sim m\text{-OMe} > p\text{-CF}_3 > p\text{-F}$. When the reaction was performed in presence of **4.2e** which contains electron-donating methyl group, a much higher yield of 89% lactate **4.3'** with 93% selectivity was obtained (entry 7, Table 4.3). When cyclopentanone **4.2f** was used as acceptor, a lower reactivity was observed when compared to the corresponding activity with another aliphatic acceptor, acetone (Compare entry 8 with entry 1, Table 4.3). It might be attributed to the fact, that cyclopentanone is more sterically crowded than acetone. Poor yield of lactate **4.3'** (18%) was observed in presence of nitro-derivative of acetophenone **4.2g** (entry 9, Table 4.3) along with the formation of ethylene glycol EG (3%) and formic acid FA (11%), ultimately resulting in very low selectivity towards LA (56%). When benzophenone **4.2h** was used, 50% yield of lactate **4.3'** was obtained (entry 10, Table 4.3).

One would observe that in all entries in Table 4.2, the yield of IPA **4.4a** is slightly lower than **4.3'** which apparently can be attributed to the secondary dehydrogenation of **4.4a** back to **4.2a** along with the generation of hydrogen. Accordingly, hydrogen was detected in GC measurements for representative examples (see figures C1a-C1f, Appendix C for H_2 detected from entries 4, 28, 31-34, Table 4.2). Alternatively, the possibility of competing aldol reaction of **4.2a** with the corresponding aldol products acting as hydrogen acceptors can also explain the lower yields of **4.4a-4.4q** in Table 4.3 relative to **4.3'**.

In future, for a potential scale-up reaction, some factors have to be considered such as employing $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ will be more cost-effective than a pincer-Cr complex. In terms of reactivity, a pincer-Cr complex will show better performance. For better results, the reaction time might be continued for a prolonged time.

4.3.2. Mechanistic investigation on the pincer-Cr catalysed net transfer dehydrogenation of glycerol to lactic acid using acetone. To check the homogeneity of the reaction, three well-established catalyst poisons⁶³ involving PPh_3 , CS_2 and mercury were used. Negligible lowering of reactivity towards production of **4.3'** was observed when the transfer dehydrogenation of GLY catalysed by $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and **4.5b** (compare equation 1 with equation 3 and equation 2 with equation 4, Scheme 4.18) were performed in presence of PPh_3 . Similar observation was made in presence of CS_2 (compare equation 1 vs. equation 5, Scheme 4.18 and equation 1 vs. equation 6, Scheme 4.18). Considering the fact that PPh_3 or CS_2 can poison both homogeneous

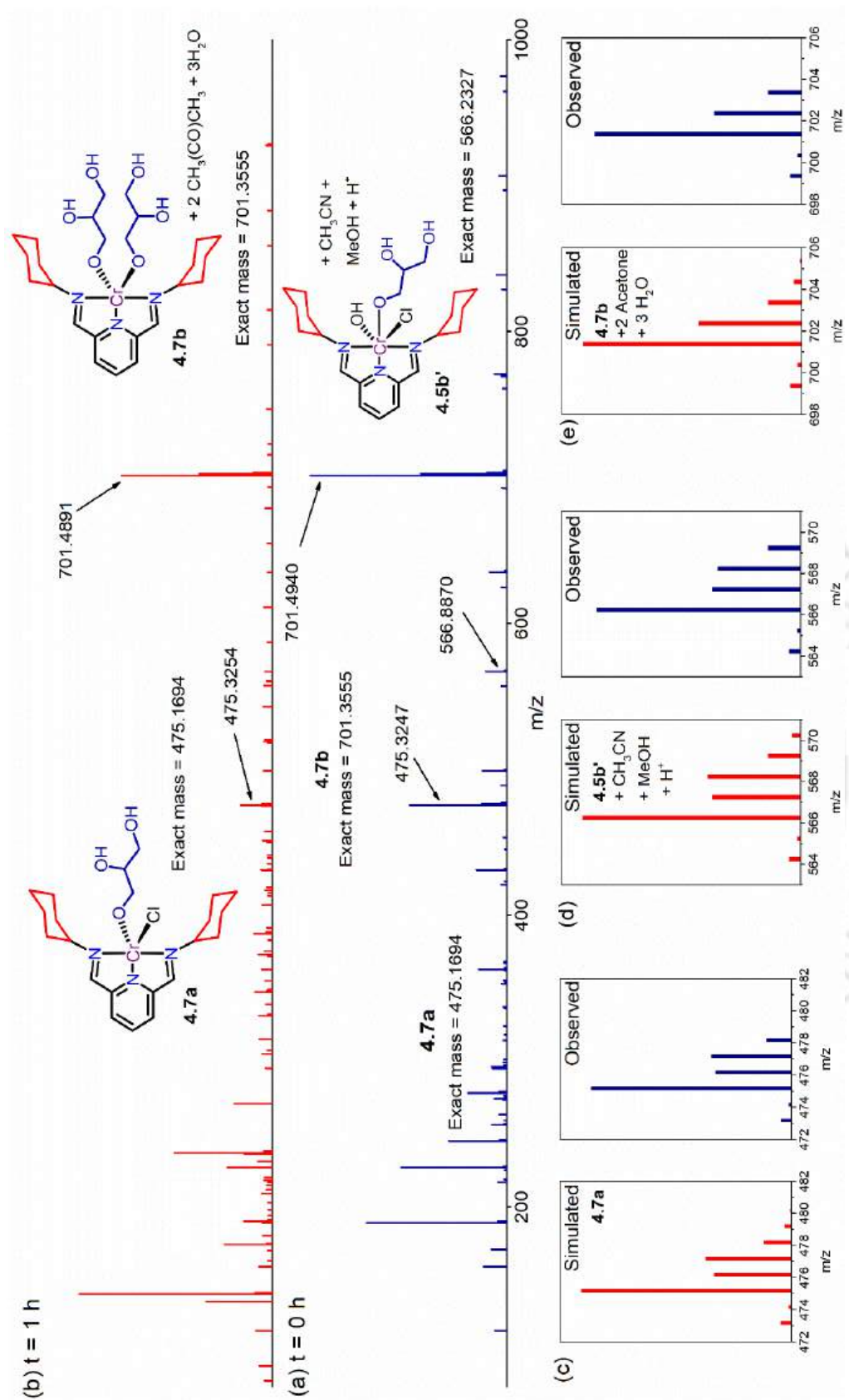
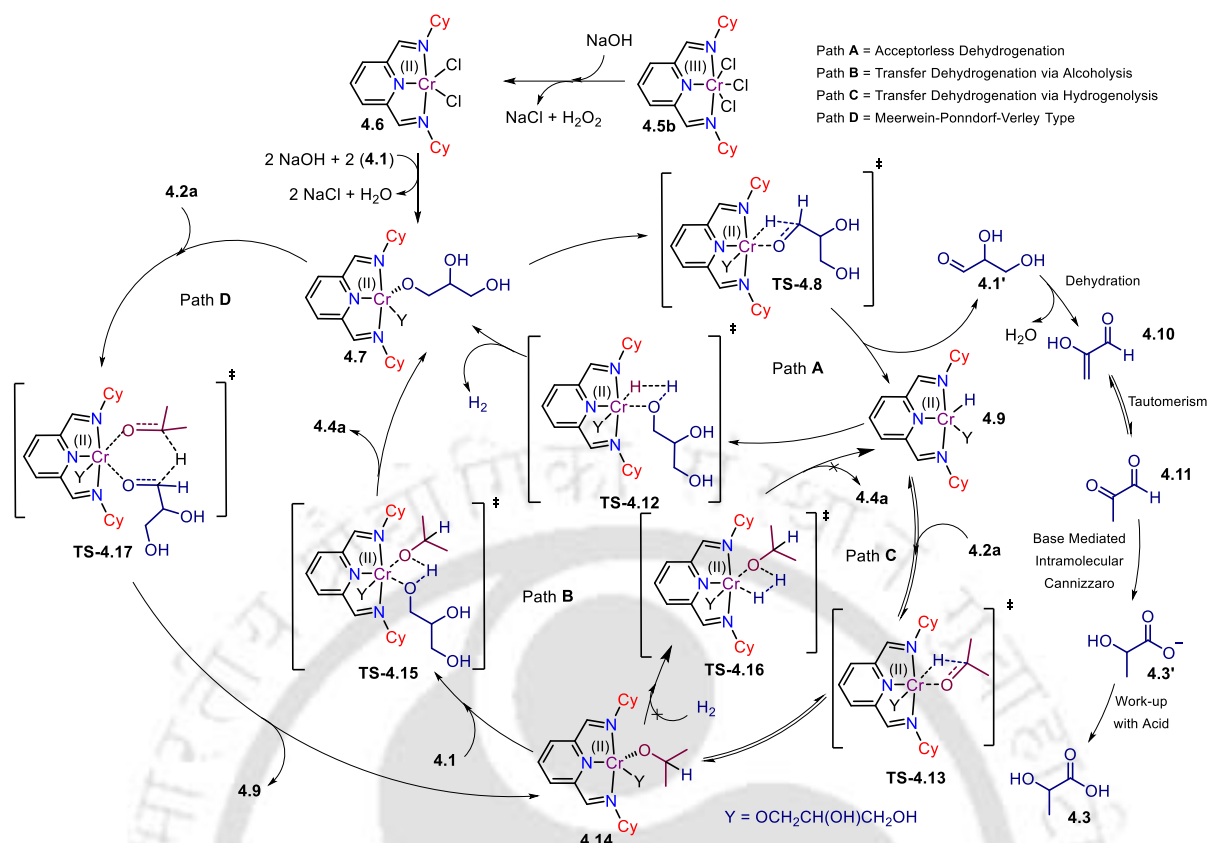


Figure 4.4. HRMS analysis of the reaction mixture obtained from the optimized transfer dehydrogenation of glycerol (Entry 2, Table 4.2 and equation 2, Scheme 4.18) at (a) $t = 0$ h at room temperature and (b) $t = 1$ h at 160°C . (c) HRMS(ESI) expanded spectrum of $m/z = 475.3254$: Simulated (red) and observed (blue). (d) HRMS(ESI) expanded spectrum of $m/z = 566.8870$: Simulated (red) and observed (blue). (e) HRMS(ESI) expanded spectrum of $m/z = 701.4891$: Simulated (red) and observed (blue).



Scheme 4.19. Plausible mechanism.

and heterogeneous catalysts⁶³ a confirmatory mercury poisoning test was also performed, where slight lowering of yield was observed (compare equation 2 vs. equation 7, Scheme 4.18). These observations draw an evidence of the reaction being mostly homogeneous. Interestingly, the high reactivity in open vessel conditions (compare equation 2 vs. equation 8, Scheme 4.18) in the presence of acetophenone (boiling point is 202 °C) under the optimized reaction conditions, gives an indication of the involvement of both hydrogenolysis as well as alcoholysis.

From the EPR analysis of the reaction mixture (entry 28, Table 4.2) at 0 h in the absence of NaOH and 1 h in the presence of NaOH, it is evident that at 0 h at room temperature, Cr (III) species ($g = 2.0006$)⁶³⁻⁶⁷ is present, whereas at 1 h at 160 °C Cr (II) species ($g = 1.9843$)⁶³⁻⁶⁷ is involved (Figure 4.2). HRMS analysis (Figure 4.4) of the reaction mixture demonstrated the presence of several pincer-Cr mono-glyceroxide and pincer-Cr-bis-glyceroxide species. Magnetic moment measurements (via Evan's method) of **4.5b** in absence and presence of base in 2% ^tBuOH in D₂O (Figure 4.3) bodes well with the observation from EPR and HRMS of reaction mixture. Magnetic moment of 3.42 BM of the reaction mixture before the addition of

base corresponds to Cr (III) species, which converts to a Cr (II) species with magnetic moment of 4.5 BM in presence of base. Subjecting a mixture of glycerol (2.5 mmol) and glycerol-D8 (2.5 mmol) to the optimized reaction conditions (equation 10, Scheme 4.18), resulted in a modest KIE of 1.3 along with 46% lactate **4.3'**. This KIE gives an indication of the involvement of C-H activation as a part of the catalytic cycle but it might not be a part of the rate determining step. Kinetic studies indicate that the reaction demonstrates a first-order dependence of rate on the concentration of **4.5b** and NaOH (Figure 4.5). Thus, from the control experiments, it may be inferred that well-defined molecular pincer-Cr (II) complexes are involved in the catalytic cycle with a likely contribution from the alcoholysis and/or a Meerwein-Ponndorf-Verley type pathway (Scheme 4.19).

The first step in the pincer-Cr catalysed net transfer dehydrogenation of glycerol to lactic acid using acetone involves the generation of the active Cr (II) species **4.6** from the Cr (III) precursors (**4.5b**) in presence of base (Scheme 4.19). Subsequent salt metathesis of **4.6** with NaOH in presence of glycerol **4.1** will generate the alkoxide species **4.7** along with the loss of water. This will be followed by a β -hydride elimination at **4.7** which will give rise to the hydride species **4.9** via **TS-4.8** along with the extrusion of a molecule of glyceraldehyde **4.1'**. The glyceraldehyde **4.1'** will follow a series of base mediated reactions which involves dehydration of **4.1'** to **4.10** and subsequent tautomerization of **4.10** to **4.11**. Ultimately, a base mediated intramolecular Cannizzaro reaction in **4.11** leads to the final lactate **4.3'**.

The pincer-Cr hydride species **4.9** has three paths (Path A-C) at its disposal (Scheme 4.19). Along Path A, the Cr-H bond in **4.9** would undergo a σ -bond metathesis with the O-H bond of glycerol **4.1** leading to the regeneration of alkoxide species **4.7** via **TS-4.12** along with the extrusion of H₂. Notably, hydrogen was detected from the headspace of the reaction mixture (equation 1 and equation 2, Scheme 4.18 and figure C1a-C1b, Appendix C). Along path B, **4.2a** would insert into the Cr-H bond in **4.9** to give the pincer-Cr isopropoxide **4.14** while going through **TS-4.13**. The species **4.14** can undergo a σ -bond metathesis (alcoholysis) with the O-H bond of glycerol **4.1** leading to the regeneration of alkoxide species **4.7** via **TS-4.15** while generating the isopropanol **4.4a** (Scheme 4.19). Reactivity under open-vessel conditions (equation 8, Scheme 4.18) are suggestive of the involvement of the alcoholysis along Path B. Alternatively, if the pincer-Cr isopropoxide species **4.14** undergoes a σ -bond metathesis (hydrogenolysis) with hydrogen, the pincer-Cr hydride **4.9** would be regenerated along with the formation of **4.4a**. Notably, though hydrogen is detected from the head space of the reaction mixture (equation 1 and equation 2, Scheme 4.18 and Figure C1a- C1b, Appendix C), the

hydrogenolysis through Path **C** is unlikely to contribute to the observed catalysis as independent experiments with molecular hydrogen under the optimized reaction conditions yielded no product (equation 9, Scheme 4.18).

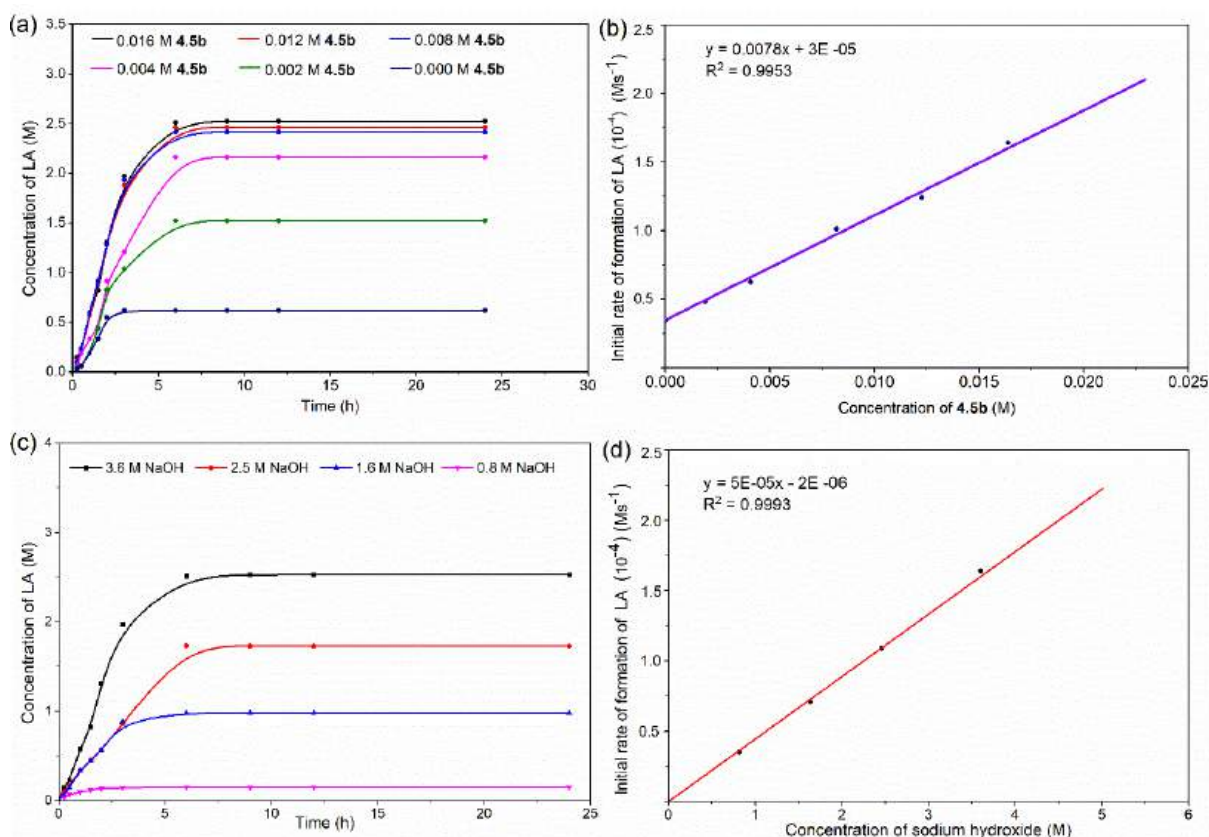


Figure 4.5. (a) Time-profile of transfer dehydrogenation of glycerol in open vessel using glycerol (0.460 g, 5 mmol, 3.3 M), NaOH (0.2198 g, 5.4956 mmol, 3.6 M), acetophenone (1.2 g, 10 mmol, 6.6 M), at 160 °C, in the presence of **4.5b** (0.0013-0.0114 g, 0.003-0.025 mmol, 0.002-0.016 M). (b) Dependence of initial rate of transfer dehydrogenation of glycerol reaction on the concentration of **4.5b** (extracted from 15 minutes data of Figure 4.5a). (c) Time-profile of transfer dehydrogenation of glycerol in open vessel using glycerol (0.460 g, 5 mmol, 3.3 M), **4.5b** (0.0114 g, 0.025 mmol, 0.016 M), acetophenone (1.2 g, 10 mmol, 6.6 M), at 160 °C, in presence the of NaOH (0.05-0.22 g, 1.25-5.5 mmol, 0.8-3.6 M). (d) Dependence of initial rate of transfer dehydrogenation of glycerol reaction on the concentration of NaOH (extracted from 15 minutes data of Figure 4.5c. Reaction conditions: glycerol (0.460 g, 5 mmol, 3.3 M), **4.5b** (0.0114 g, 0.025 mmol, 0.016 M), acetophenone (1.2 g, 10 mmol, 6.6 M), at 160 °C, in the presence of NaOH (0.05-0.22 g, 1.25-5.5 mmol, 0.8-3.6 M)).

In an alternative Path **D**, the pincer-Cr glyceroxide species **4.7** would interact with **4.2a** to initiate a direct transfer of the β -hydrogen via Meerwein-Ponndorf-Verley type **TS-4.17** leading to the extrusion of glyceraldehyde **4.1'** and formation of pincer-Cr isopropoxide species **4.14** (Scheme 4.19). The species **4.14** upon alcoholysis would regenerate **4.7** and produce **4.4a**. Notably, while Path **B** has a sequence of β -hydride elimination and insertion steps, Path **D** has

a concerted Meerwein-Ponndorf-Verley type β -hydride transfer step prior to the alcoholysis step that is common to both the paths.

4.4. Conclusions

Commercially available first-row transition metal salt $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its corresponding pincer complexes in presence of a sacrificial hydrogen acceptor, acetone were found to accomplish the transfer dehydrogenation of glycerol (GLY) to lactic acid (LA). In particular, the pincer-Cr complex, $(^{\text{Cy}2}\text{NNN})\text{CrCl}_3$ (0.5 mol%) was found to efficiently bring about the catalytic net transfer dehydrogenation of glycerol in presence of 1.1 equivalents of NaOH, at 160 °C to afford 94% lactic acid at 98% selectivity along with another value added product isopropanol (IPA).

While reactions with catalyst poisons such as PPh_3 , CS_2 and elementary mercury revealed the homogeneous molecular nature of the catalyst, EPR studies and magnetic moment measurements using Evan's method revealed that these homogeneous molecular species are likely to be based on Cr (II). Detailed mechanistic studies are indicative of the sole contribution of the alcoholysis path towards the observed reactivity with a KIE of 1.3.

4.5. Experimental section

Materials and methods: All the complexes were synthesized in anhydrous THF under Argon using Schlenk technique at room temperature. All the reactions were performed in sealed vessel under air. Kinetic experiments were performed in open vessel under air. Glycerol, NaOH, KOH, Na_2CO_3 , K_2CO_3 , NaHCO_3 , KHCO_3 were purchased from Himedia. Deuterated glycerol- D_8 , D_2O , NaO^tBu , KO^tBu , NaOEt were purchased from Sigma-Aldrich. The ketones were purchased from MERCK or Sigma-Aldrich or SRL or Alfa Aesar or TCI and used as such.

4.5.1. Physical measurements: ^1H , $^{13}\text{C}\{\text{H}\}$ and ^2H NMR were recorded either on a Bruker ASCEND 600 operating at 600 MHz for ^1H and ^2H and 151 MHz for $^{13}\text{C}\{\text{H}\}$ or on a Bruker AVANCE 400 operating 400 MHz for ^1H . Chemical shifts (δ) are reported in ppm, spin-spin coupling constants (J) are expressed in Hz, and other data are reported as follows: s = singlet, d = doublet and q = quartet. HRMS measurements were recorded using an Agilent Accurate-Mass QTOF ESI-MS 6520. The X-band EPR spectra was recorded on a JESFA200 ESR spectrometer. GC analysis (TCD detection) was performed on an Agilent 7820-GC instrument fitted with Agilent Front SSZ Inlet N2 using a HPLOT Q column (30 m length $\times$ 530 μm $\times$ 40 μm). Agilent 7820-GC back detector TCD Oven temperature: 50 °C, time at starting temp: 0

min Hold time = 10 min, inlet temperature: 100 °C, detector temperature (TCD): 250 °C, detector temperature (FID): 300 °C, flow rate (carrier): 5 mL/min (N₂), split ratio: 10.

Crystal of (*Ph*²NNN)CrCl₃ (4.5a): The complex **4.5a** was previously reported by our group.^{22b} Fortunately, we could get the crystal structure after several attempts. Green crystal was obtained in a solution of MeOH and H₂O via slow evaporation. The molecular structure of **4.5a** is provided as ORTEP figure drawn at 50% probability in Figure 4.1.

Synthesis of (*t*Bu²NNN)CrCl₃] (4.5d). To a solution of *t*Bu²NNN ligand⁴⁸ (0.20 g, 0.8150 mmol) in 10 mL of anhydrous THF was added CrCl₃.6H₂O (0.2178 g, 0.8150 mmol) in a pear-shaped flask under argon atmosphere. The resultant mixture was stirred at room temperature for 24 h. After stirring for 24 h, the solvent was evaporated under reduced pressure. The light bluish green solid obtained was washed with diethyl ether (3 × 2 mL) to remove the excess ligand, if any followed by evacuation. A light bluish green solid (0.2368 g, yield = 72%) was obtained. HRMS (ESI) *m/z* calculated for [**4.5da** + H]⁺: 364.1692, found 364.1768; calculated for [**4.5db** + 2H₂O]⁺: 403.0885, found *m/z* = 403.2921; calculated for [**4.5db'** + CH₃CN + CH₃OH]⁺: 422.1985, found *m/z* = 422.2189; calculated for [**4.5db''** + CH₃CN + H₂O + CH₃OH]⁺: 450.2298, found *m/z* = 450.2136. EPR analysis revealed a single peak with a *g* value of 1.98715 (Figure 4.6).

4.5.2. General procedure for transfer dehydrogenation of glycerol to lactic acid using

4.5b: In a 15 mL sealed tube, glycerol (0.460 g, 5 mmol, 6.8 M) followed by sodium acetate (0.05 g, 0.6095 mmol, 0.8 M), NaOH (0.2198 g, 5.4956 mmol, 7.5 M), **4.5b** (0.0114 g, 0.025 mmol, 0.02 M) and acetone (0.37 mL, 5 mmol, 6.8 M) were added. The reaction mixture was heated in a preheated oil bath at 160 °C for 24 hours. After 24 hours the reaction mixture was brought to room temperature, dipped in liquid nitrogen and then was allowed to warm to room temperature. Subsequently, 0.5 mL H₂O was added to the reaction mixture and was allowed to homogenize under continuous stirring for 10 minutes. An aliquot was drawn and submitted for NMR analysis in D₂O as NMR solvent. Yield of Lactate (**4.3'**) was determined as 94% from ¹H NMR using sodium acetate as an internal standard.

4.5.3. General procedure for kinetic studies

(a) **Variation in the loading of 4.5b:** To each of five round-bottomed flasks, glycerol (0.460 g, 5 mmol, 3.3 M) followed by sodium acetate (0.05 g, 0.6095 mmol, 0.4 M), NaOH (0.2198

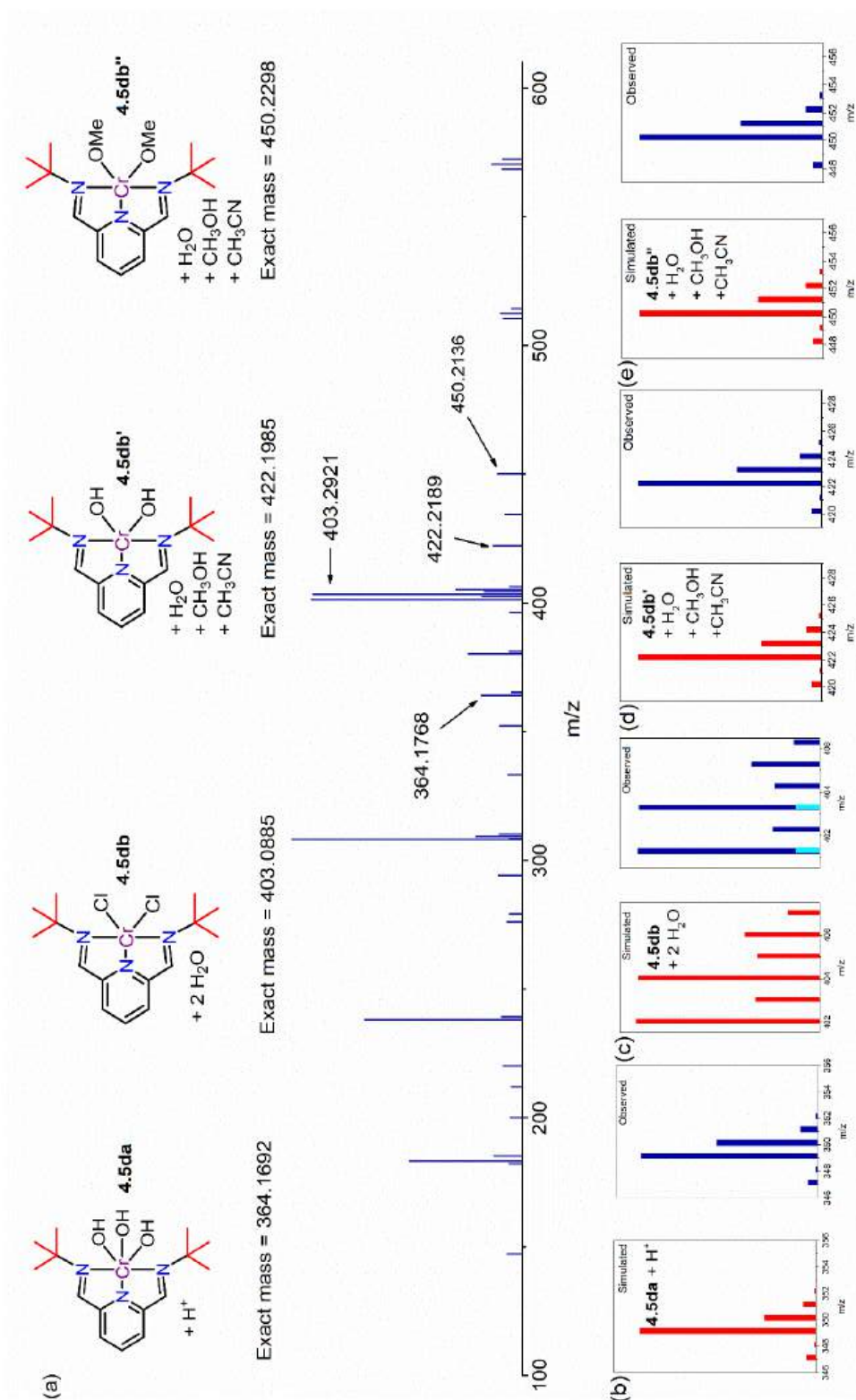


Figure 4.6. (a) HRMS analysis of the complex **4.5d** in MeOH. (b) HRMS(EI) expanded spectrum of $m/z = 364.1768$: Simulated (red) and observed (blue). (c) HRMS(EI) expanded spectrum of $m/z = 403.0885$: Simulated (red) and observed (blue). (d) HRMS(EI) expanded spectrum of $m/z = 422.2189$: Simulated (red) and observed (blue). (e) HRMS(EI) expanded spectrum of $m/z = 450.2136$: Simulated (red) and observed (blue).

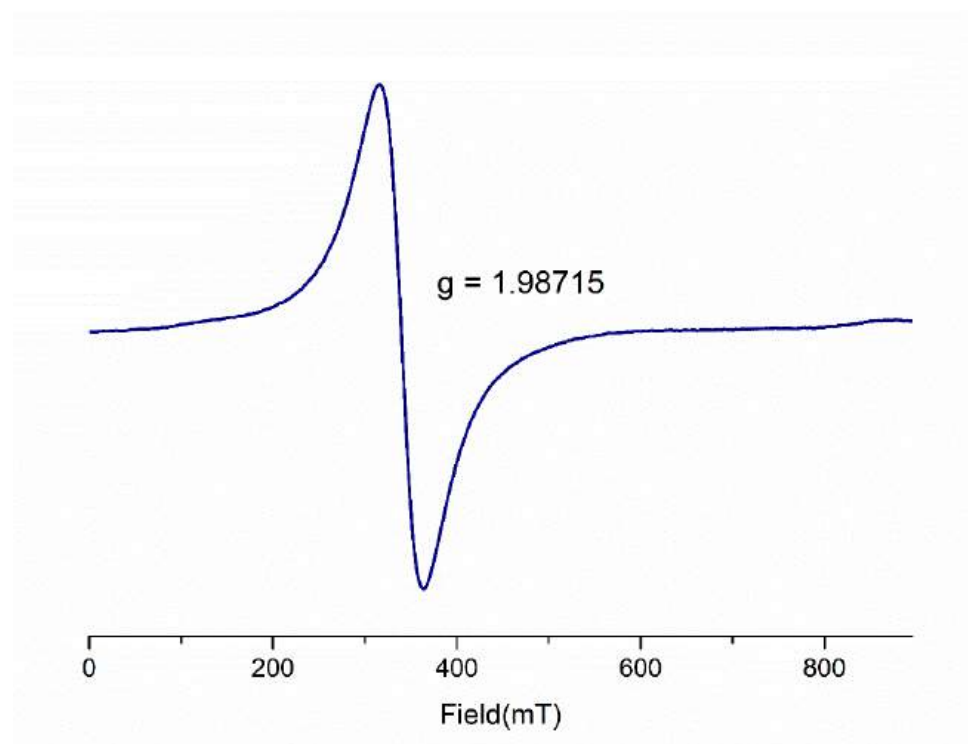


Figure 4.7. The X-band EPR spectra of the complex **4.5d** recorded on a JES-FA200 ESR spectrometer at 77K in methanol with microwave power of 0.998 mW and microwave frequency of 9.14 GHz.

g, 5.4956 mmol, 3.6 M) and acetophenone (1.2 g, 10 mmol, 6.6 M) were added in presence of **4.5b** (0.0013-0.0114 g, 0.003-0.025 mmol, 0.002-0.016 M). The reaction mixture was heated at 160 °C. Aliquots (10 μ L) were collected at regular intervals. The yield of lactate (**4.3'**) was determined from ^1H NMR analysis using sodium acetate as an internal standard and D_2O as NMR solvent.

(b) **Variation in the loading of NaOH:** To each of four round-bottomed flasks, glycerol (0.460 g, 5 mmol, 3.3 M) followed by sodium acetate (0.05 g, 0.6095 mmol, 0.4 M), **4.5b** (0.0114 g, 0.025 mmol, 0.016 M) and acetophenone (1.2 g, 10 mmol, 6.6 M) were added in presence of NaOH (0.05-0.22 g, 1.25-5.5 mmol, 0.8-3.6 M). The reaction mixture was heated at 160 °C. Aliquots (10 μ L) were collected at regular intervals. The yield of lactate (**4.3'**) was determined from ^1H NMR analysis using sodium acetate as an internal standard and D_2O as NMR solvent.

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Appendix C

C1. Representative GC Spectra

GC analysis (TCD detection) was performed on a Agilent 7820-GC instrument fitted with Agilent Front SS7 inlet N2 HP-PLOT Q column (30 m length x 530 μm x 40 μm ID) using the following method:

Agilent 7820-GC Detector TCD

starting temperature 40 °C

Oven temperature 70 °C

Time at starting temp: 0 min

Hold time = 5 min

Ramp : 40 °C/min up to 250 °C

Flow rate (carrier): 25 mL/min (N₂)

Split ratio: 195

Inlet temperature: 40 °C

Detector temperature: TCD: 250 °C

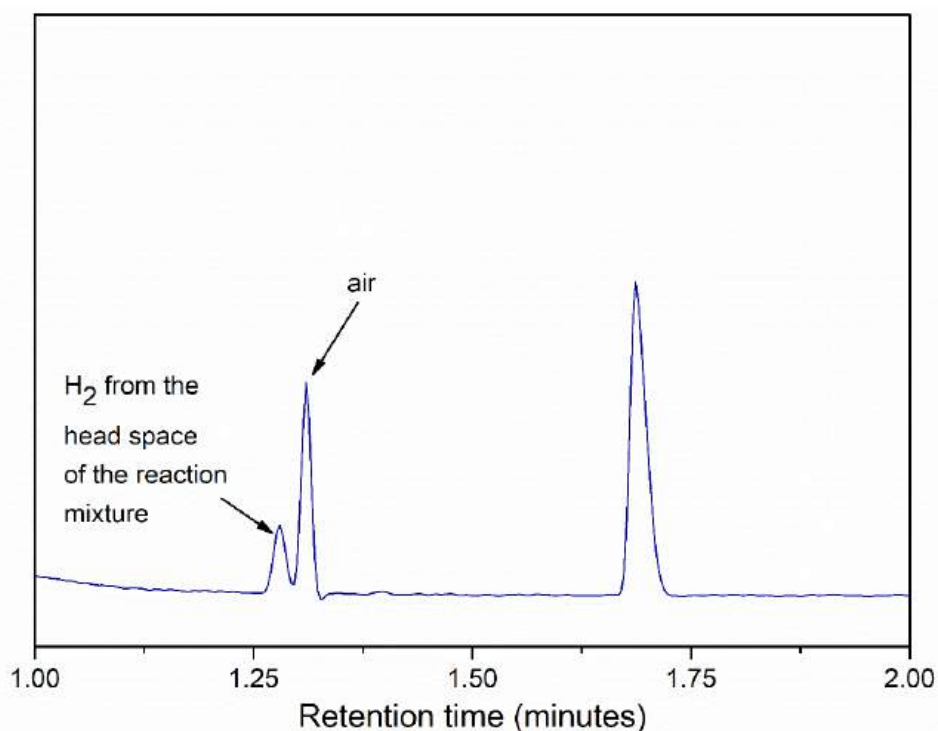


Figure C1a. GC data of the head space of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃·6H₂O, 1.1 equivalent KOH, at 160 °C. (entry 4, Table 4.2).

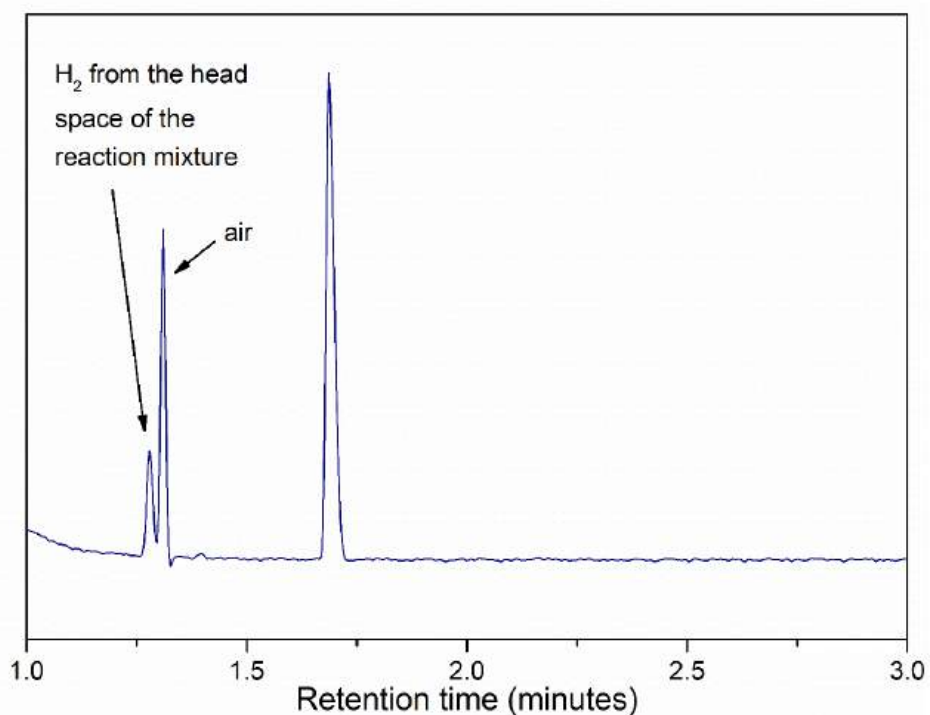


Figure C1b. GC data of the head space of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **5b**, 1.1 equivalent NaOH, at 160 °C. (entry 28, Table 4.2).

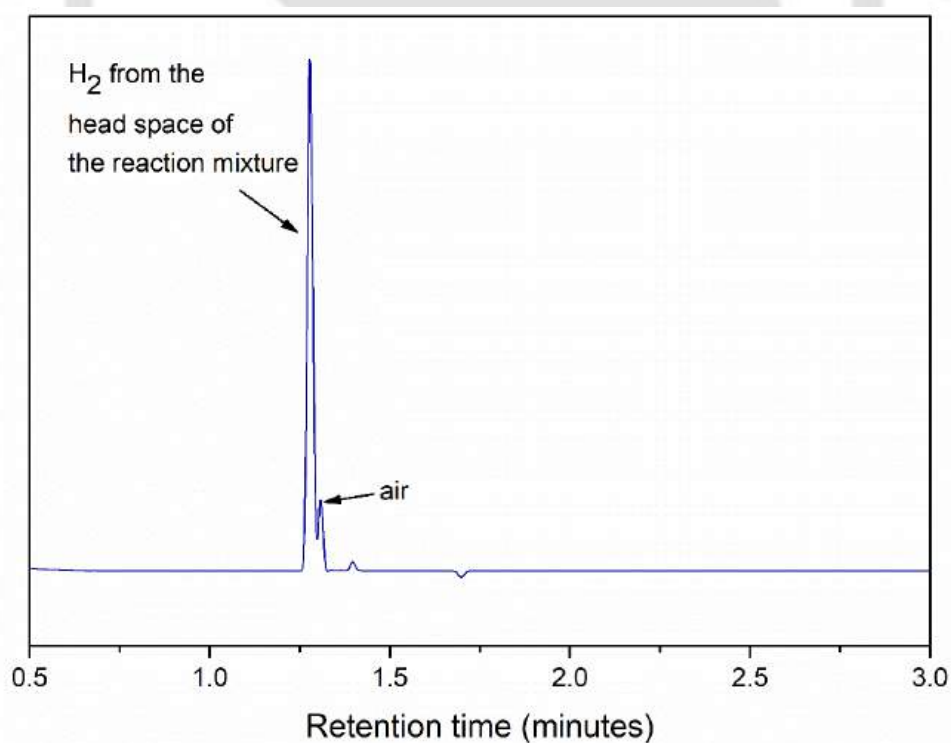


Figure C1c. GC data of the head space of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.75 mol% **5b**, 1.1 equivalent NaOH, at 160 °C. (entry 31, Table 4.2).

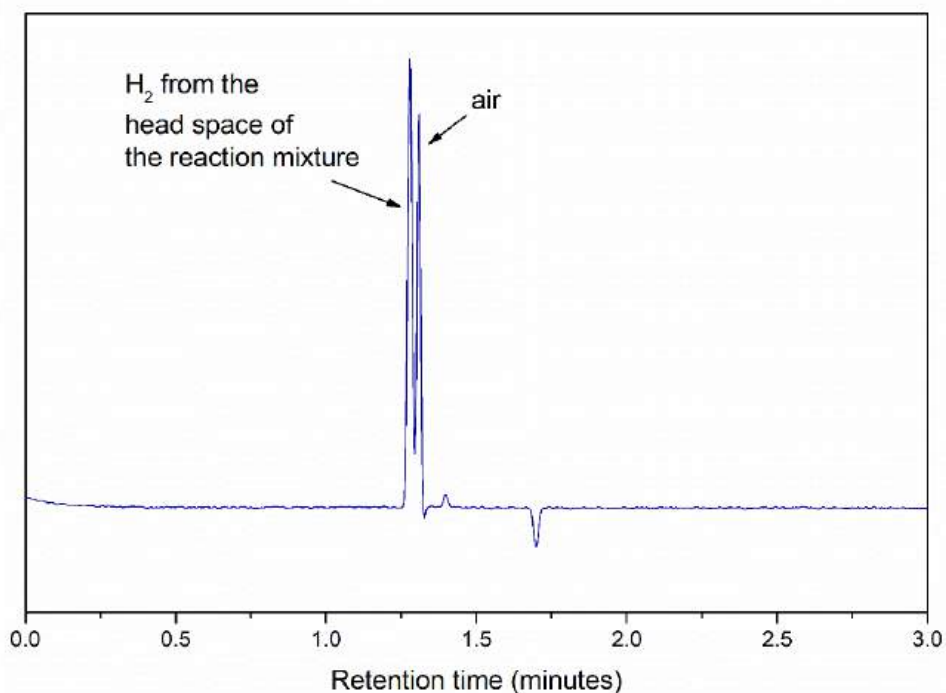


Figure C1d. GC data of the head space of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.25 mol% **5b**, 1.1 equivalent NaOH, at 160 °C. (entry 32, Table 4.2).

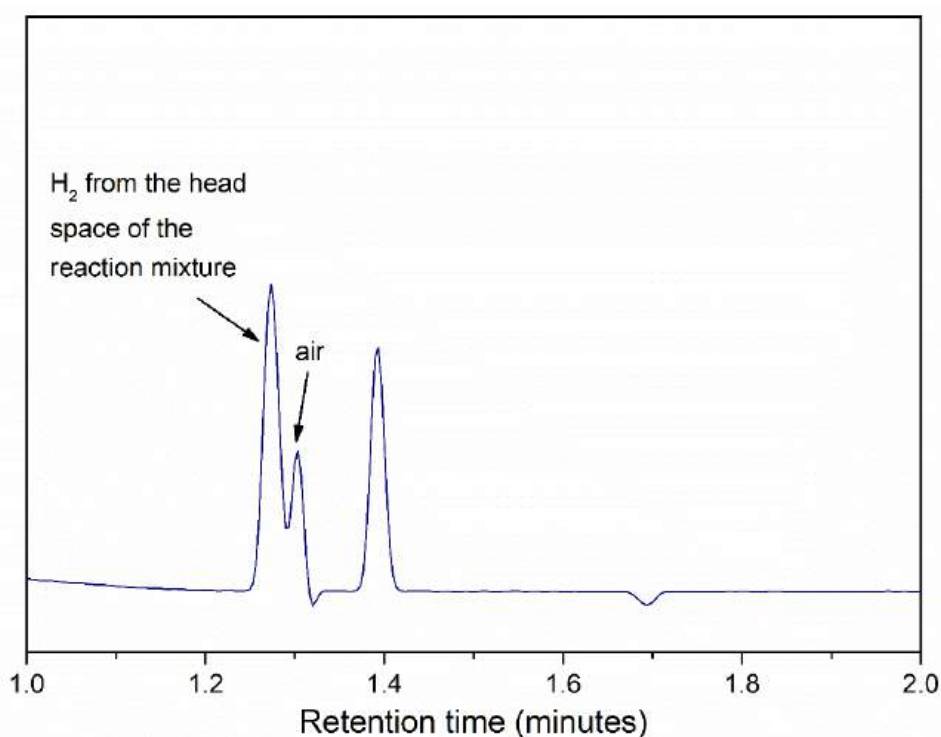


Figure C1e. GC data of the head space of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.05 mol% **5b**, 1.1 equivalent NaOH, at 160 °C. (entry 33, Table 4.2).

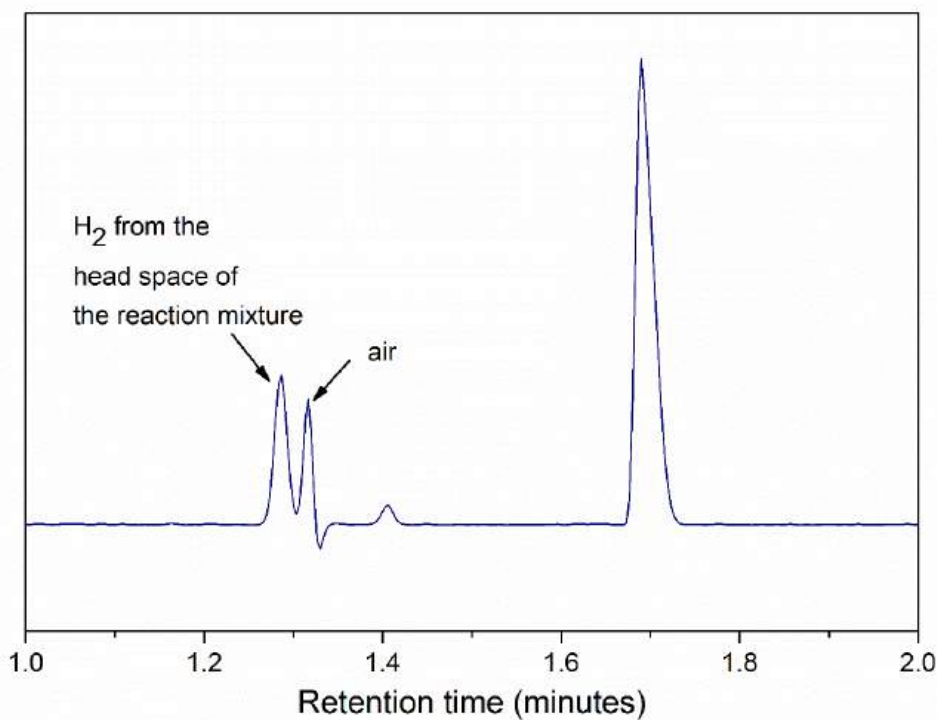


Figure C1f. GC data of the head space of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.005 mol% **5b**, 1.1 equivalent NaOH, at 160 °C. (entry 34, Table 4.2).

C2. NMR spectra of crude reaction mixture

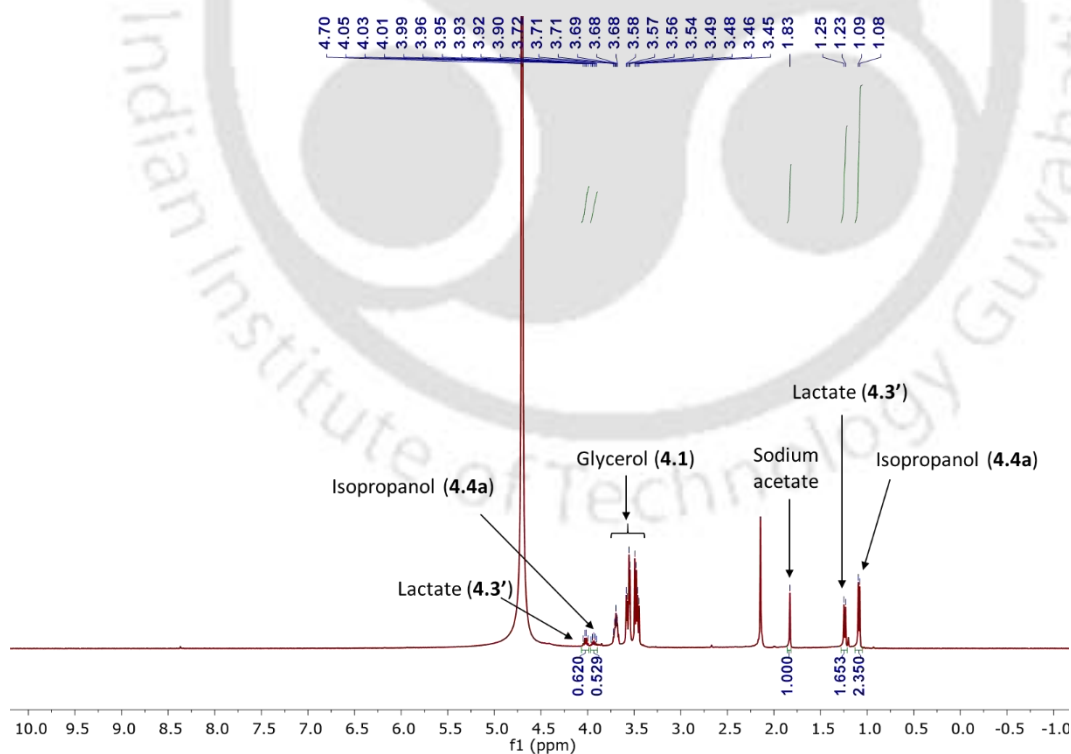


Figure C2: 1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% $CrCl_3 \cdot 6H_2O$, 0.5 equivalents KOH, at 160 °C (entry 1, Table 4.2).

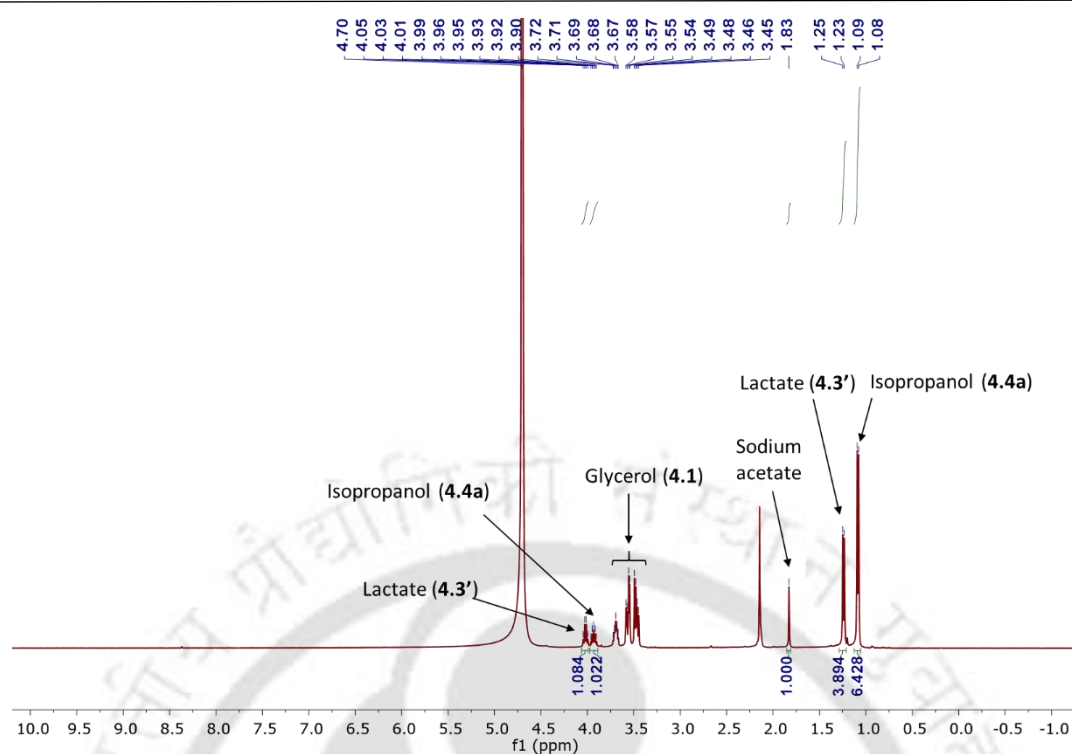


Figure C3: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃.6H₂O, 0.75 equivalents KOH, at 160 °C (entry 2, Table 4.2).

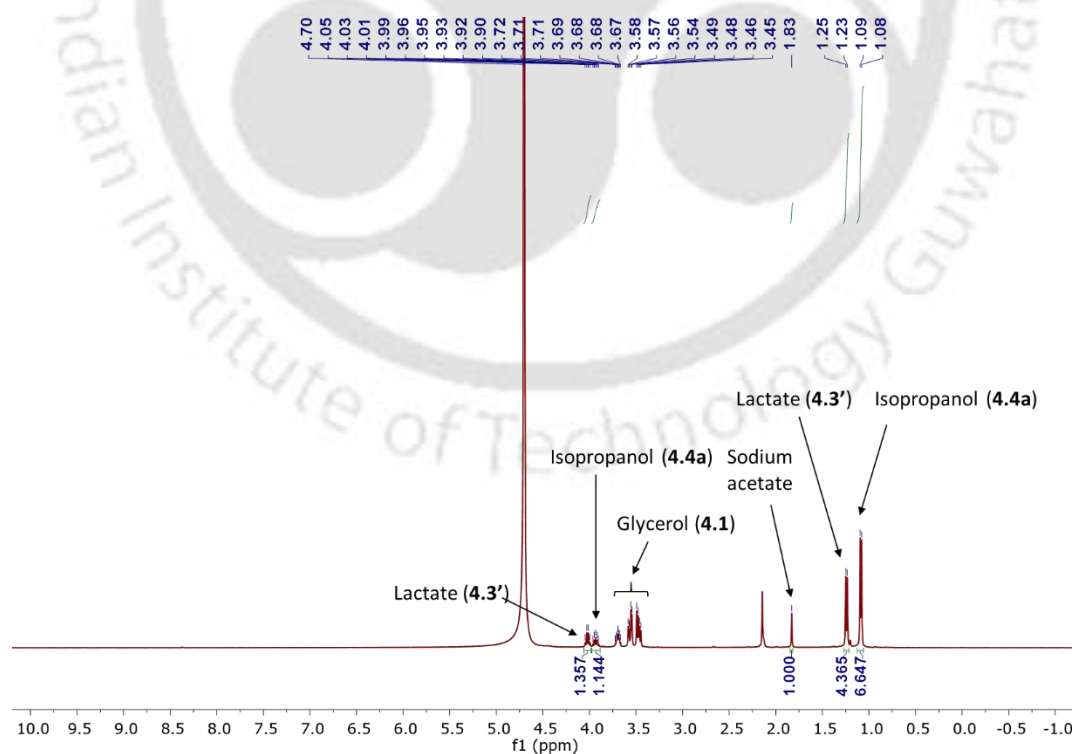


Figure C4: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃.6H₂O, 1 equivalent KOH, at 160 °C (entry 3, Table 4.2).

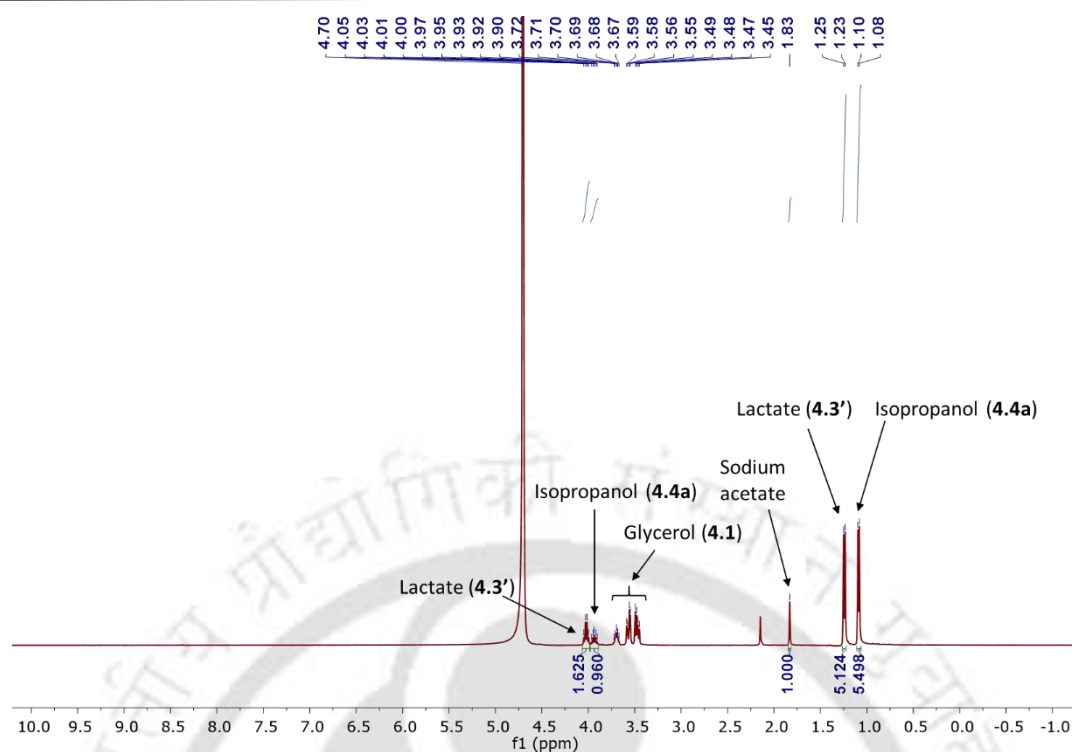


Figure C5: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃.6H₂O, 1.1 equivalents KOH, at 160 °C (entry 4, Table 4.2).

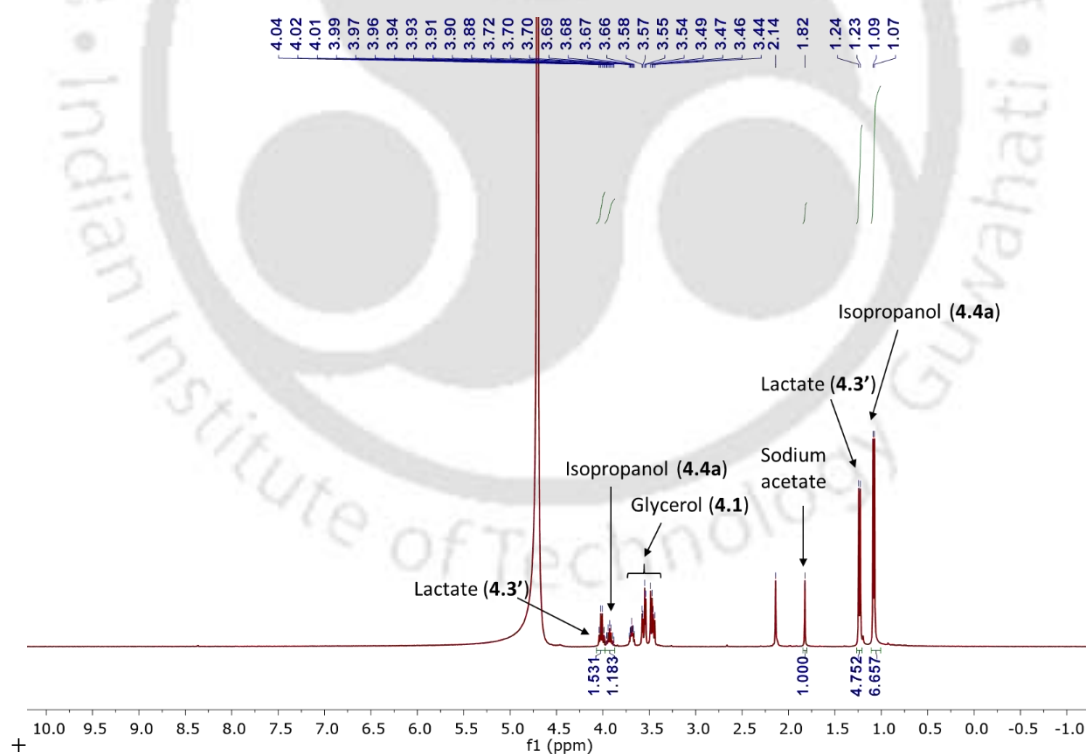


Figure C6: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃.6H₂O, 1.2 equivalents KOH, at 160 °C (entry 5, Table 4.2).

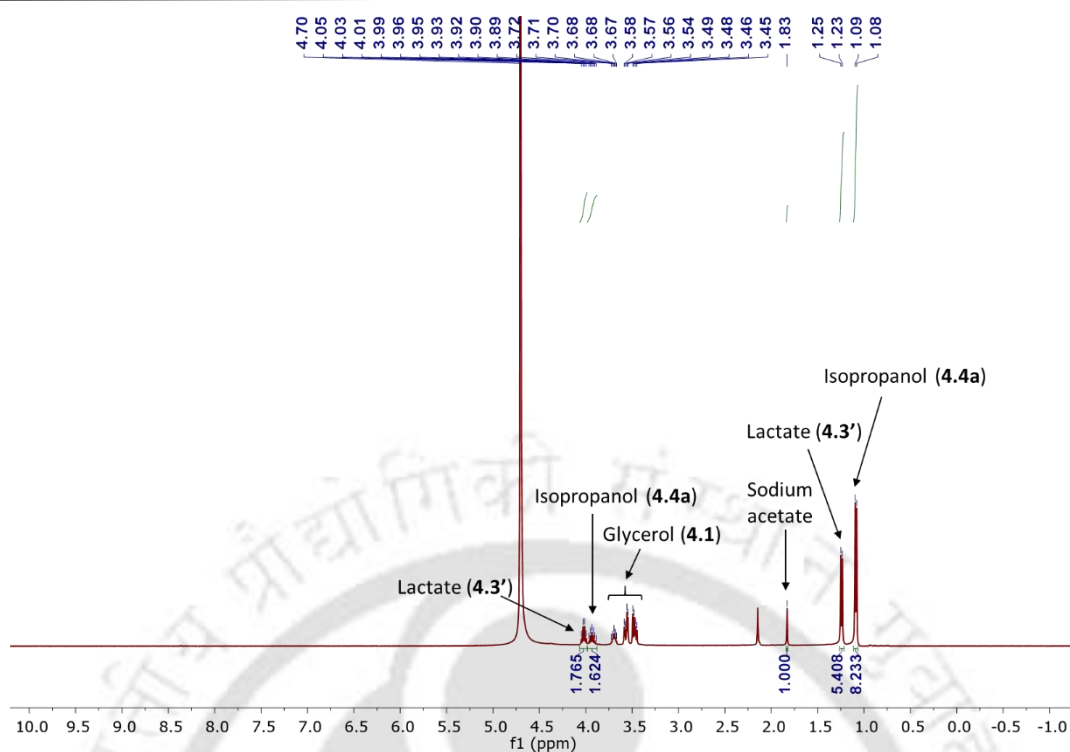


Figure C7: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.3 equivalents KOH, at 160 °C (entry 6, Table 4.2).

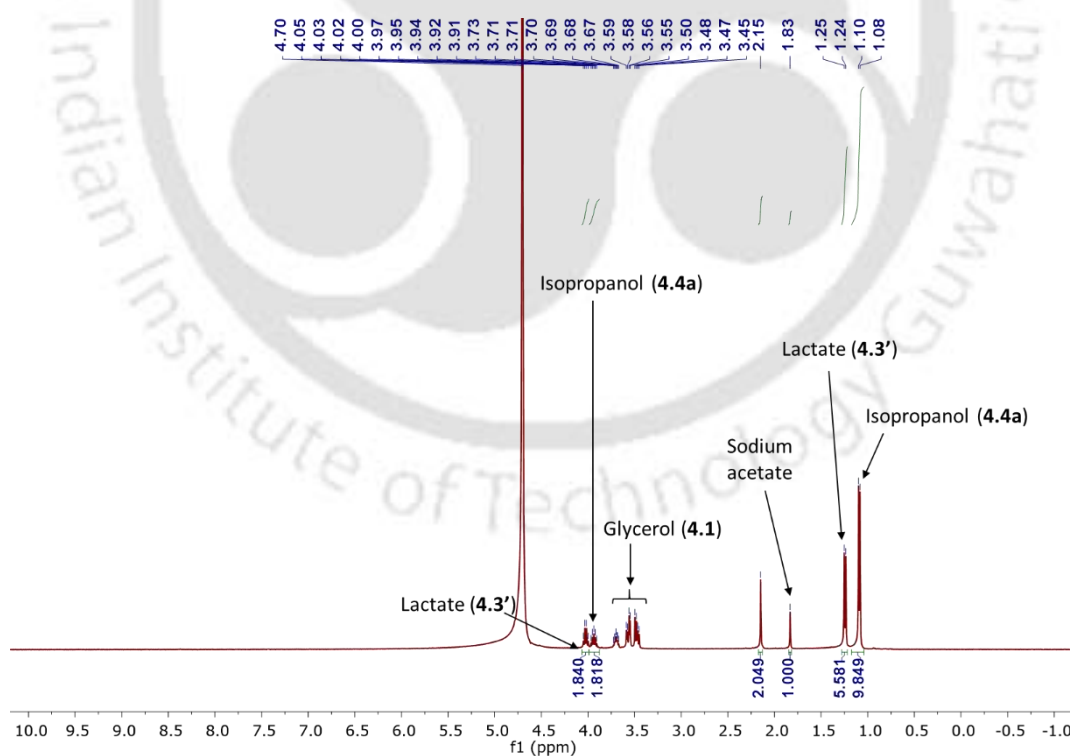


Figure C8: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.75 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH, at 160 °C (entry 7, Table 4.2).

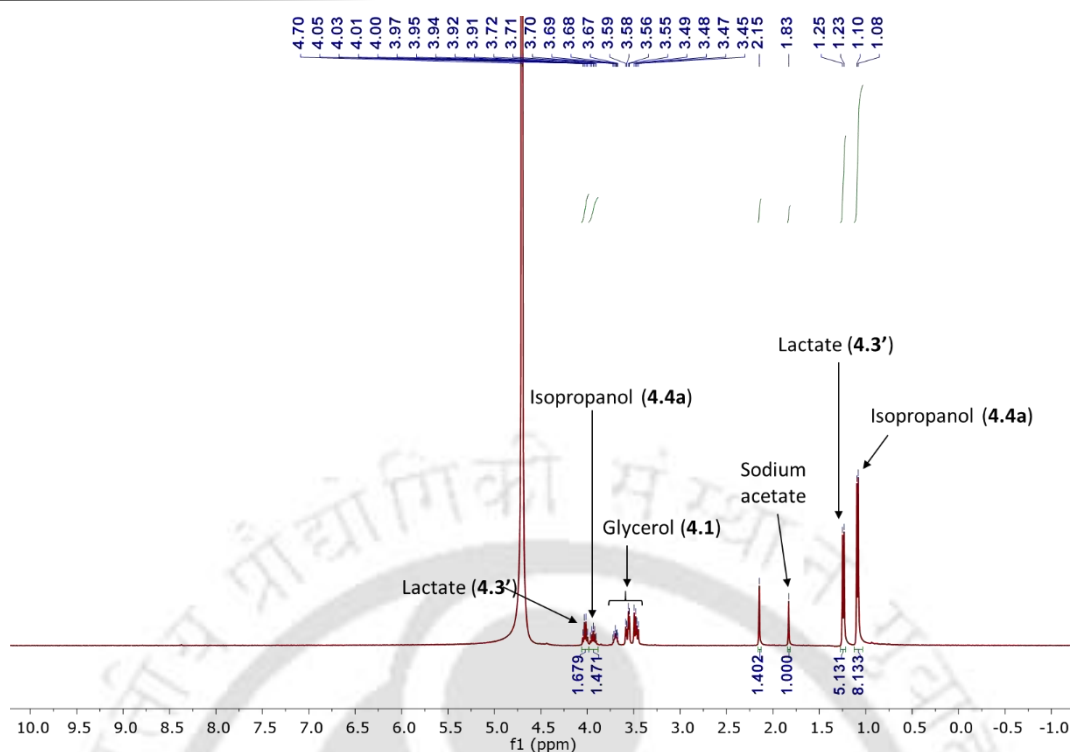


Figure C9: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.25 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH, at 160 °C (entry 8, Table 4.2).

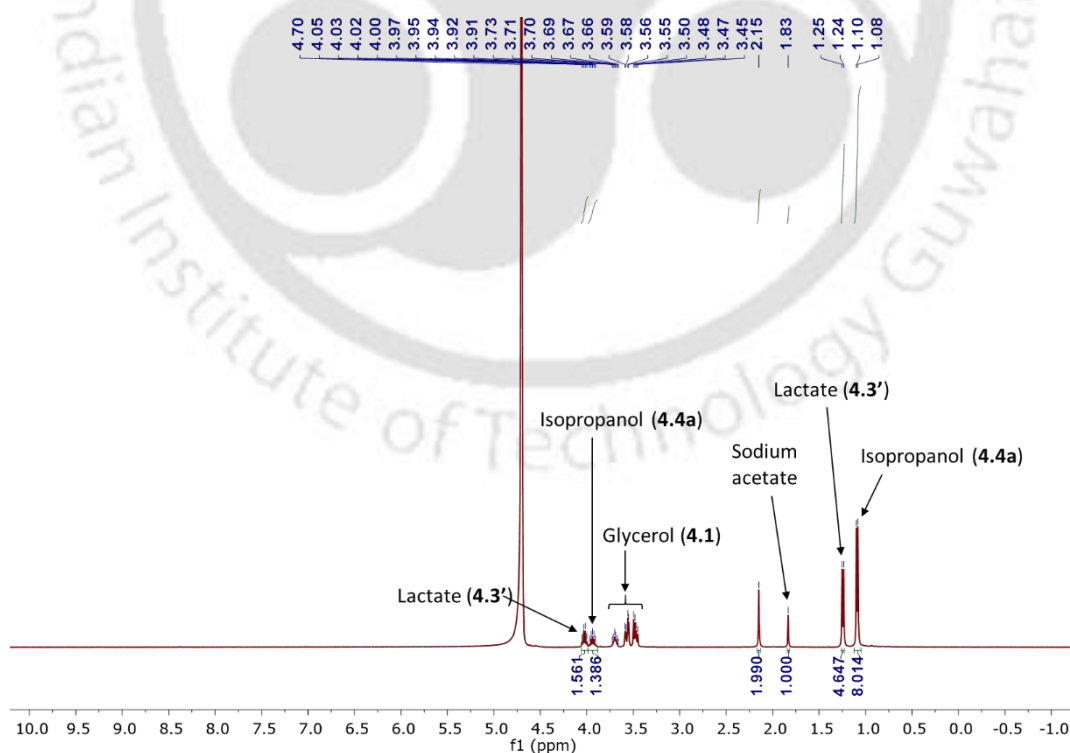


Figure C10: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.1 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH, at 160 °C (entry 9, Table 4.2).

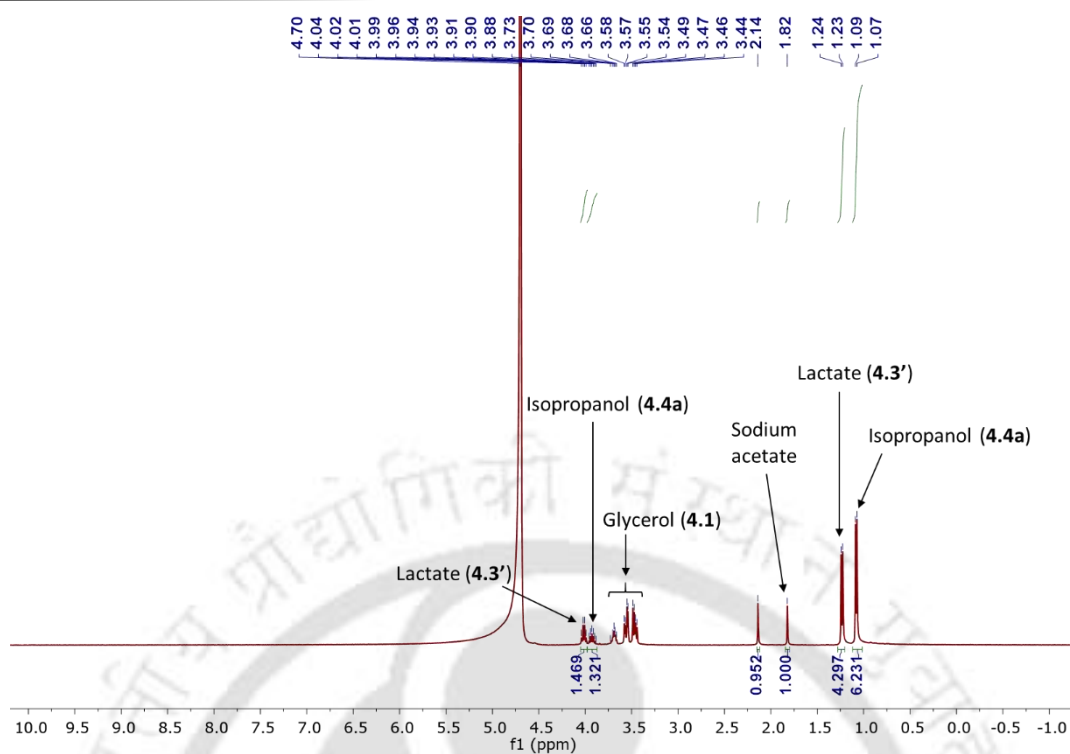


Figure C11: ¹H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.075 mol% CrCl₃·6H₂O, 1.1 equivalents KOH, at 160 °C (entry 10, Table 4.2).

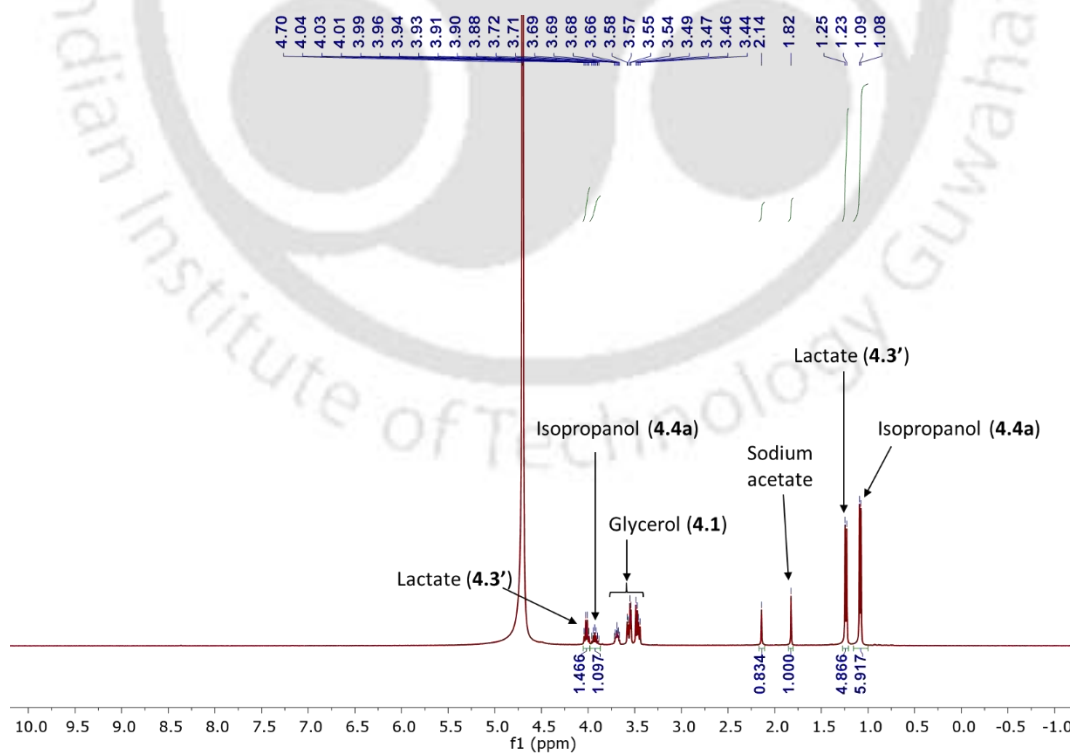


Figure C12: ¹H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.05 mol% CrCl₃·6H₂O, 1.1 equivalents KOH, at 160 °C (entry 11, Table 4.2).

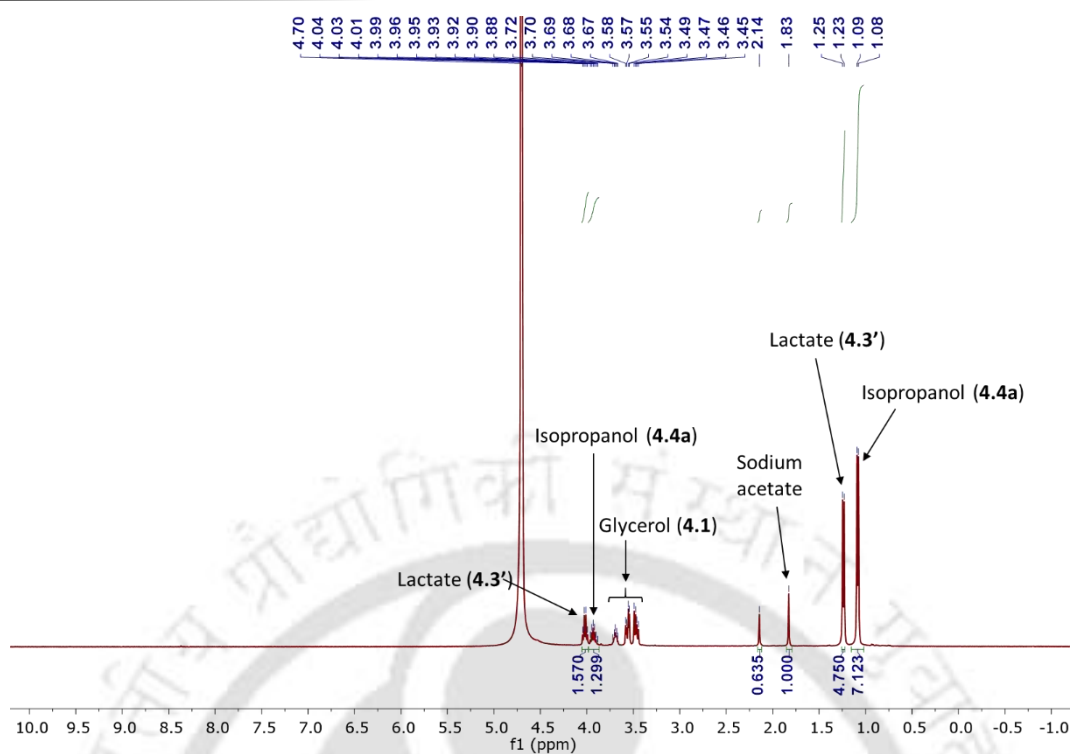


Figure C13: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.025 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH, at 160 °C (entry 12, Table 4.2).

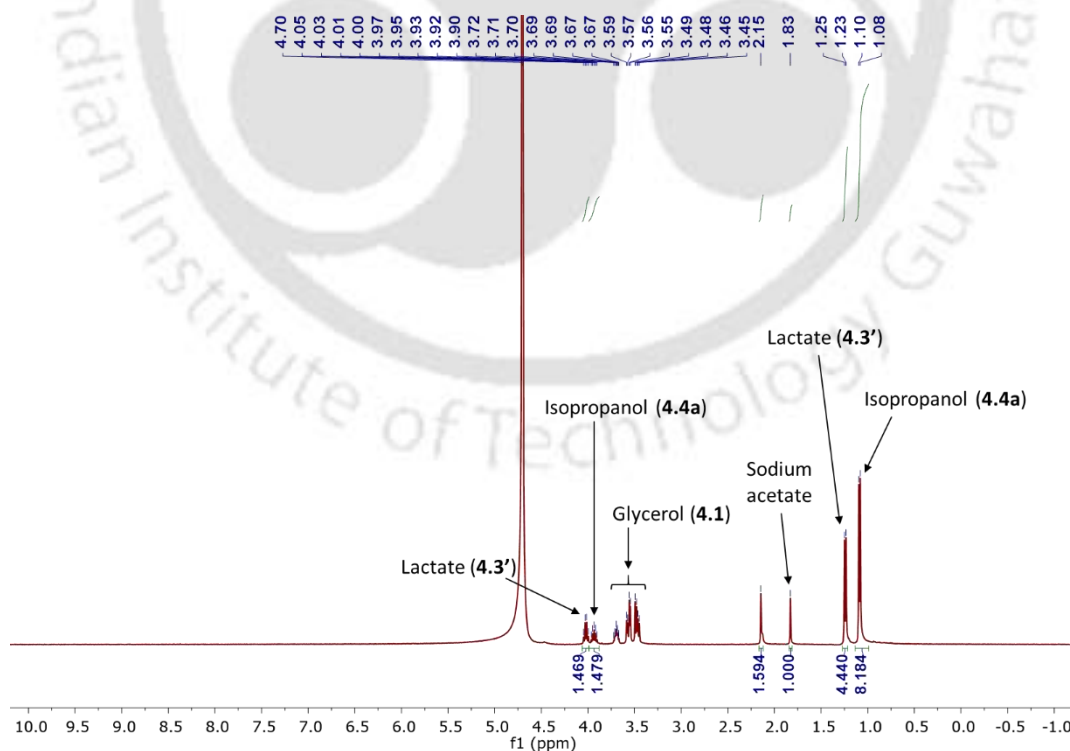


Figure C14: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.01 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH, at 160 °C (entry 13, Table 4.2).

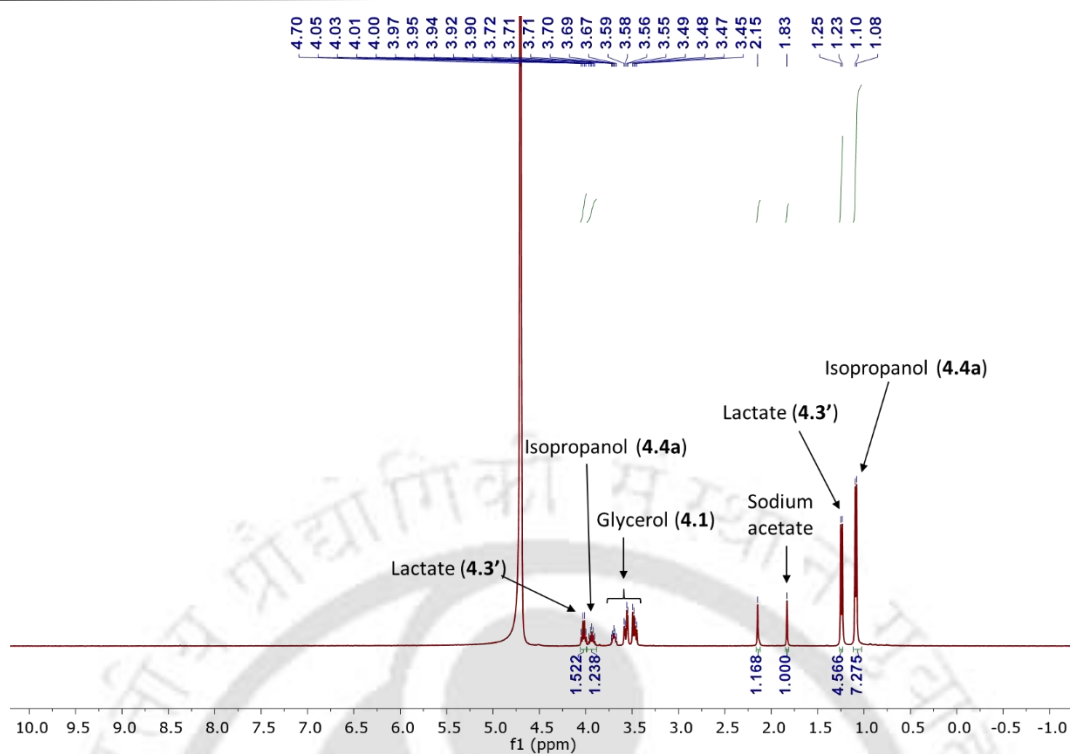


Figure C15: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.0075 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH, at 160 °C (entry 14, Table 4.2).

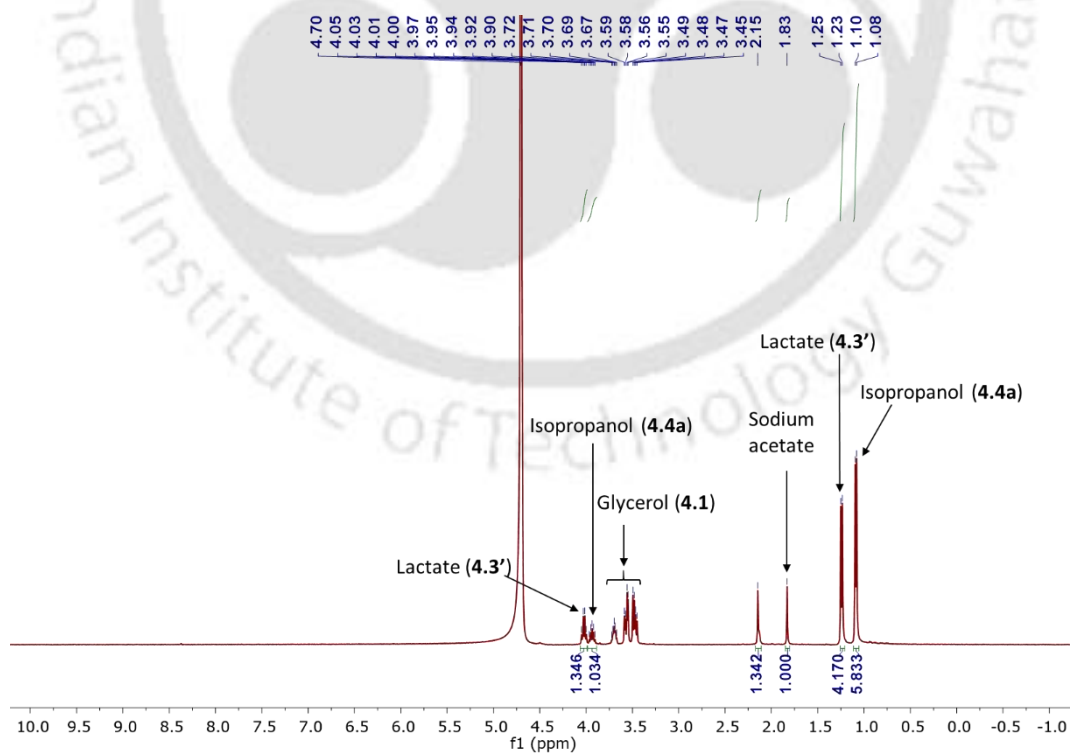


Figure C16: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.005 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH, at 160 °C (entry 15, Table 4.2).

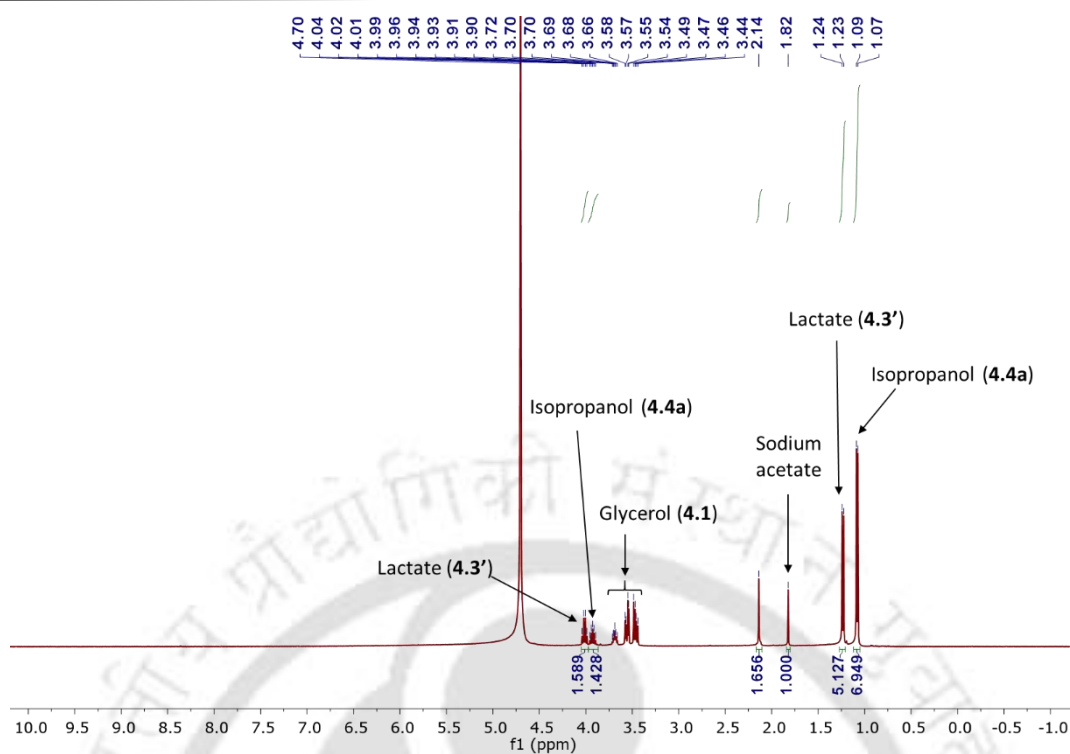


Figure C17: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.0025 mol% CrCl₃·6H₂O, 1.1 equivalents KOH, 1.5 equivalents acetone, at 160 °C (entry 17, Table 4.2).

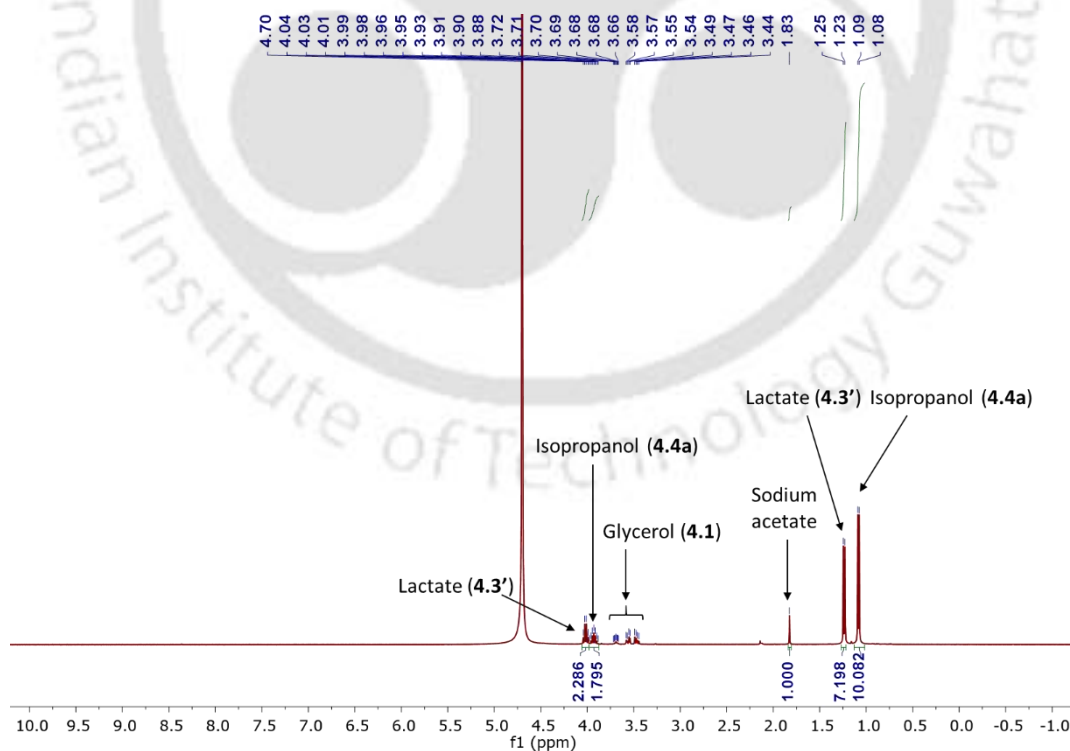


Figure C18: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃·6H₂O, 1.1 equivalents NaOH, at 160 °C (entry 18, Table 4.2).

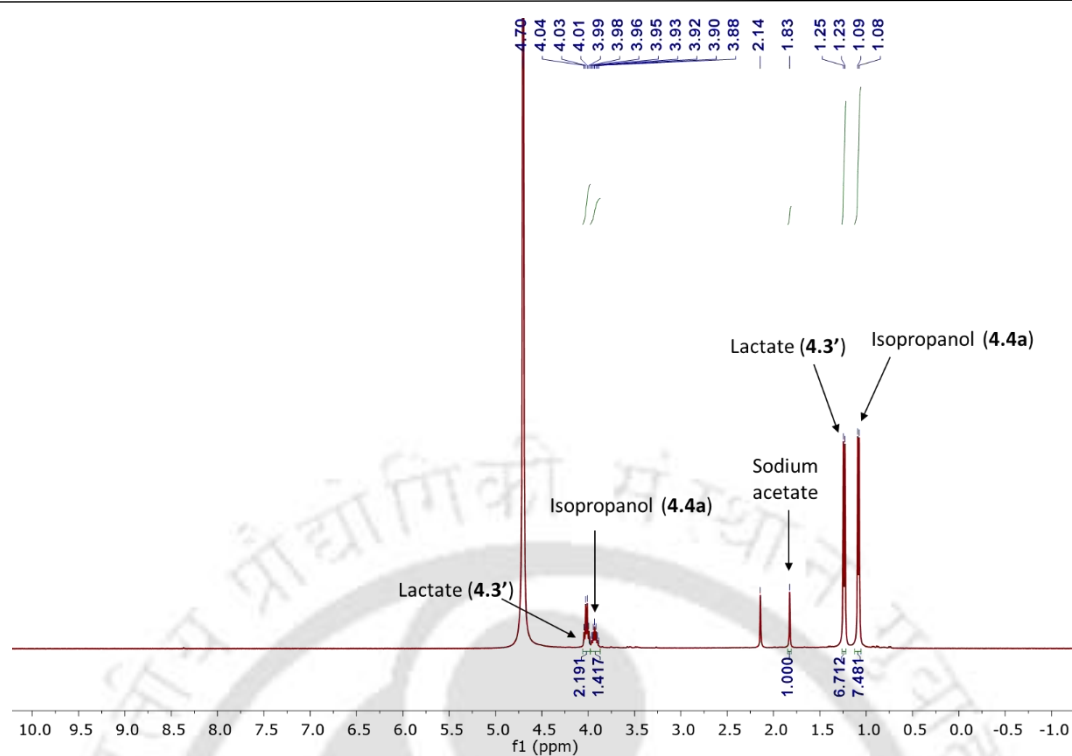


Figure C19: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents NaOH , 1.5 equivalents acetone (4.2a), at 160 °C (entry 19, Table 4.2).

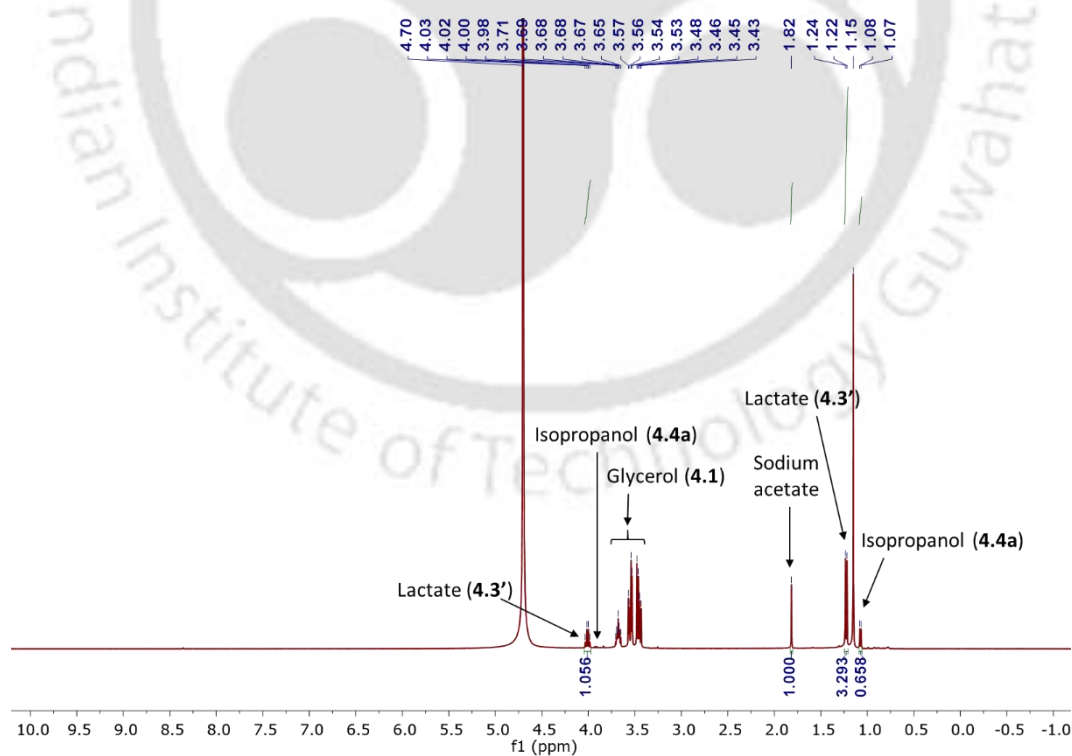


Figure C20: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents NaO^iBu , at 160 °C (entry 20, Table 4.2).

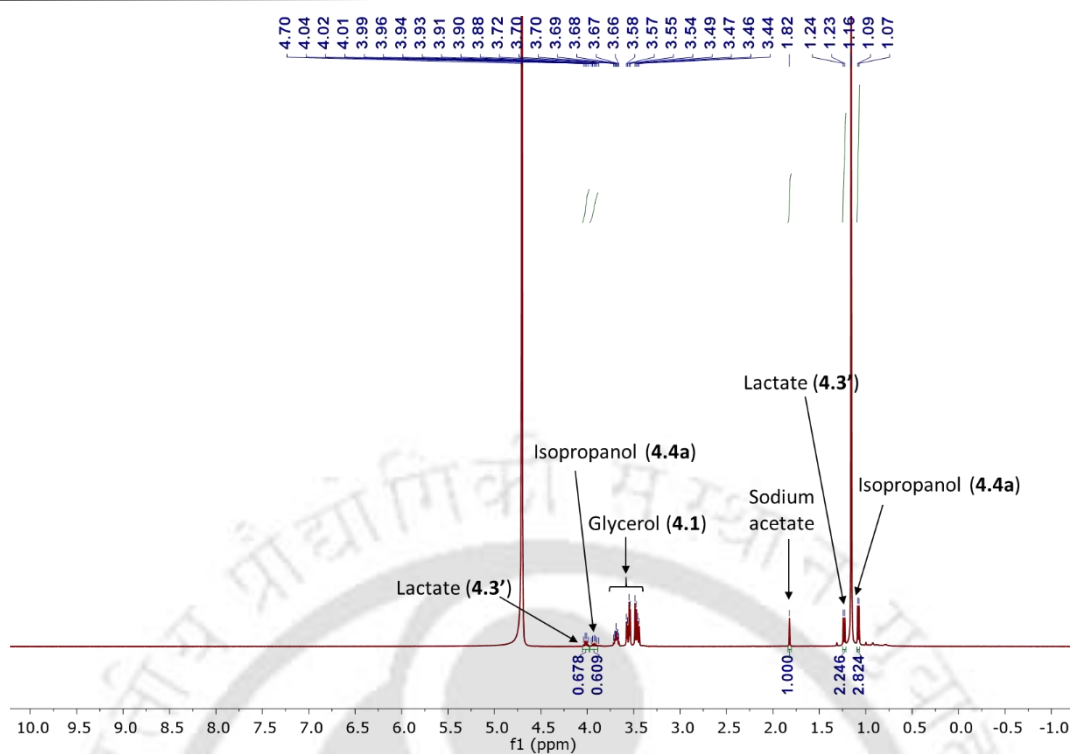


Figure C21: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃·6H₂O, 1.1 equivalents KO^tBu, at 160 °C (entry 21, Table 4.2).

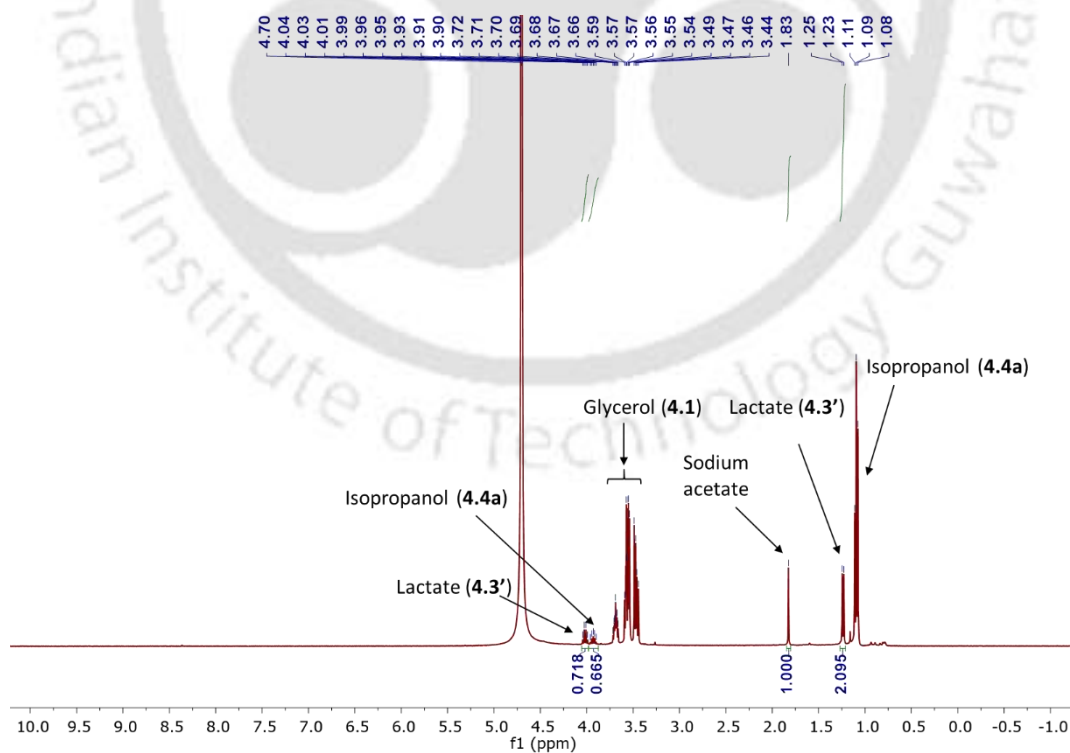


Figure C22: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% CrCl₃·6H₂O, 1.1 equivalents NaOEt, at 160 °C (entry 22, Table 4.2).

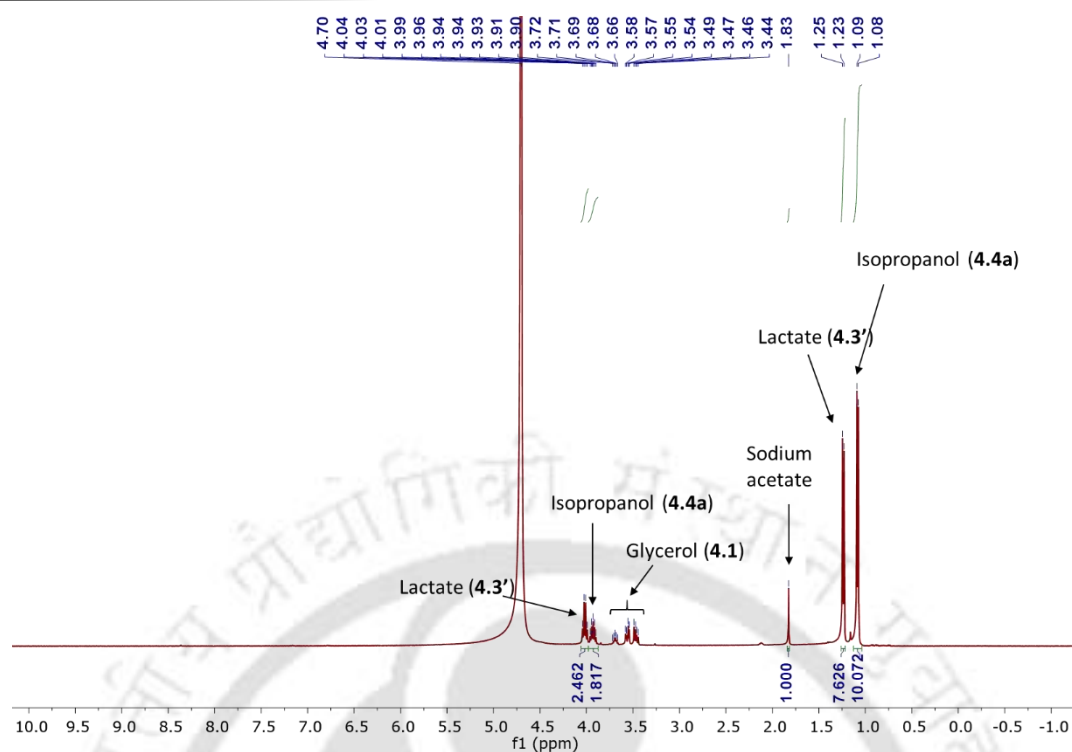


Figure C23: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5a**, 1.1 equivalents NaOH, at 160 °C (entry 27, Table 4.2).

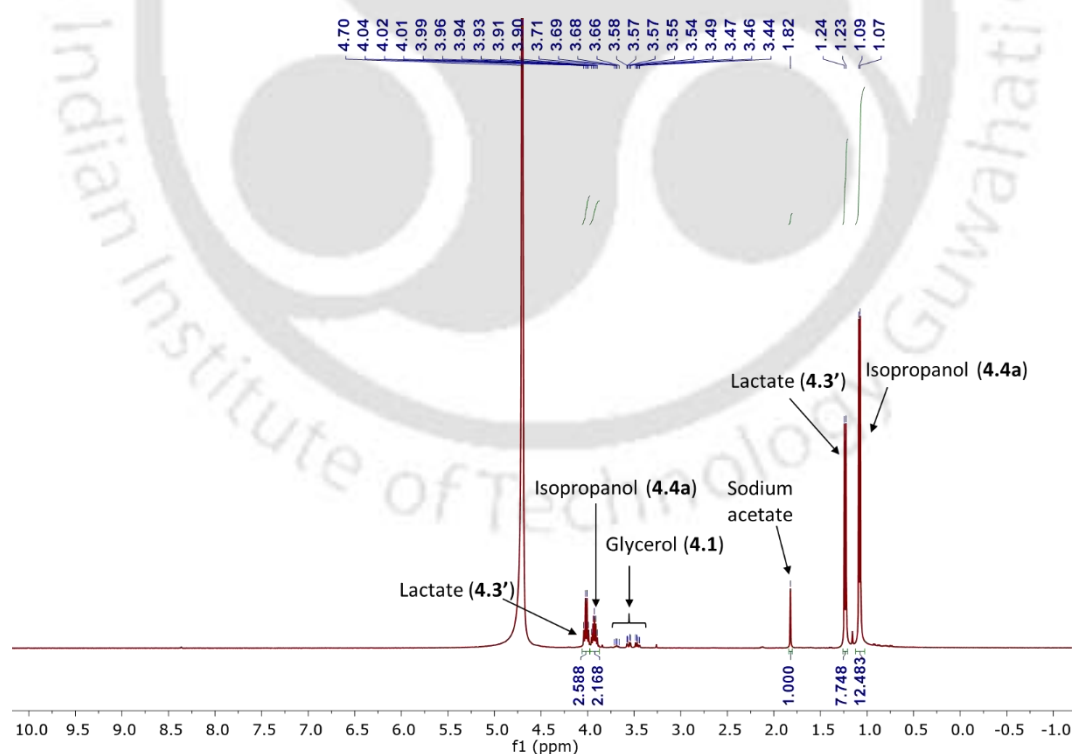


Figure C24: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, at 160 °C (entry 28, Table 4.2).

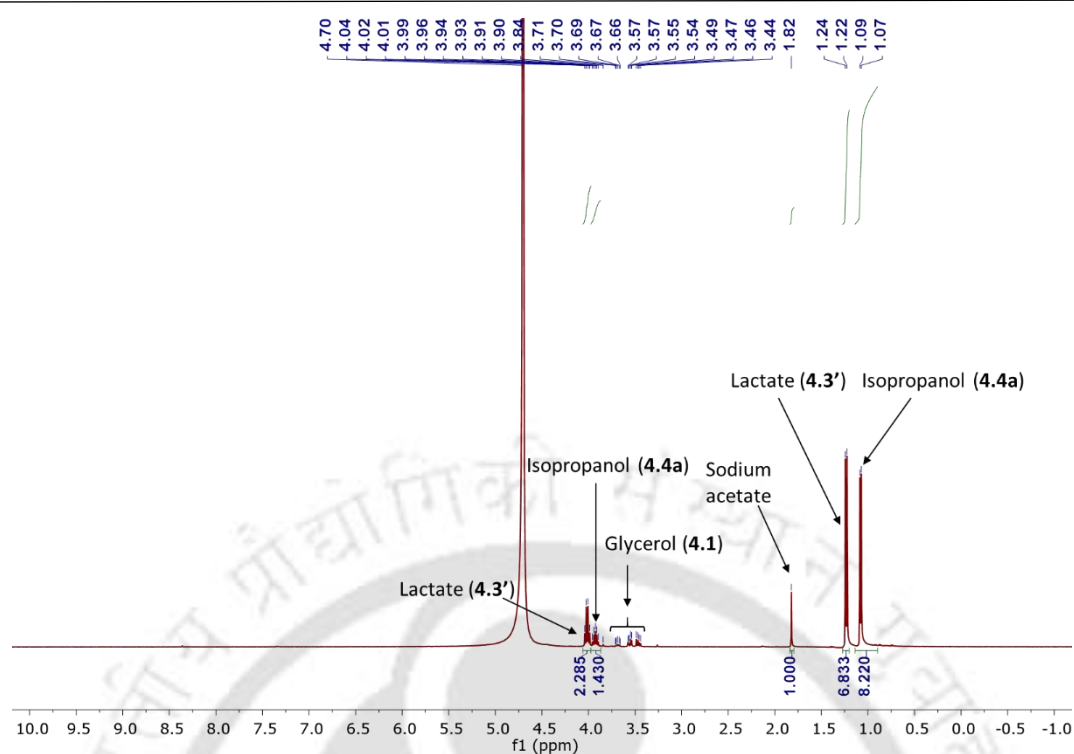


Figure C25: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% 4.5c, 1.1 equivalents NaOH, at 160 °C (entry 29, Table 4.2).

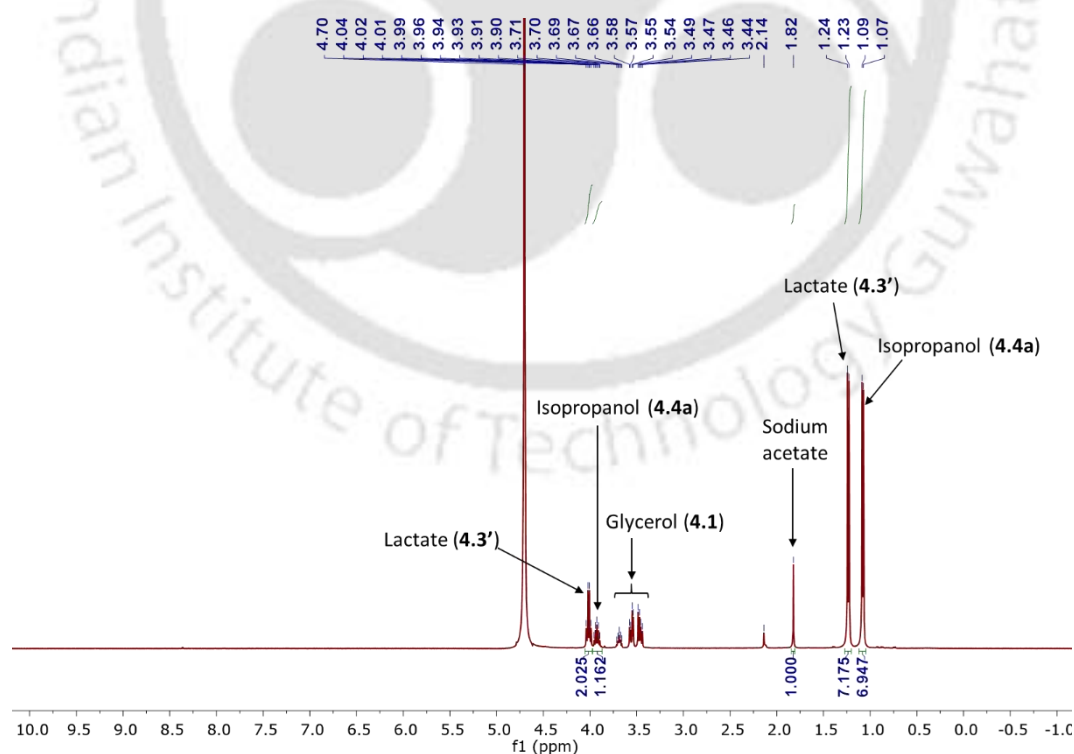


Figure C26: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% 4.5d, 1.1 equivalents NaOH, at 160 °C (entry 30, Table 4.2).

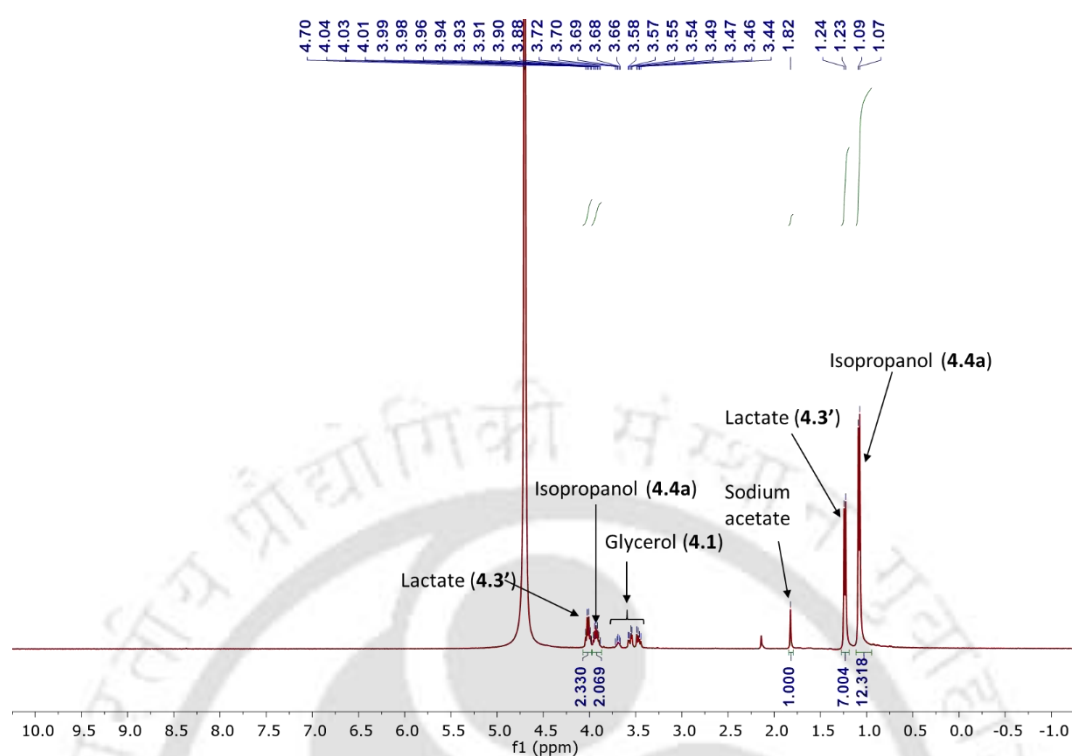


Figure C27: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.75 mol% **4.5b**, 1.1 equivalents NaOH, at 160 °C (entry 31, Table 4.2).

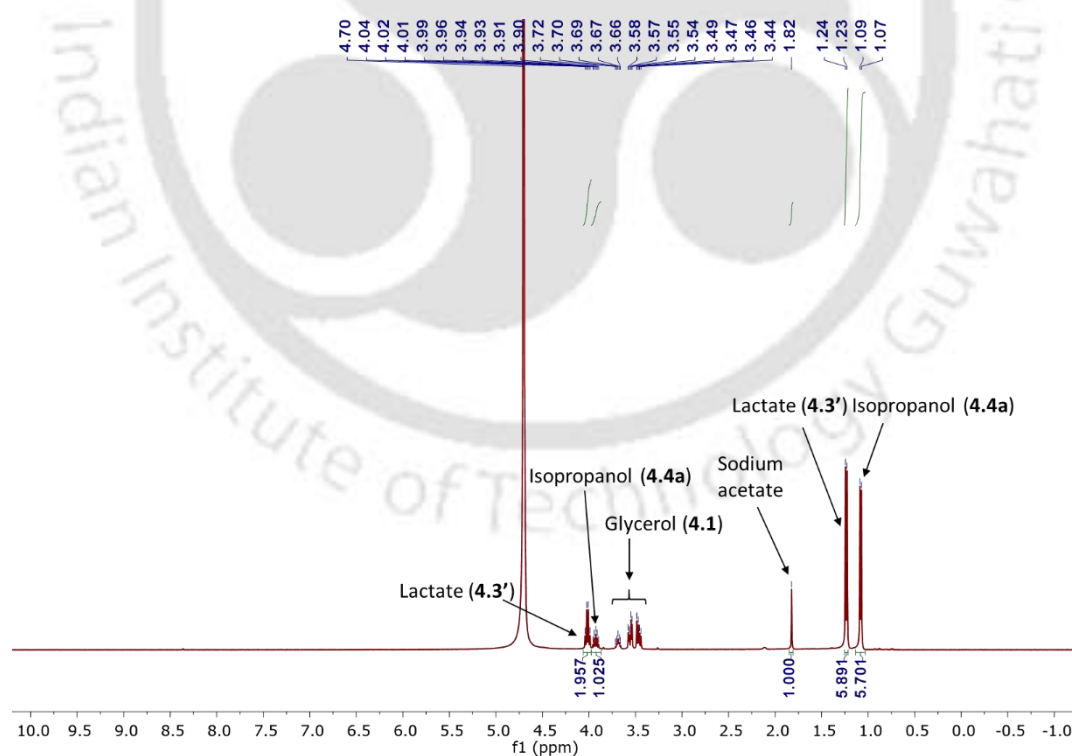


Figure C28: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.25 mol% **4.5b**, 1.1 equivalents NaOH, at 160 °C (entry 32, Table 4.2).

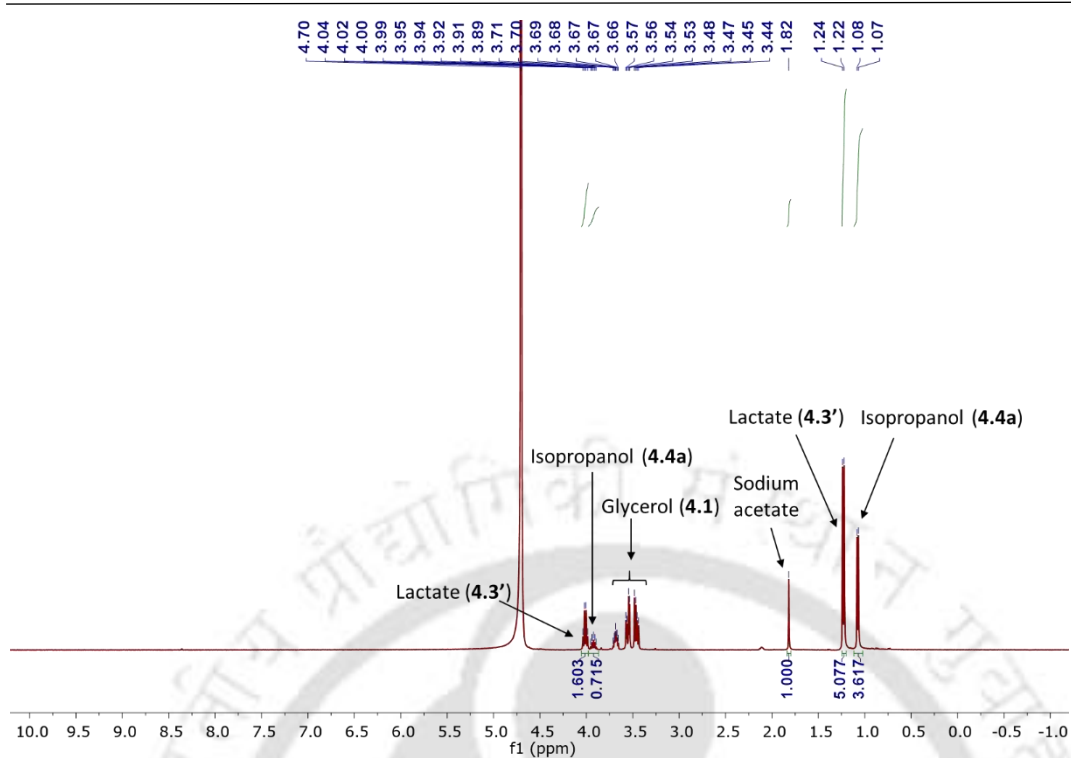


Figure C29: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.05 mol% **4.5b**, 1.1 equivalents NaOH, at 160 °C (entry 33, Table 4.2).

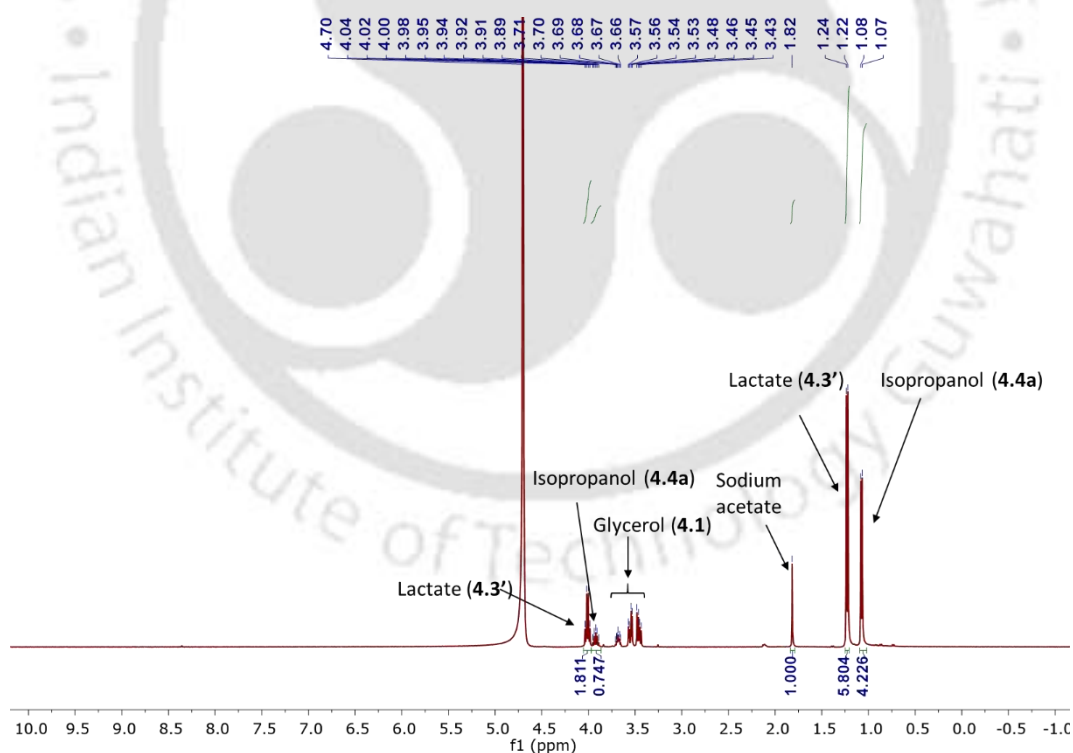


Figure C30: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.005 mol% **4.5b**, 1.1 equivalents NaOH, at 160 °C (entry 34, Table 4.2).

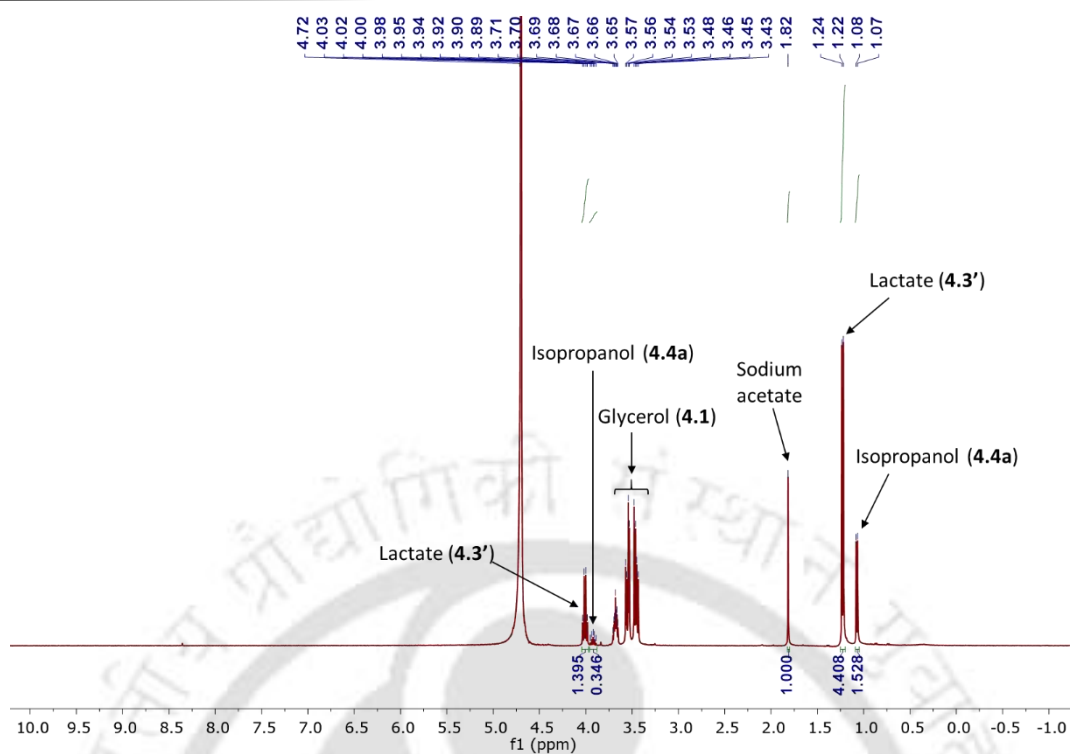


Figure C31: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.00125 mol% **4.5b**, 1.1 equivalents NaOH, at 160 °C (entry 35, Table 4.2).

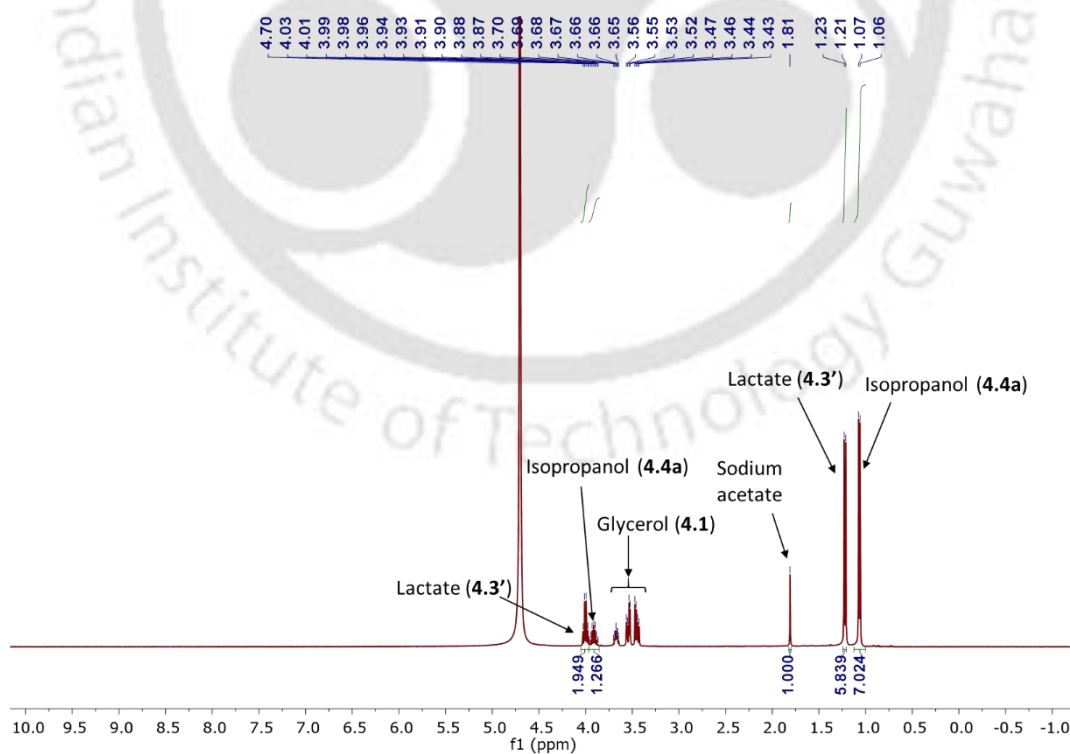


Figure C32: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, at 140 °C (entry 36, Table 4.2).

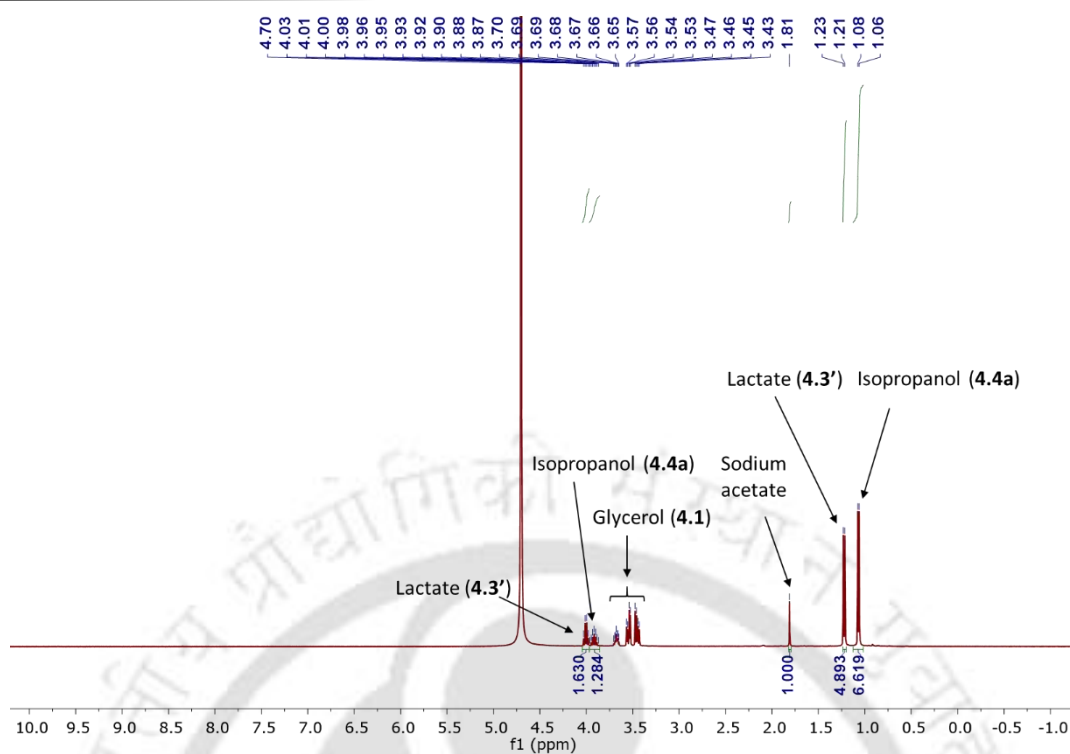


Figure C33: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, at 120 °C (entry 37, Table 4.2).

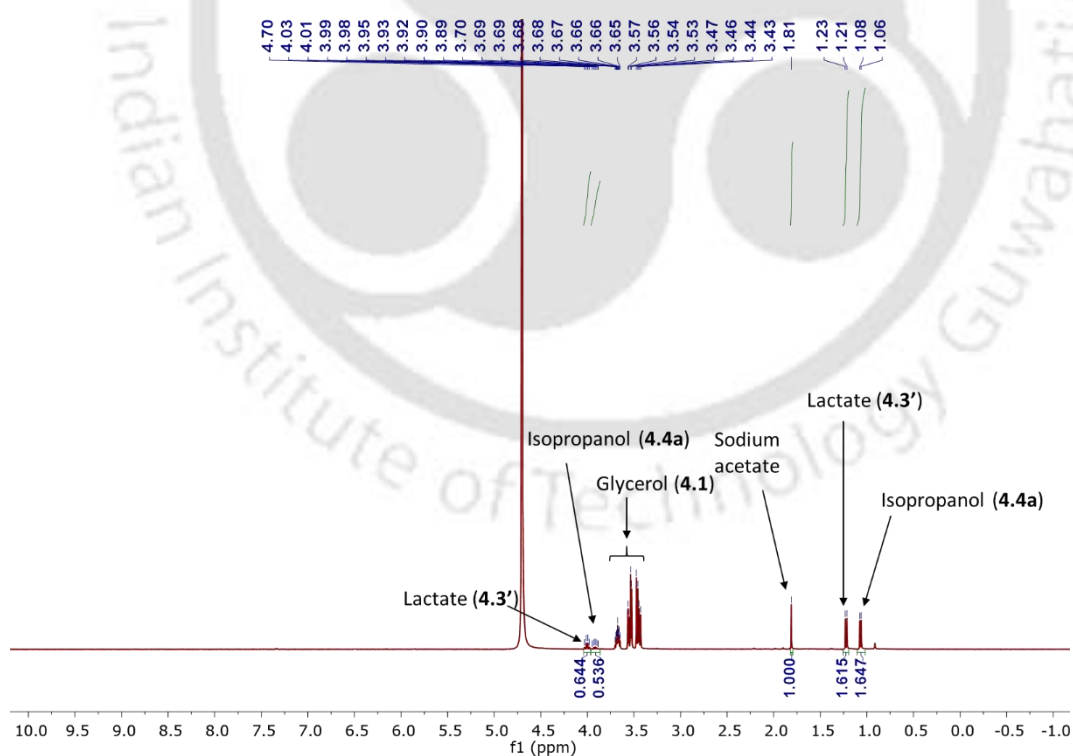


Figure C34: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, at 100 °C (entry 38, Table 4.2).

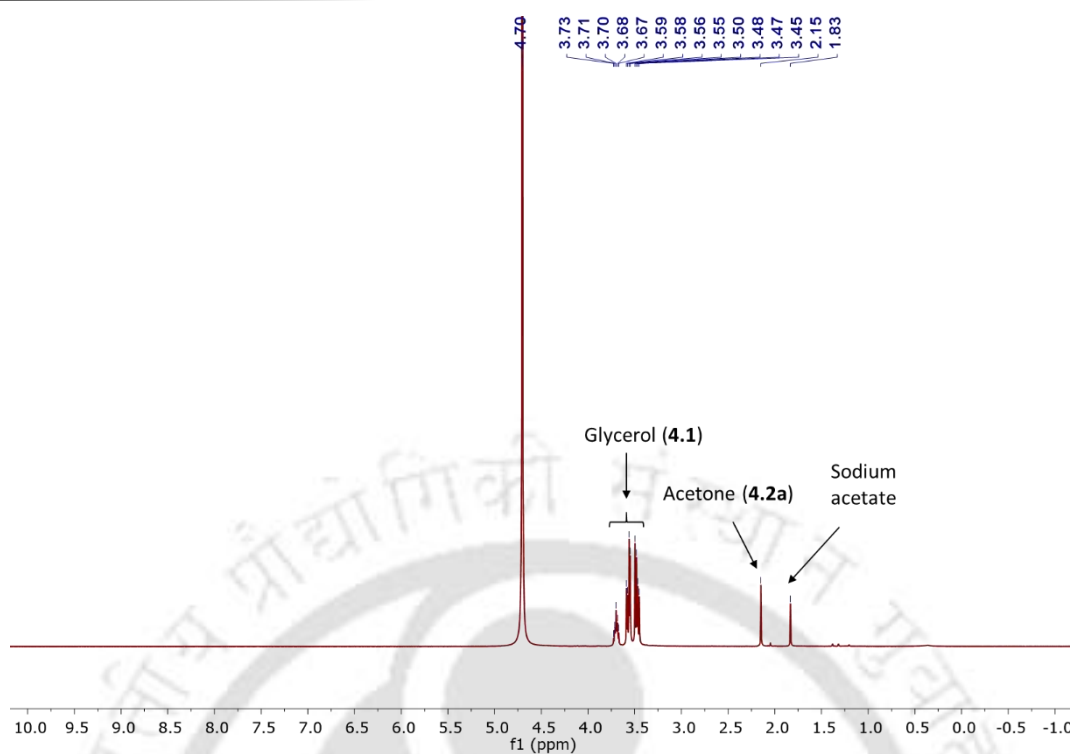


Figure C35: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, in presence of **4.2a** (entry 2, Table 4.3).

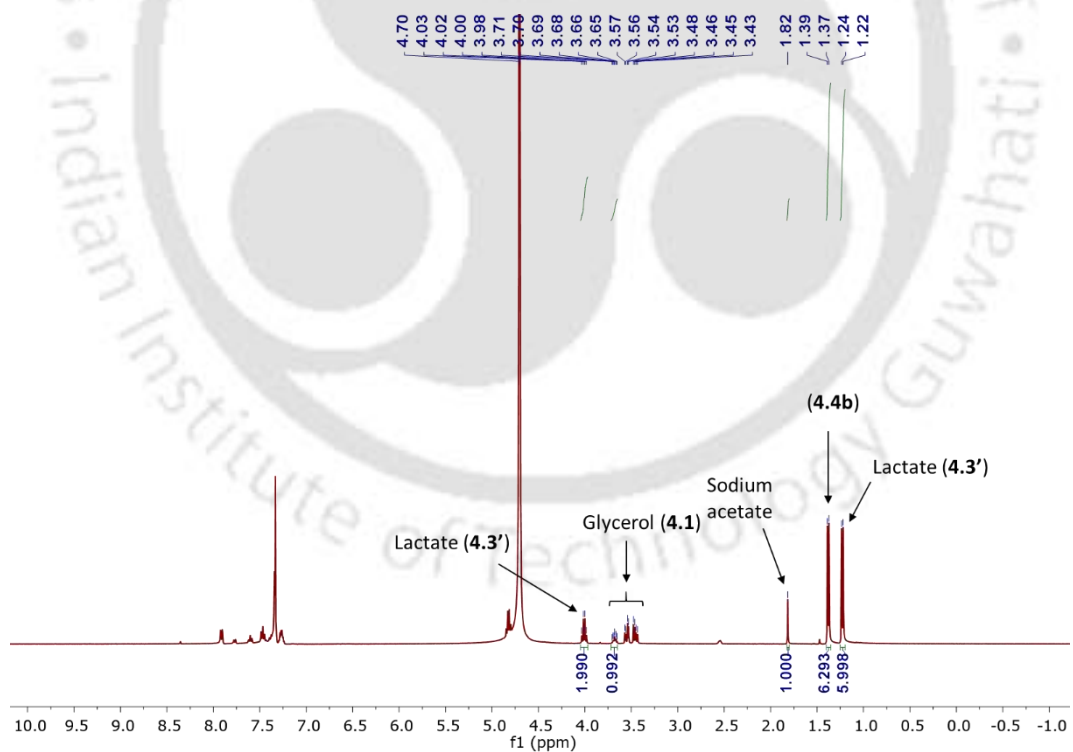


Figure C36: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2b** (entry 4, Table 4.3).

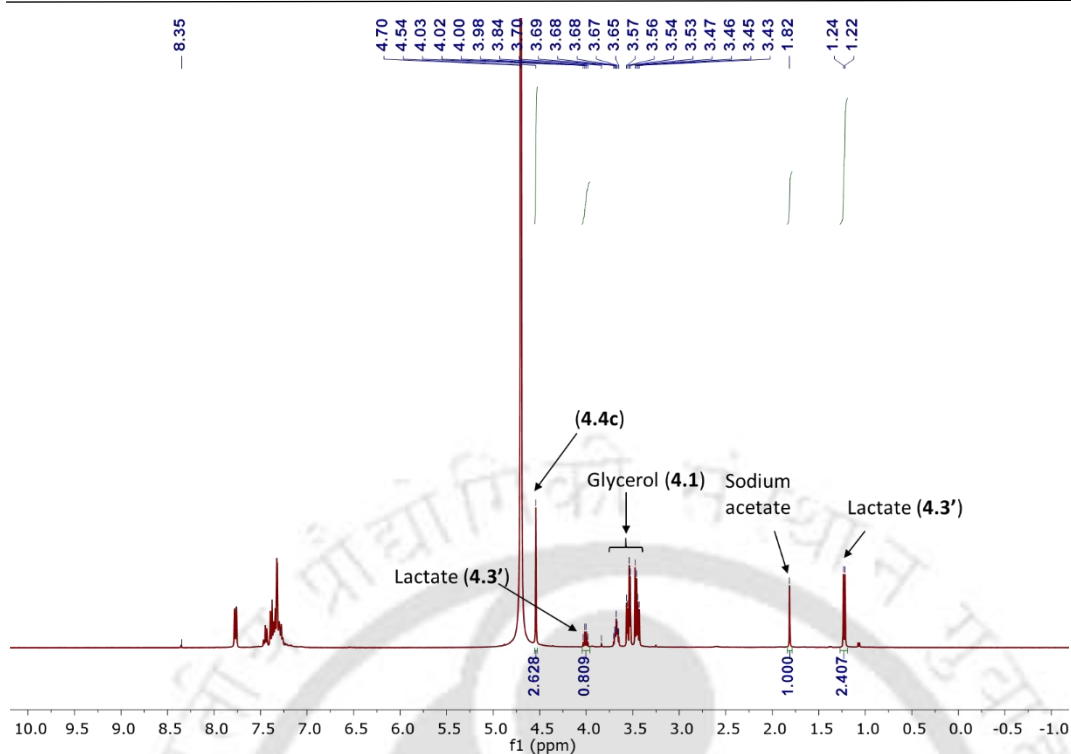


Figure C37: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2c** (entry 5, Table 4.3).

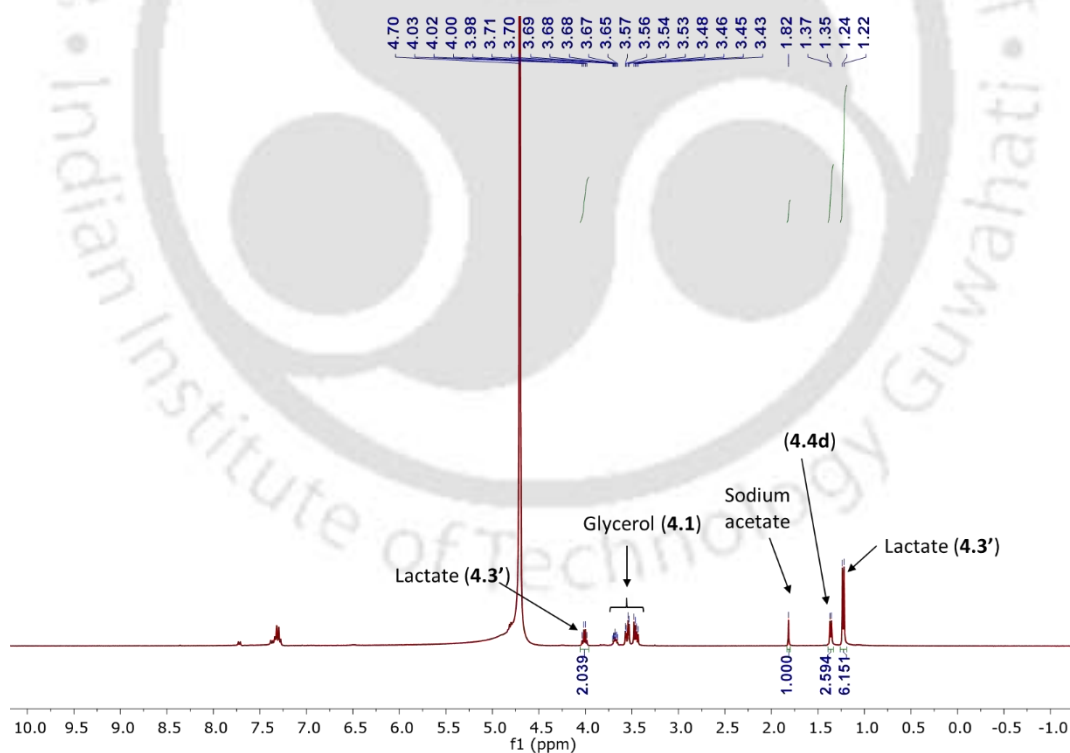


Figure C38: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2d** (entry 6, Table 4.3).

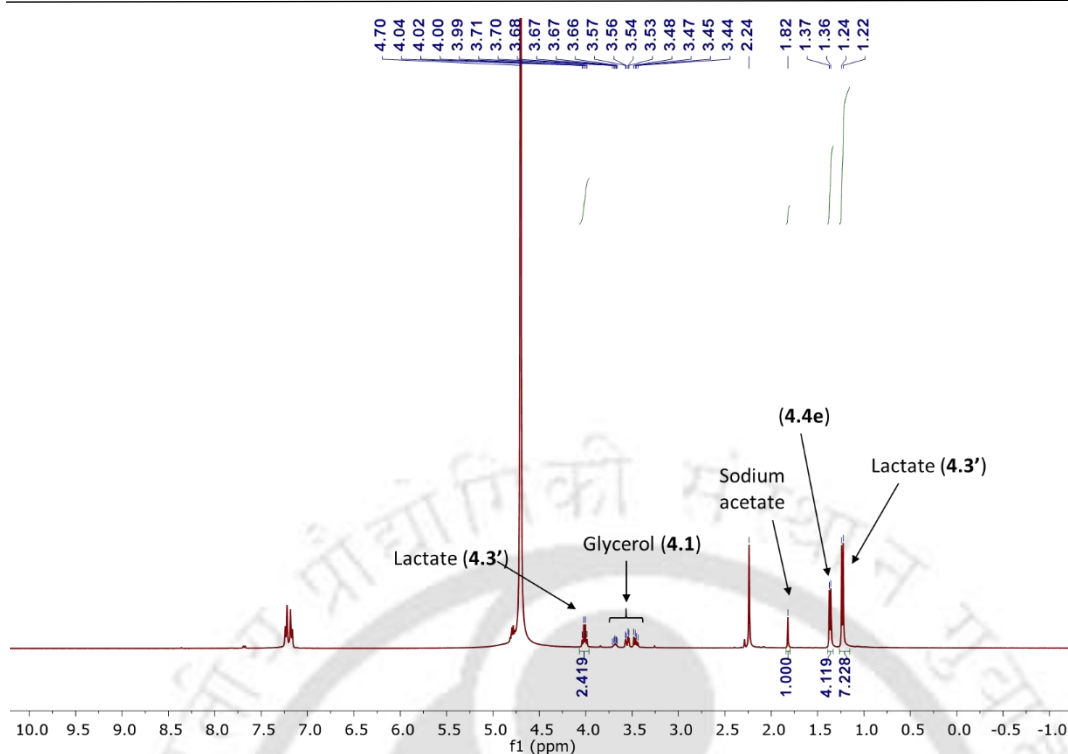


Figure C39: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2e** (entry 7, Table 4.3).

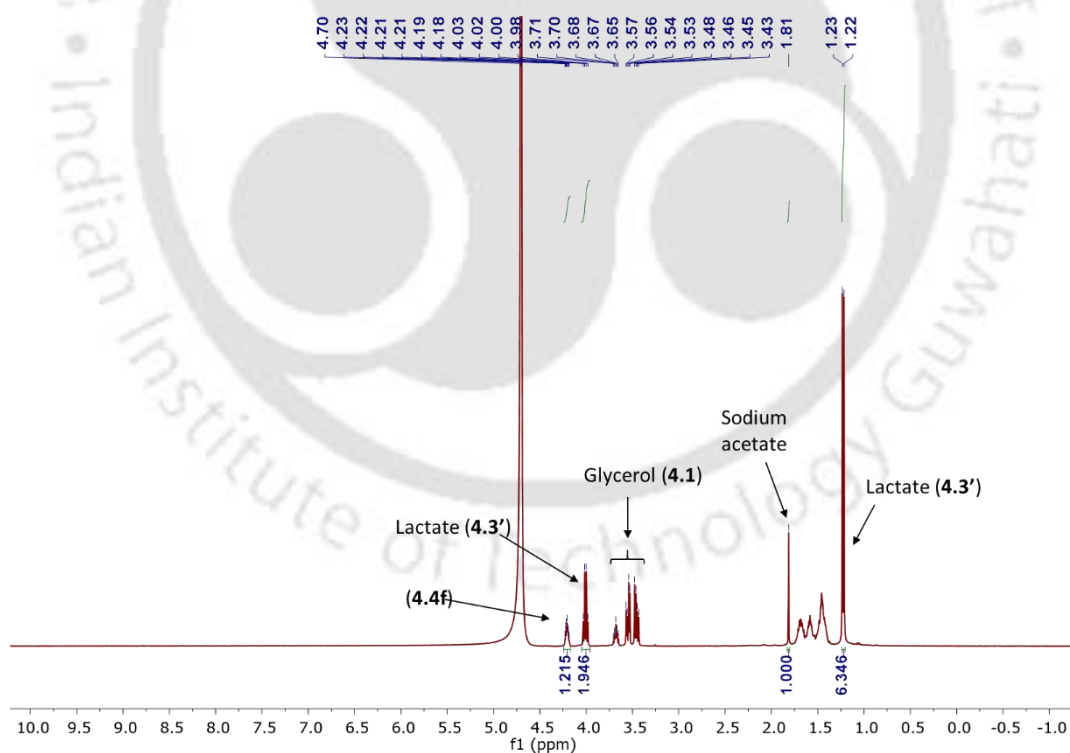


Figure C40: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2f** (entry 8, Table 4.3).

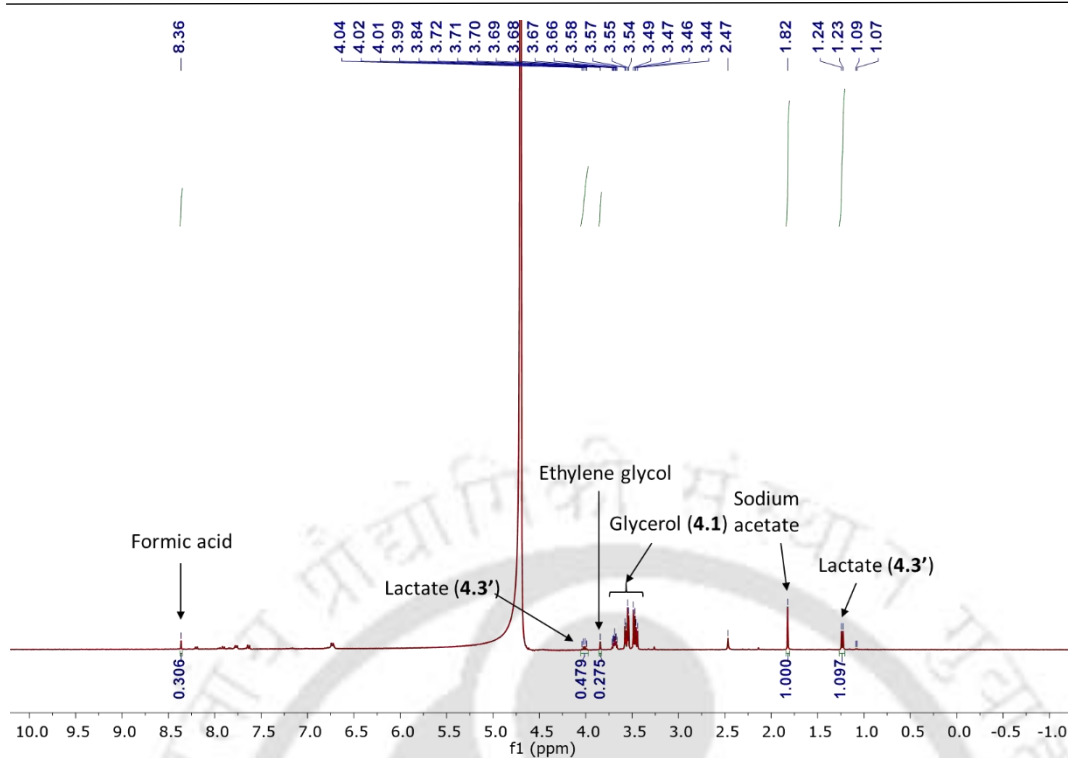


Figure C41: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2g** (entry 9, Table 4.3).

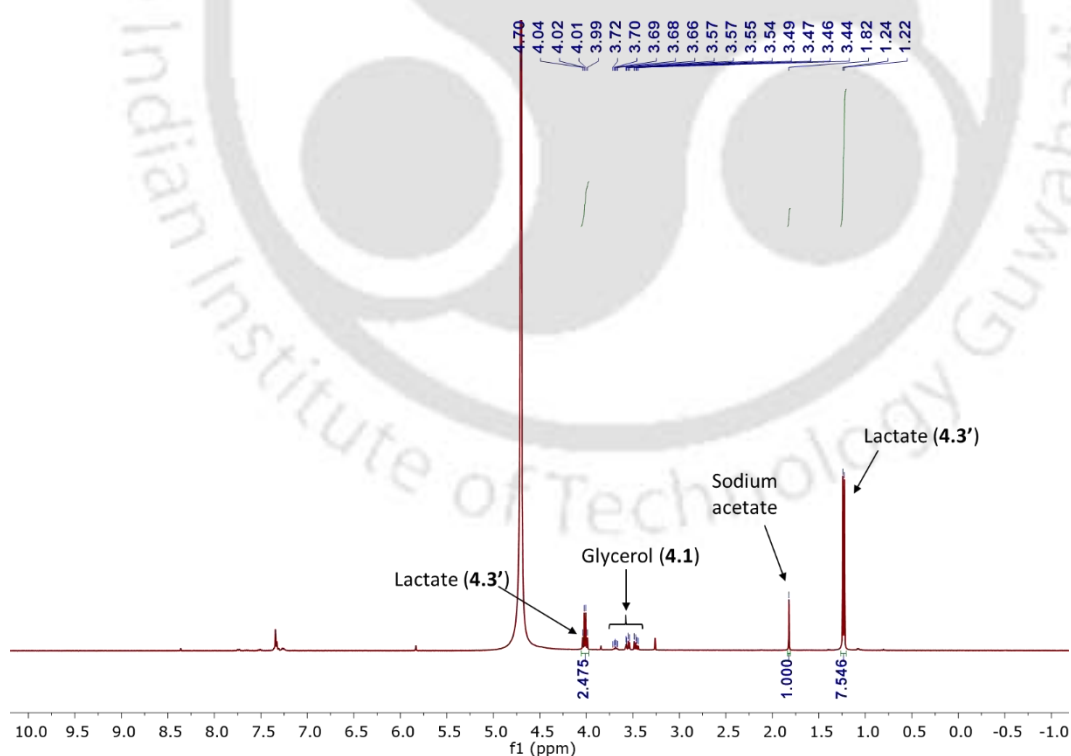


Figure C42a: ¹H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2h** in D₂O (entry 10, Table 4.3).

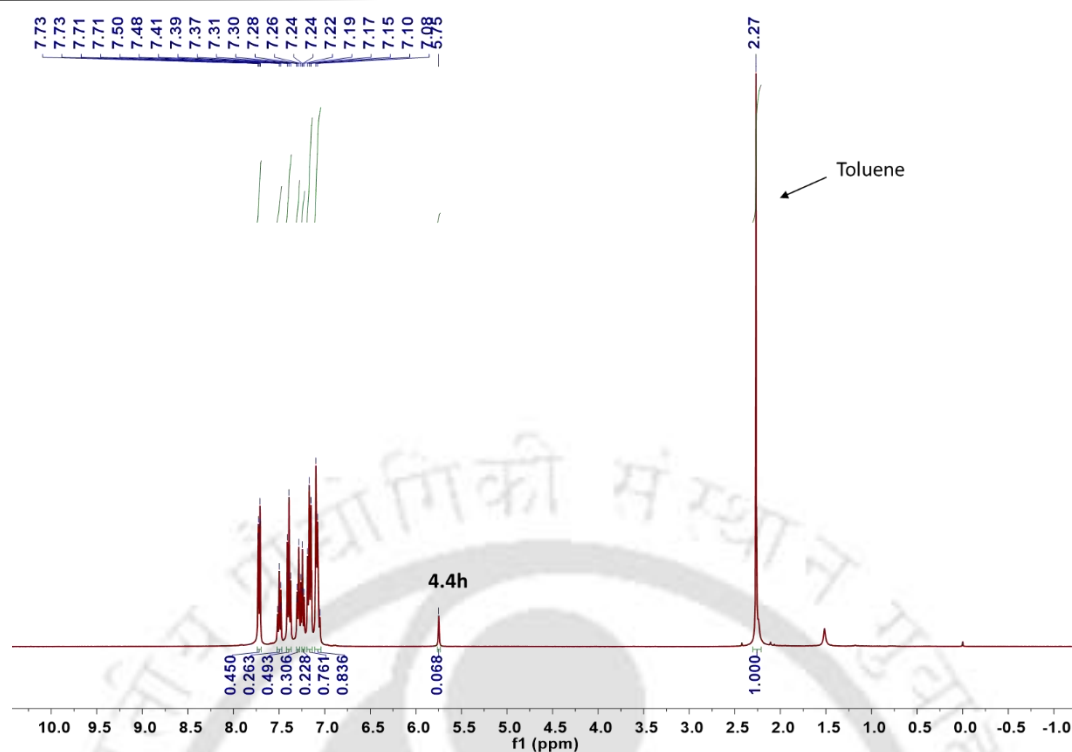


Figure C42b: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2h** in CDCl_3 (entry 10, Table 4.3).

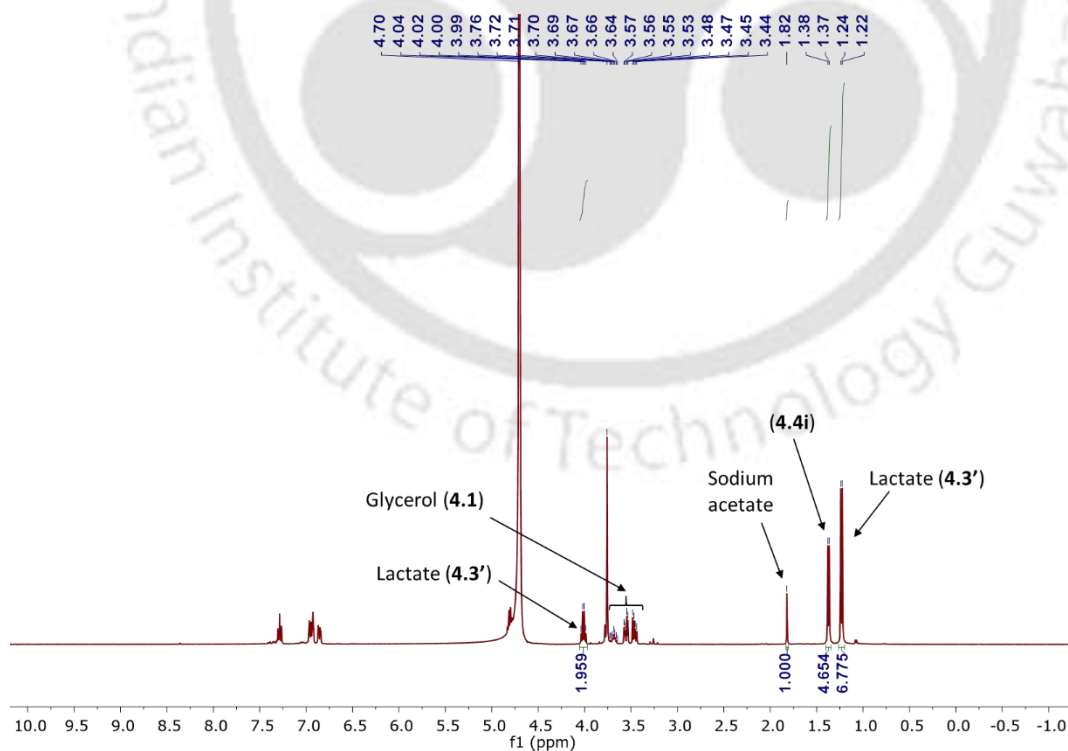


Figure C43: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2i** (entry 11, Table 4.3).

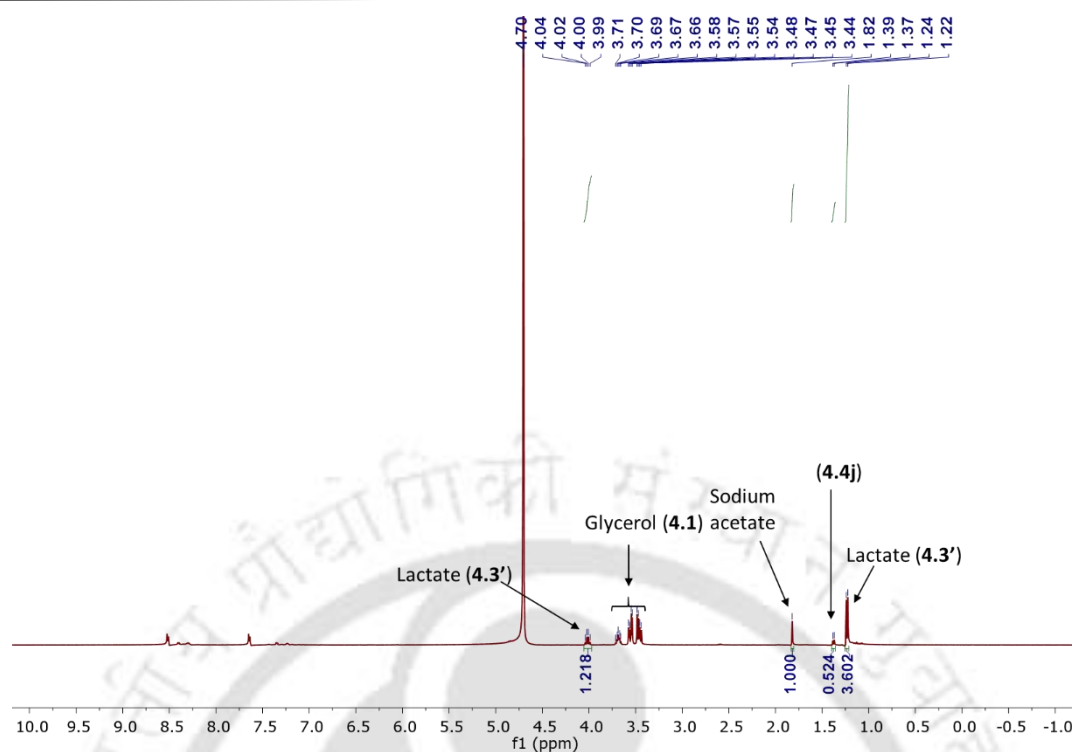


Figure C44: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2j** (entry 12, Table 4.3).

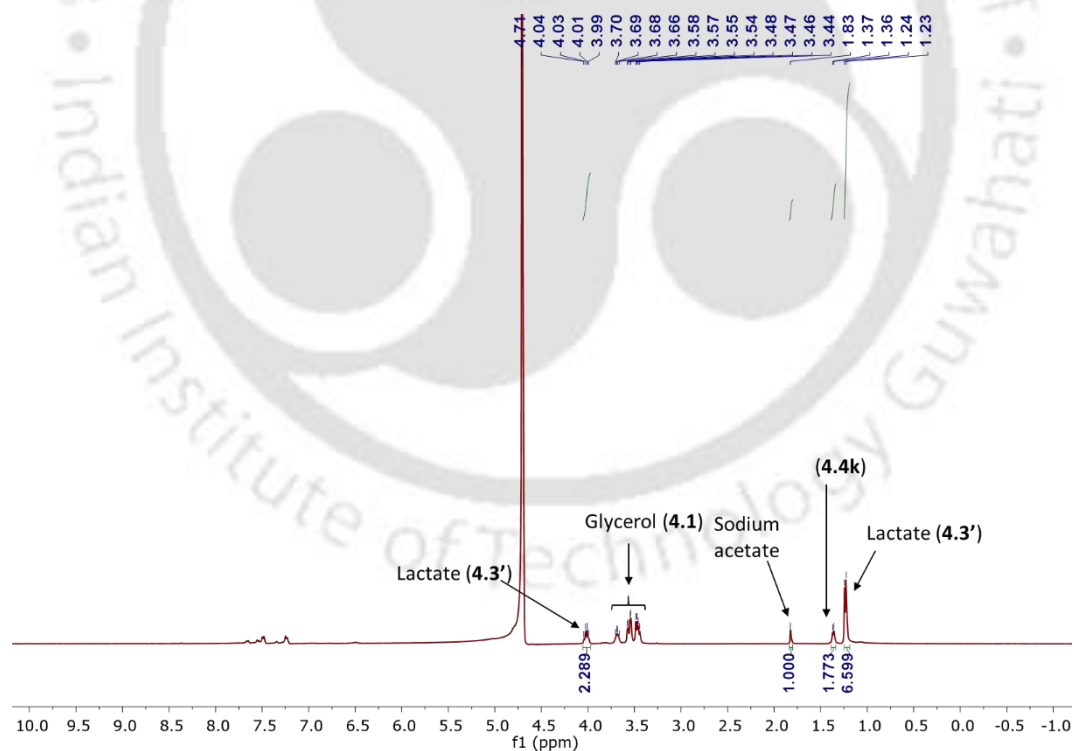


Figure C45: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2k** (entry 13, Table 4.3).

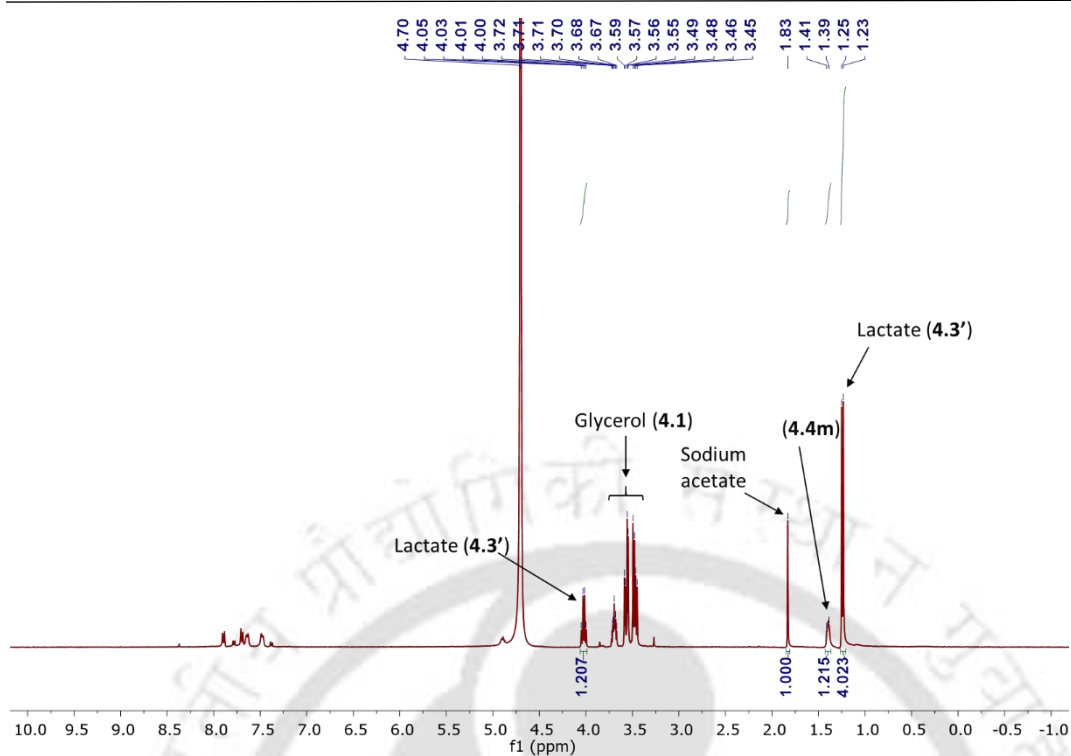


Figure C46: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2m** (entry 15, Table 4.3).

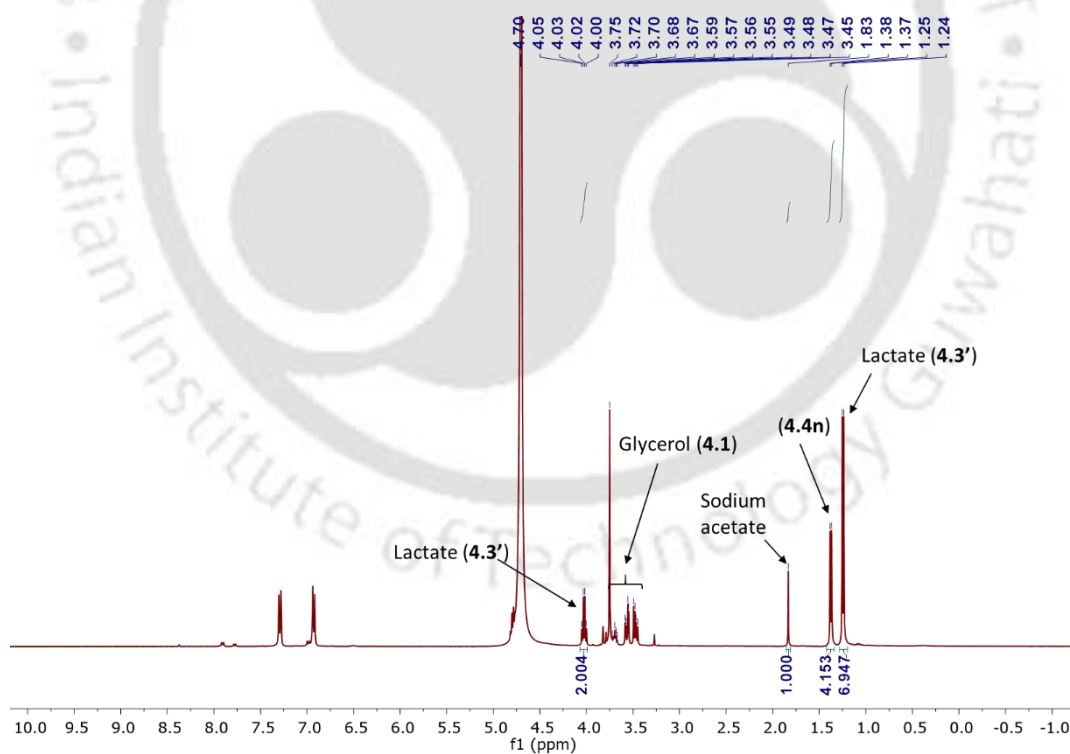


Figure C47: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2n** (entry 16, Table 4.3).

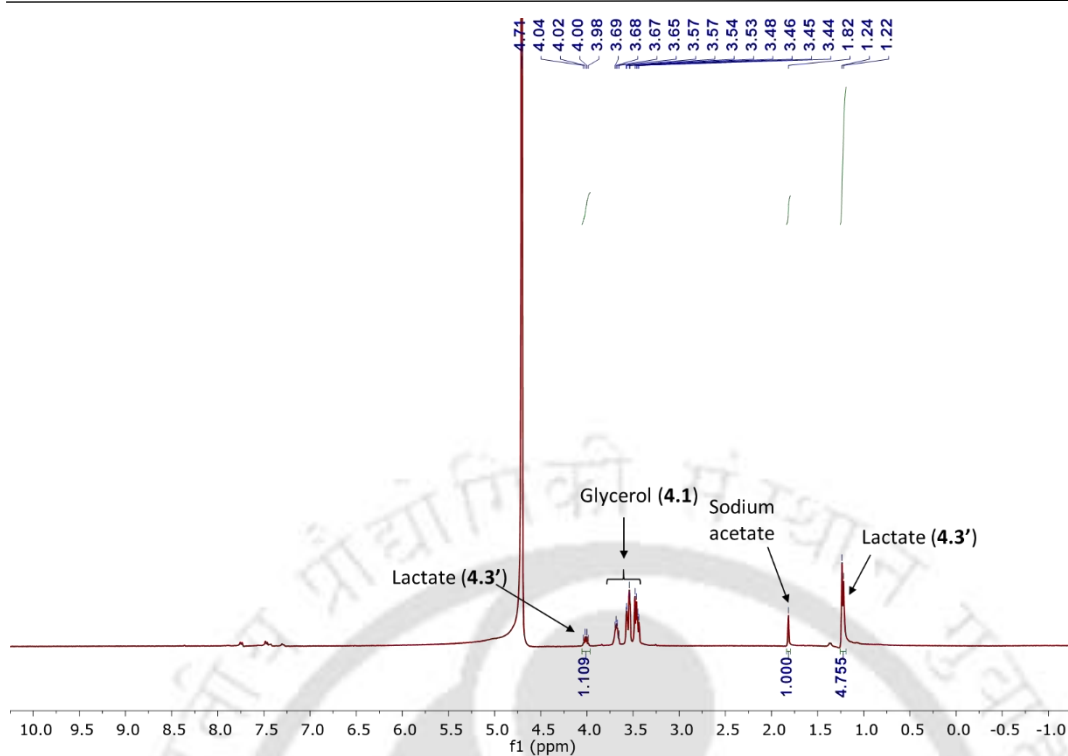


Figure C48: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2o** (entry 17, Table 4.3).

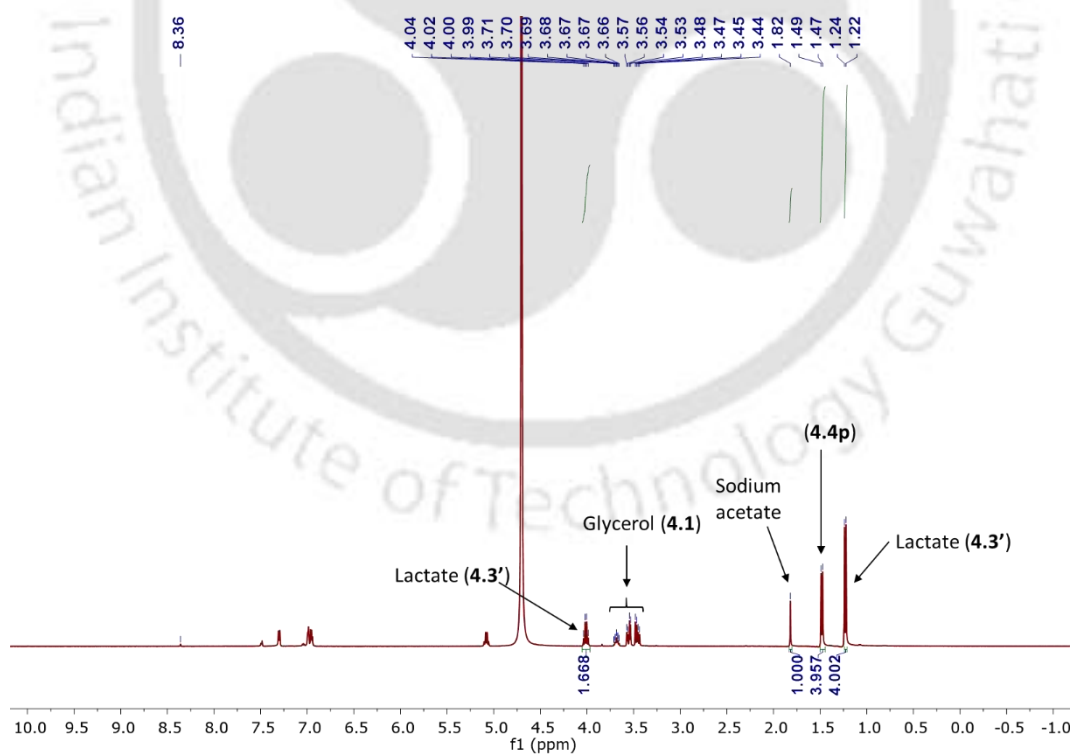


Figure C49: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2p** (entry 18, Table 4.3).

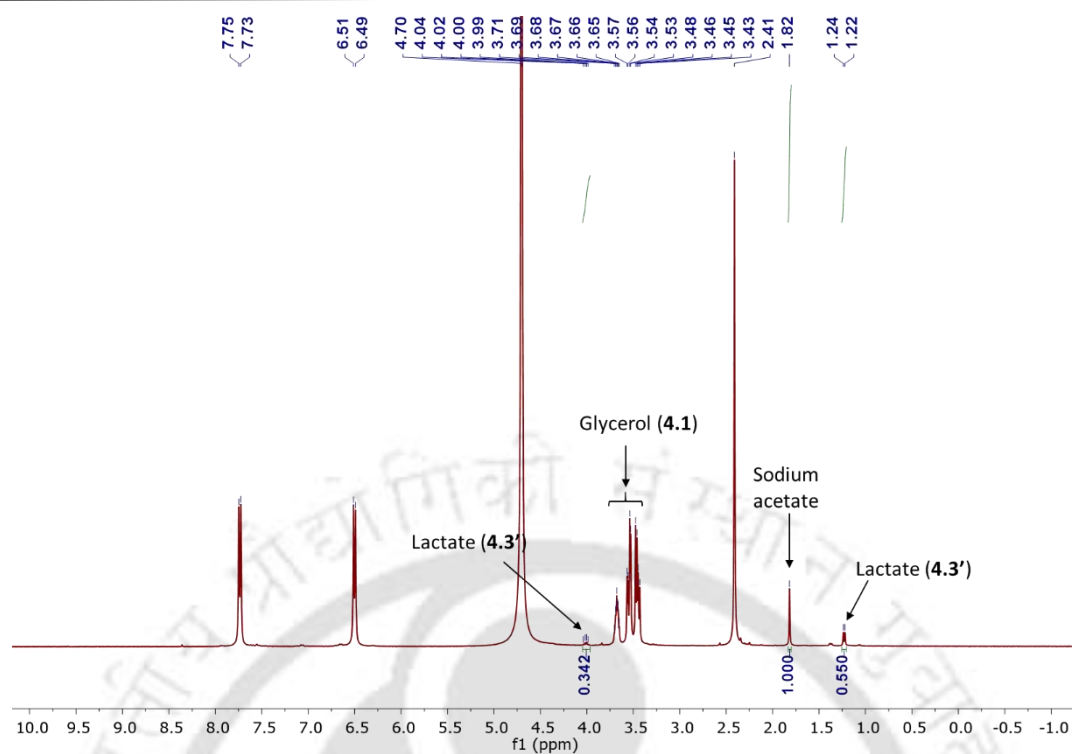


Figure C50: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of **4.2q** (entry 19, Table 4.3).

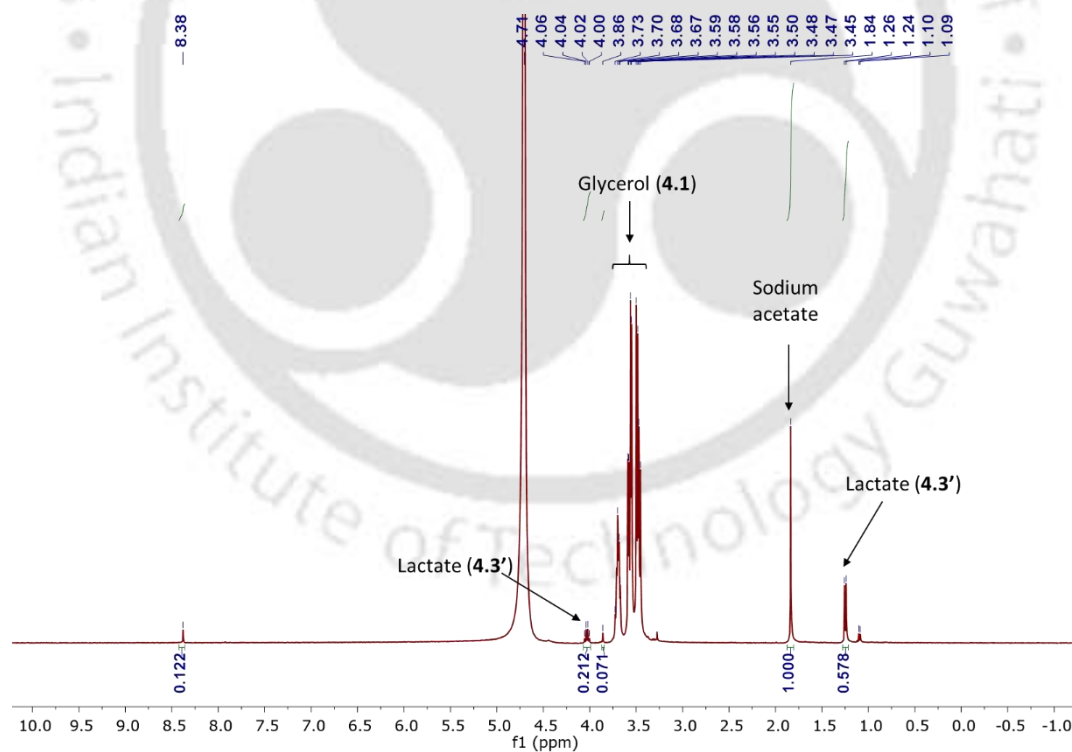


Figure C51: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in absence of any acceptor (entry 20, Table 4.3).

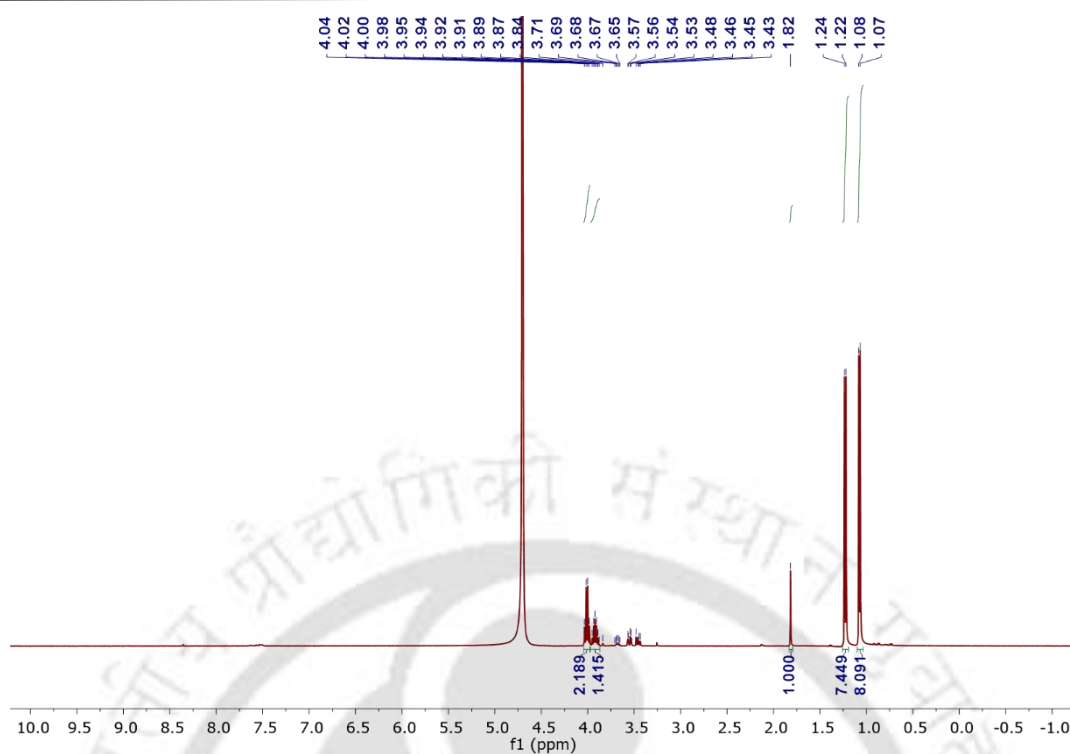


Figure C52: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents NaOH, in presence of 5 mol% PPh_3 (equation 3, Scheme 4.18).

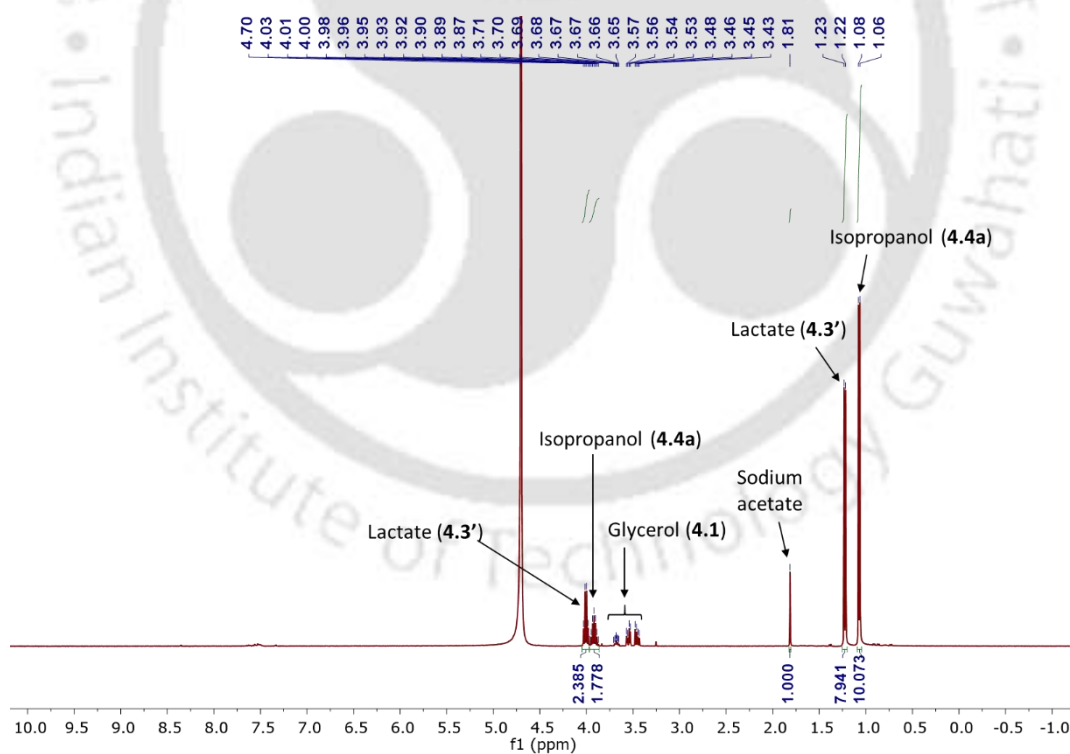


Figure C53: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% 4.5b, 1.1 equivalents NaOH, in presence of 5 mol% PPh_3 (equation 4, Scheme 4.18).

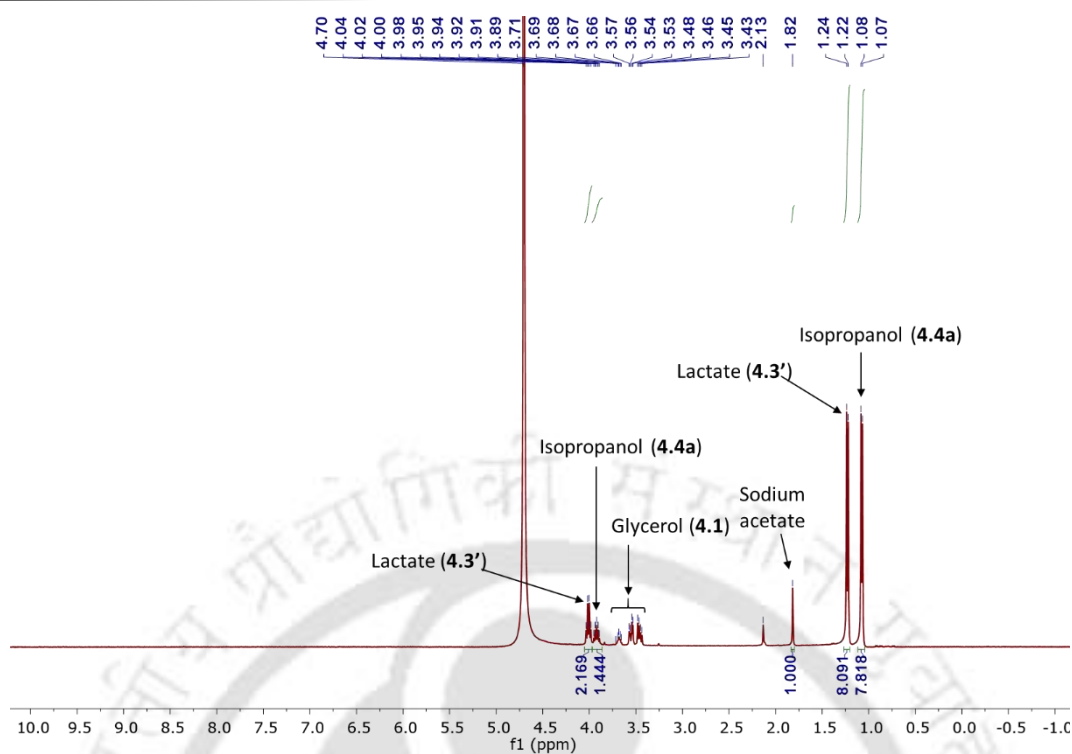


Figure C54: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents NaOH, in presence of 5 mol% CS_2 (equation 5, Scheme 4.18).

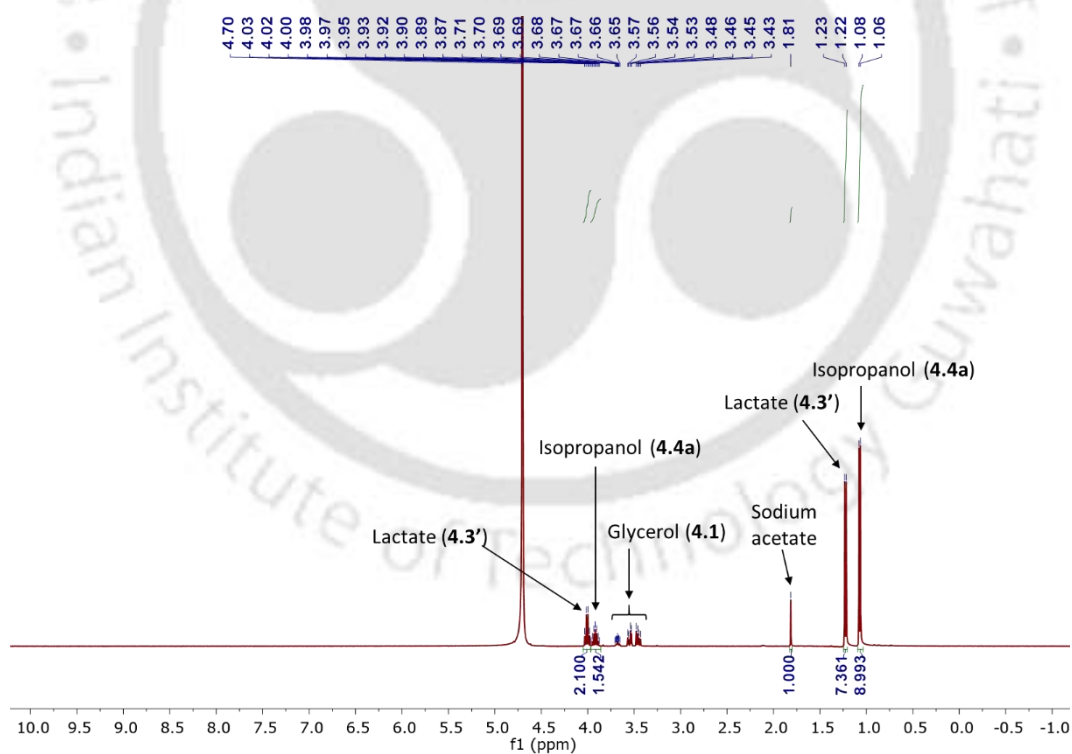


Figure C55: ^1H NMR spectra of glycerol (4.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% 4.5b, 1.1 equivalents NaOH, in presence of 5 mol% CS_2 (equation 6, Scheme 4.18).

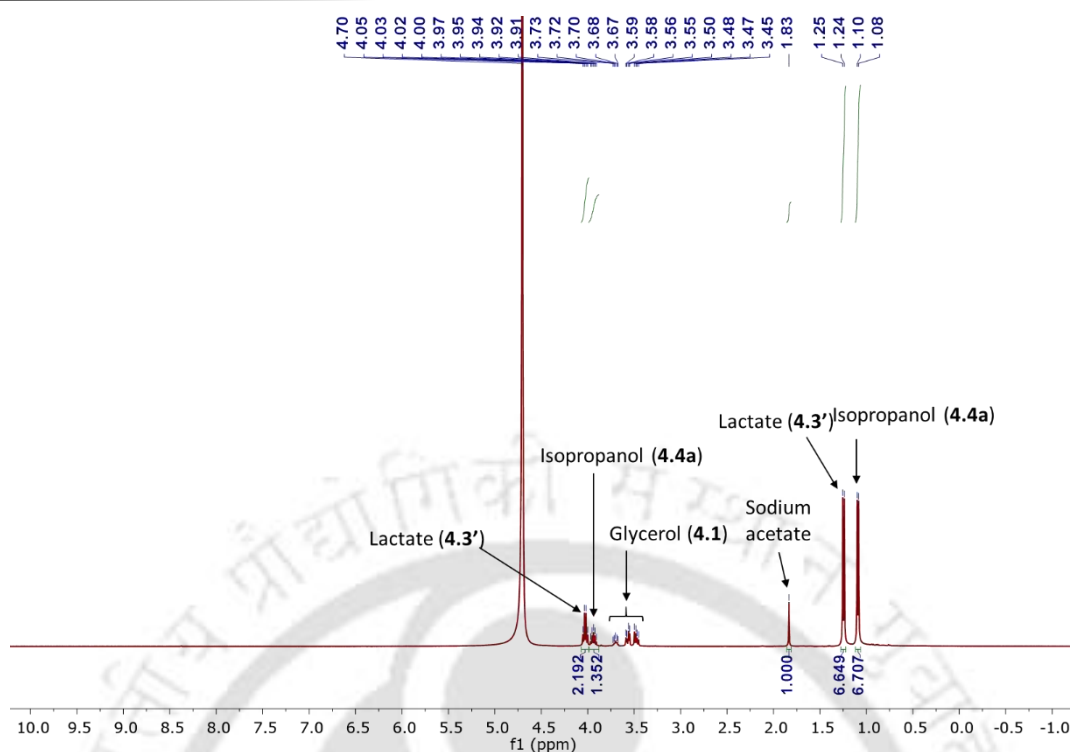


Figure C56: ^1H NMR spectra of glycerol (**4.1**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in presence of Hg (excess) (equation 7, Scheme 4.18).

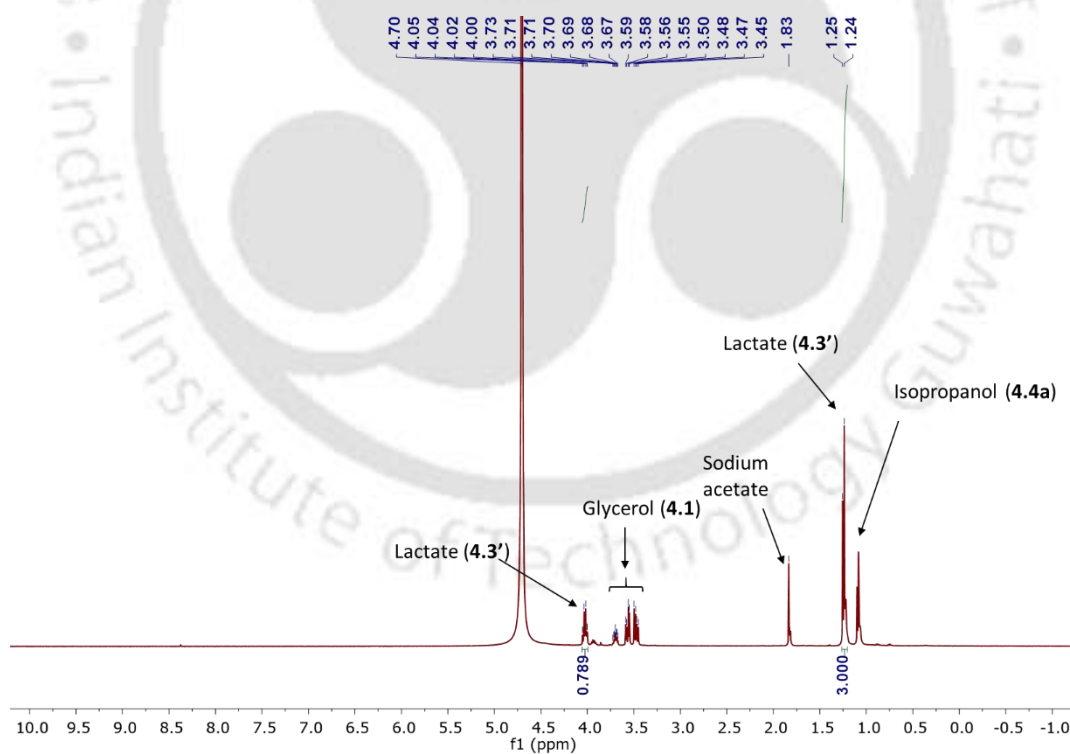


Figure C57a: ^1H NMR spectra of a mixture of glycerol (**4.1**) and glycerol-D8 (**4.1c**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH (equation 10, Scheme 4.18).

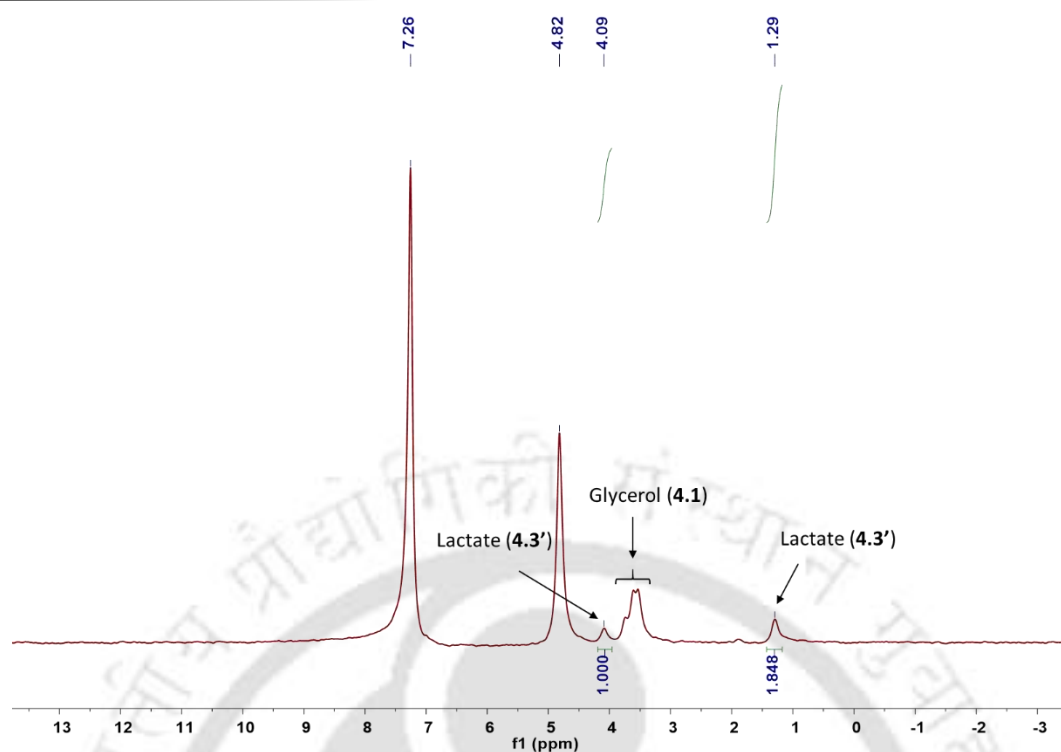
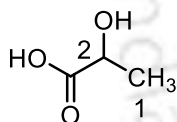


Figure C57b: ^2H NMR spectra of a mixture of glycerol (**4.1**) and glycerol-D8 (**4.1c**) transfer dehydrogenation to lactate catalysed by 0.5 mol% **4.5b**, 1.1 equivalents NaOH, in water using CDCl_3 lock (equation 10, Scheme 4.18).

C3. Calculation of K_H/K_D : (Figure C57a and Figure C57b)



Considering zero deuteration at C1 in ^1H NMR (Figure C57a) and full deuteration at C2 in ^2H NMR (Figure C57b)

From Figure C57a, integration value of the peak for CH_3 is 3

From Figure C57b, integration value of the peak for CD_3 is 1.848

Hence, protonation in CD_3 in Figure C57b = $(3 - 1.848) = 1.152$

From Figure C57a, integration value of the peak for CH_3 is 3

From Figure C57b, integration value of the peak for CH_3 is 1.152

Total proton retained in C1 considering both from ^1H NMR and ^2H NMR = $(3 + 1.152) = 4.152$

If we normalise 4.152 as 3.

Then, from Figure C57a, 0.789 will be normalised to $[(0.789 \times 3)/4.152] = 0.570$

Hence, the revised integrations after normalization are 3 for C1 and 0.570 for C2.

So, the deuterium incorporation in C2 = $(1 - 0.570) = 0.43$

From Figure C57a, D incorporation in C2 = $(1 - 0.789) = 0.211$

From Figure C57b, D incorporation in C2 = 1

So, the total deuterium incorporation in C2 = $1 + 0.211 = 1.211$

Again, if we normalise 1.211 as 1

Then from Figure C57b, 1.848 will be $[(1.848 \times 1) / 1.211] = 1.53$

Therefore, deuterium content in C1 = 1.53

KIE = $0.570 / 0.43 = 1.32$



Chapter-V

Cobaltous Chloride Catalysed Dehydrogenative Transformation of Glycerol to Lactic Acid

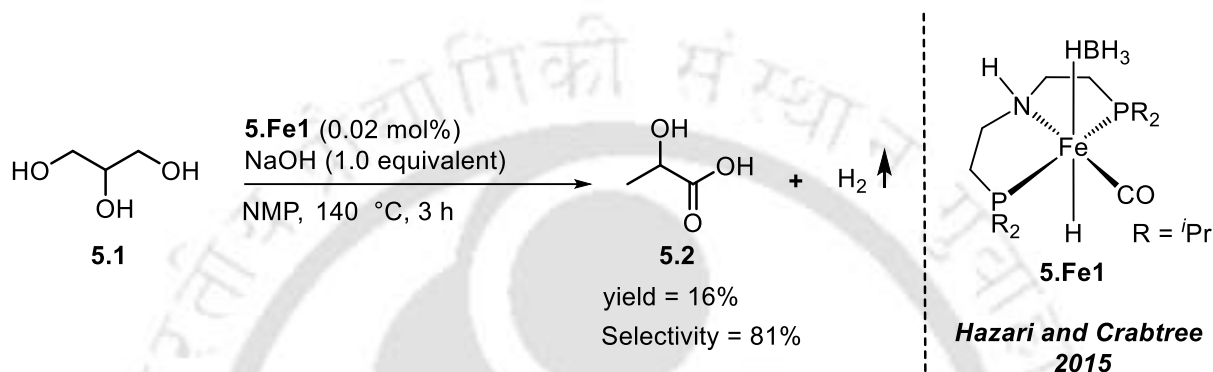


The content of this chapter has been adapted from “Acceptorless or Transfer Dehydrogenation of Glycerol Catalysed by Base Metal Salt Cobaltous Chloride – Facile Access to Lactic Acid and Hydrogen or Isopropanol” by Narjinari, H.; Dhole, S.; Kumar, A. *Chem. Eur. J.*, **2024**, e202302686.



5.1. Introduction

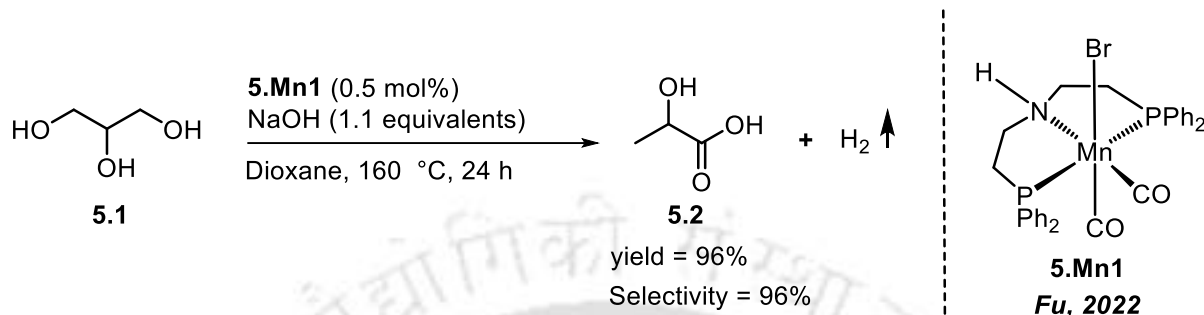
Recent years have witnessed a significant advancement in the utilization of biodiesel¹ as an alternative to fossil-fuel based resources. This has led to an unexpected surge in glycerol (GLY) generation as a major by-product.² Glycerol being a non-toxic³ waste product from different industrial processes of cellulose hydrogenolysis⁴ as well as microbacterial fermentation processes,⁵ can be transformed into various speciality chemicals and value-added products such as propanediol,⁶⁻¹⁰ dihydroxyacetone¹¹⁻¹⁵ and lactic acid (2-hydroxy propionic acid).¹⁶⁻¹⁸



Scheme 5.1. The transformation of glycerol to lactic acid catalysed by a pincer-iron complex reported by Crabtree and Hazari.¹⁹

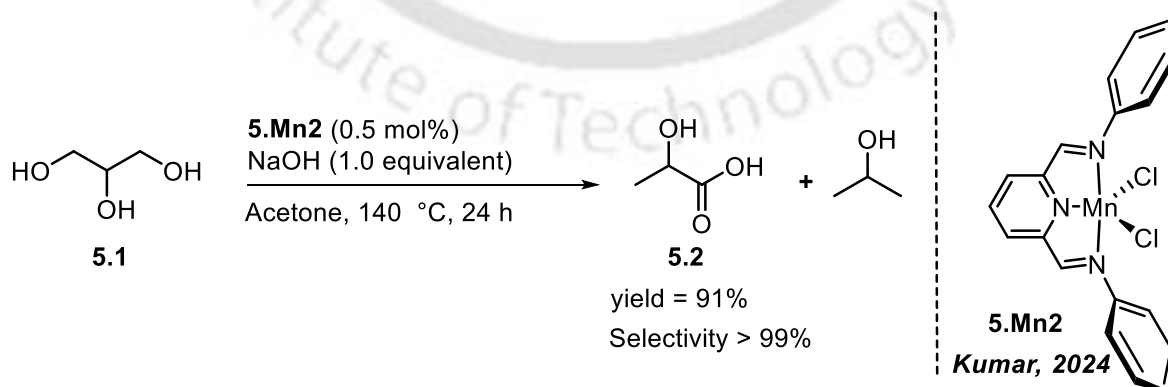
Glycerol, is the smallest highly functionalized polyol containing hydroxyl groups which can readily serve either as a potential²⁰ solvent or as a hydrogen source for various metal catalysed organic transformations.²¹⁻²⁵ Reforming of glycerol to lactic acid (LA) along with the generation of hydrogen^{2, 26} promises to be an attractive value addition strategy. LA can serve as a beneficial feedstock, green solvent apart from being extensively employed in food,²⁷ pharmaceutical,²⁷ cosmetic,²⁸ biodegradable polyethenes,²⁸ chemical industries,²⁷ green solvent synthesis,²⁷ detergent synthesis²⁸ and synthesis of poly lactic acid (PLA).²⁷⁻²⁸ The traditional approach of LA synthesis from glycerol involves bacterial fermentation via bioconversion²⁹ and heterogeneous catalysis.^{3, 17, 20, 31-42} But the traditional approaches such as heterogeneous catalysis are limited by catalyst degradation at high temperature and stoichiometric amount of base leading to lower yield with low selectivity due to various side reactions,⁴² increasing the difficulty in separation of the product⁴² while bioconversion is accompanied with major drawbacks such as impaired survival of bacteria in the harsh reaction conditions, difficult complex separation steps and lower yields.⁴² On the contrary, homogeneous catalysis is advantageous compared to that of heterogeneous catalysis,⁴³ as it demonstrates good reactivity and selectivity under milder reaction conditions.²⁰ In the previous chapter we have discussed

the reports on glycerol to lactic acid transformation that was accomplished by complexes based on precious metals like Ru^{18, 44-45} and Ir^{18, 46-48}. With an objective to move away from precious metal-based catalysts, there have been many attempts recently to use catalysts derived from earth-abundant base metals.



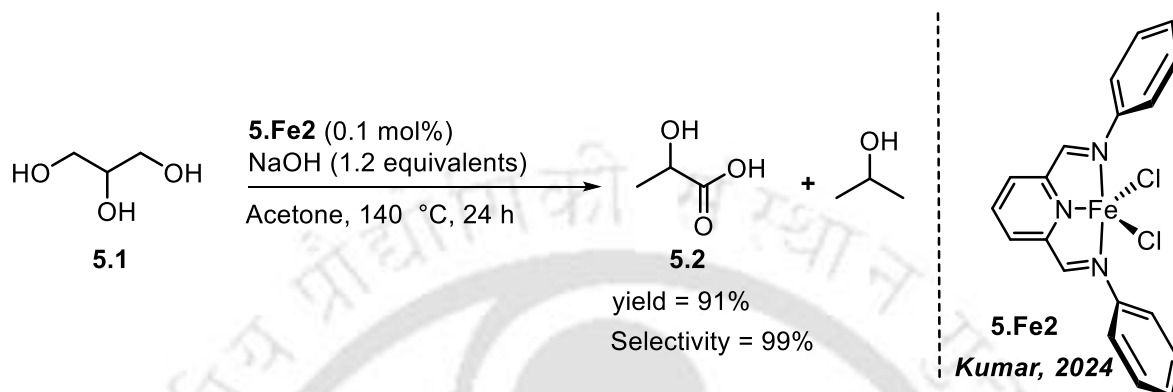
Scheme 5.2. The conversion of glycerol to lactic acid catalysed by a pincer-manganese complex reported by Fu.³⁰

The first report of 3d-metal catalysed acceptorless dehydrogenation of glycerol to lactic acid came from Crabtree and Hazari, where they have showed that the PNP-Fe complex (0.02 mol%) can lead to about 20% glycerol conversion with 81% selectivity towards LA resulting in 770 TONs (Scheme 5.1).¹⁹ Fu and co-workers have shown the high reactivity of a pincer-Mn complex (0.5 mol%) towards catalytic dehydrogenative transformation of GLY and yielded 96% yield of LA with 96% selectivity in presence of NaOH (1.1 equivalents) at 160 °C in 24 hours (Scheme 5.2).³⁰ In one of their recent reports, the research group of Kumar have demonstrated that NNN pincer-Mn (0.5 mol%) complexes demonstrated very good reactivity towards net transfer dehydrogenation of glycerol to lactic acid in presence of ketones as acceptors. This catalytic system could achieve 91% yield of lactic acid with 99% selectivity



Scheme 5.3. The transformation of glycerol to lactic acid catalysed by a pincer-manganese reported by Kumar.⁴³

in presence of NaOH (1 equivalent) and acetone (1 equivalent) at 140 °C in 24 hours (Scheme 5.3).⁴³ In a similar vein, Kumar has also reported that the net transfer dehydrogenation of GLY with acetone could be brought about by using catalytic amounts (0.1 mol%) of a pincer-Fe complex which afforded 91% yield of lactic acid at 99% selectivity in presence of NaOH (1.2 equivalents) at 140 °C in 24 hours.⁴⁹

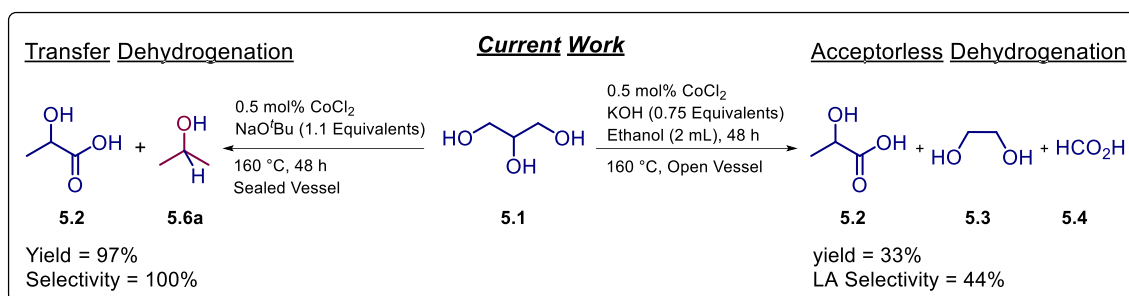


Scheme 5.4. The transformation of glycerol to lactic acid catalysed by a pincer-iron complex reported by Kumar.⁴⁹

5.2. Objectives of the current work:

A comprehensive literature study reveals that the dehydrogenative transformation of glycerol to lactic acid has been accomplished using various homogeneous pincer catalytic systems based not only on precious metals like Ru and Ir, but also based on 3d-metals like Mn and Fe. In chapter IV, we have demonstrated that the transfer dehydrogenation of glycerol with various ketones as acceptors is effectively catalysed by $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its corresponding pincer complexes. Encouraged by our recent success on the use of simple base metal salts⁵⁰⁻⁵⁶ including cobaltous chloride⁵¹⁻⁵² (a more environmentally friendly metal compared to Cr) and their corresponding pincer complexes⁵¹ for the dehydrogenative transformation of alcohols, the present chapter attempts to address the following questions :

- Can one use greener and more environmentally benign metal salts such as cobaltous chloride (CoCl_2) for the synthetically valuable conversion of GLY to LA in air without any compromise on the overall performance?
- Along with transfer dehydrogenation can we also accomplish acceptorless dehydrogenation of glycerol leading to the generation of hydrogen?



Scheme 5.5. Current work based on cobaltous chloride catalysed transformation of glycerol to lactic acid.

Apart from the studies by Crabtree and Hazari,¹⁹ Fu³⁰ and our recent reports on Fe⁴⁹ and Mn,⁴³ to the best of our knowledge there are no other reports on the transformation of glycerol to LA using catalysts based on readily available, inexpensive 3d-transition base metals. Accordingly, under acceptorless conditions, CoCl₂ could be used to catalyze the reforming of glycerol to lactic acid and hydrogen albeit with moderate yields (33%) and selectivity (44%) at 160 °C. Gratifyingly, using an inexpensive acceptor acetone, the transfer dehydrogenation of glycerol could efficiently be accomplished by CoCl₂ at 160 °C leading to two value-added products, LA (97% at 100% selectivity) and isopropanol.

5.3. Results and Discussions

The investigation on the dehydrogenation of glycerol (5.1) to lactic acid (LA, 5.2) was commenced by treating 5 mmol of glycerol with 0.5 mol% of anhydrous CoCl₂, 0.25 equivalents of KOH and 2 mL ethanol in a 50-mL round-bottom flask (entry 1, Table 5.1). The reaction mixture was then stirred and allowed to homogenize at room temperature for 10 minutes. The resulting green solution was then heated under open vessel conditions under air in a round-bottom flask using a preheated oil bath at 160 °C for 48 hours. Within the first few minutes of the reaction, ethanol (bp = 78 °C) is lost giving rise to a bluish foam which gradually turns into a brown gel as the reaction proceeds. There is no evidence of ethanol and its dehydrogenated products in the NMR spectra of the crude reaction mixture (Figure D1, Appendix A). The yield of lactate 5.2' was determined from ¹H NMR using sodium acetate as a standard. Lactate 5.2' was observed as the major product along with ethylene glycol (EG, 5.3) (formed by decarbonylation of glyceraldehyde and hydrogenation of glycolaldehyde)^{44, 46-48, 57-61} and formate 5.4' (formed by decarbonylation of glyceraldehyde and subsequent oxidation of the resulting formaldehyde).^{44, 47-48, 57-63} To our delight, 66% of glycerol

conversion was observed with 25% of **5.2'** at 38% selectivity towards **5.2'** (entry 1, Table 5.1). An increase in the amount of KOH to 0.5 equivalents led to an increment in the yield of **5.2'** (29%) with an increased **5.2'** selectivity of 45% (entry 2, Table 5.1).

Table 5.1. The acceptorless dehydrogenative transformation of glycerol to lactic acid catalysed by CoCl₂ under varying conditions.^a

Entry	CoCl ₂ X mol%	KOH Y Equiv.	% Glycerol Conversion ^[b]	% Yield ^b (% Selectivity) ^c 5.2'	5.3	5.4'	H ₂ ^d
1	0.5	0.25	66	25 (38)	18 (27)	16 (24)	24
2	0.5	0.5	65	29 (45)	14 (21)	14 (21)	25
3	0.5	0.75	75	33 (44)	14 (19)	27 (36)	30
4	0.5	1	81	32 (39)	20 (25)	24 (30)	30
5	0.25	0.75	54	23 (42)	12 (22)	16 (30)	22
6	0.75	0.75	76	33 (43)	22 (29)	14 (18)	31
7	1	0.75	77	34 (44)	22 (29)	16 (21)	29
8 ^e	0.5	0.75	45	19 (53)	10 (22)	7 (16)	16
9 ^f	0.5	0.75	12	5 (42)	4 (33)	3 (25)	Not Detected
10	0.0	0.75	11	5 (45)	1 (9)	2 (18)	Not Detected
11	0.5	0.0	0	0	0	0	0
12 ^g	0.5	0.75	35	17±1 (48)	9±1 (26)	7±0 (20)	15
13 ^h	0.5	0.75	0	0	0	0	0
14 ⁱ	0.5	0.75	31	16 (51)	9 (29)	6 (19)	14
15 ^j	0.5	0.75	40	22 (55)	9 (22)	8 (20)	22
16 ^k	0.5	0.75	31	17 (55)	8 (26)	6±2 (19)	14
17 ^l	0.5	0.75	35	18 (51)	9 (26)	8 (23)	16

^a Reaction conditions: 5 mmol glycerol, X mol% CoCl₂, KOH (Y equivalents with respect to glycerol), 2 mL ethanol, 160 °C, 48 h in an open vessel (one neck round-bottom flask) under air. ^bDetermined from ¹H NMR using sodium acetate as a standard. ^cSelectivity of lactic acid = (yield of lactic acid/conversion of glycerol)100. The poor selectivity in some instances (say 59% total yield Vs. 66% conversion at 89% total selectivity, entry 1) is attributed to undetectable by-products. ^dHydrogen evolution was determined by burette measurements after deducting the blank contribution. Yield of hydrogen was calculated as (moles of H₂ (as observed from GC and the amount of gas evolved)/moles of **5.1**)100. ^e Reaction performed at 170 °C. ^f Reaction performed at 140 °C. ^g 1 mL dioxane was used. ^h 1 mL DMF was used. ⁱ 1 mL *o*-xylene was used. ^j 1 mL acetone was used. ^k 1 mL water was used. ^l 1 mL methanol was used.

On further increasing the loading of KOH (0.75 equivalents) an improvement in the **5.2'** yield (33%, 66 TON at 1.37 TOs/h) was observed along with the increment in the yield of side products EG and **5.4'** with a selectivity of 44% towards LA (entry 3, Table 5.1). Further increase in the loading of KOH to 1 equivalent, yielded 32% of **5.2'** similar to the result

obtained with 0.75 equivalents of KOH albeit at a higher glycerol conversion (81%) at a cost of **5.2'** selectivity (entry 4, Table 5.1). Hence, subsequent optimization of the reaction conditions was done using 0.75 equivalents of KOH. Under these conditions, upon decreasing the catalyst loading to 0.25 mol% there was a decrease in glycerol conversion (54%) as well as yield of **5.2'** (23%) (entry 5, Table 5.1) but with comparable selectivity as that of 0.5 mol% CoCl₂ (entry 3, Table 5.1). The **5.2'** yield (33%) (entry 6, Table 5.1) at higher CoCl₂ loading (entries 6 and 7, Table 5.1) were similar to that at 0.5 mol% CoCl₂ (entry 3, Table 5.1) apart from maintaining similar glycerol conversion and **5.2'** selectivity. Operating at higher temperatures led to a decrease in LA yield by about 1.76 folds (entry 8, Table 5.1) presumably due to deactivation of catalytically active species. On the other hand, on lowering the reaction temperature to 140 °C, a sudden drop was seen in the yield of **5.2'** to 5% (entry 9, Table 5.1). The reaction gives very poor yield of **5.2'** (5%) in absence of CoCl₂ (entry 10, Table 5.1) which underlines the role of CoCl₂ as catalyst in these reactions. There was no reactivity in absence of a base (entry 11, Table 5.1). The progress of the reaction under the best optimized condition (entry 3, Table 5.1) was monitored with time and a saturation was observed after 48 h (Figure D48, Appendix D).

The dehydrogenation of glycerol in presence of dioxane, *o*-xylene, water and methanol gave comparable yield of **5.2'** between 16–18% (entries 12, 14, 16, and 17, Table 5.1). The reaction did not proceed in DMF (entry 13, Table 5.1). Solvents were used only for the initial homogenization of the reaction mixture and under the reaction conditions, low boiling solvents (entries 3, 12 and 16–17, Table 5.1) relative to reaction temperature are apparently lost within first few minutes of the reaction. Use of ethanol (entry 3, Table 5.1), in particular demonstrates a better activity as it may assist in the easy generation of catalytically active Co-H species via β -hydride elimination from Co(ethoxide).⁵² In acetone, the CoCl₂ catalysed dehydrogenation reaction gave moderate yield (22%) of **5.2'** (entry 15, Table 5.1) along with the formation of trace amounts isopropanol, a hydrogenated product of acetone (Figure D11, Appendix D) at 160 °C in an open vessel under air for 48 hours. Taking a cue from this observation, the CoCl₂ catalysed transfer dehydrogenation of glycerol to LA was attempted using acetone as a sacrificial acceptor in a sealed autoclave (Table 5.2). Notably, in their influential review, Tavor,²⁶ Crabtree² have independently summarized that the most straightforward application of glycerol is in transfer hydrogenation as a hydrogen donor solvent⁴⁶ that more often leads to increased selectivity or yield which otherwise are not possible with conventional transfer hydrogenation reagents such as ethanol and isopropanol.

5.3.1. The CoCl_2 catalysed transfer dehydrogenation of glycerol to lactic acid using acetone as sacrificial hydrogen acceptor

Under sealed vessel conditions, the CoCl_2 (0.5 mol%) catalysed transfer dehydrogenation of glycerol with acetone resulted in 50% of **5.2'** with 96% selectivity at 160 °C after 48 h (entry 1, Table 5.2). The yield of **5.2'** increased (entries 2 and 3, Table 5.2) upon increasing the amount of KOH and maximum of 81% of LA at 100% selectivity was obtained with 1.1 equivalents of KOH (entry 3, Table 5.2). Among the various loadings of CoCl_2 , 0.5 mol% was found to yield the best results in the presence of 1.1 equivalents of KOH at 160 °C after 48 h (compare entries 3 Vs. 4 and 5, Table 5.2). In fact, comparable glycerol conversion are obtained at a CoCl_2 loading of 0.5 mol% and 0.75 mol% which indicates that the relatively lower yield of **5.2'** in the case of latter could be attributed to some undetectable side products. Lowering the reaction temperature resulted in relatively poorer yields (compare entries 3 Vs. 6 and 7, Table 5.2).

Among the acceptors screened, acetone proved to be the best (compare entries 3 Vs. 8 and 9, Table 5.2). Use of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ provided inferior results in comparison with the results obtained from the use of anhydrous CoCl_2 as catalyst (compare entries 3 Vs. 10, Table 5.2). Owing to its high boiling point, acetophenone **5.5b** could be used as an acceptor in a pressure vessel under the microwave conditions where the reaction levelled off after 2.5 h and a maximum of 57% **5.2'** yield with 98% selectivity was obtained at 160 °C (compare entries 11 Vs. 12 and 13, Table 5.2). Use of NaO^tBu appeared to be more rewarding (93±4% **5.2'** yield at 96% selectivity) in comparison with other bases in the CoCl_2 (0.5 mol%) catalysed transfer dehydrogenation of glycerol with acetone (compare entries 15 Vs. 3, 14 and 16–21, Table 5.2). Furthermore, upon work-up of the reaction mixture using dilute HCl, LA (80%) was obtained in the pure form (Figure D44–D45, Appendix D). Under the optimized conditions (entry 15, Table 5.2), while the reaction in the absence of base did not proceed (entry 23, Table 5.2), the reaction in absence of CoCl_2 gave only 14% of **5.2'** (entry 22, Table 5.2). Under the optimized conditions (entry 15, Table 5.2), but at a lower CoCl_2 loading of 0.05 mol% and 0.005 mol%, lactate **5.2'** was obtained in 54% yield (96% selectivity, 1080 TON at 22.5 TOs/h) and 38% yield (97% selectivity, 7600 TON at 158 TOs/h, entry 27, Table 5.1) respectively.

5.3.2. Mechanistic studies on the dehydrogenative conversion of glycerol to lactic acid catalysed by CoCl_2

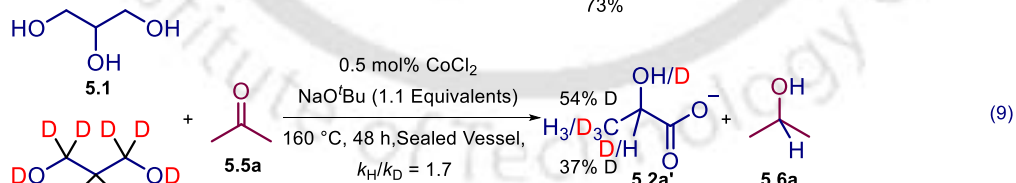
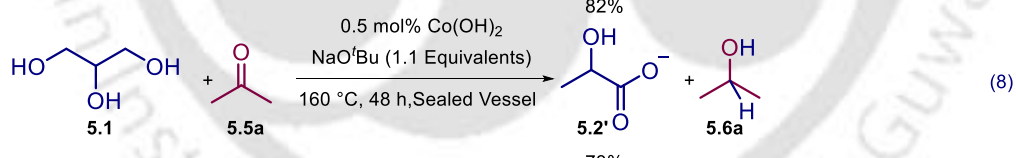
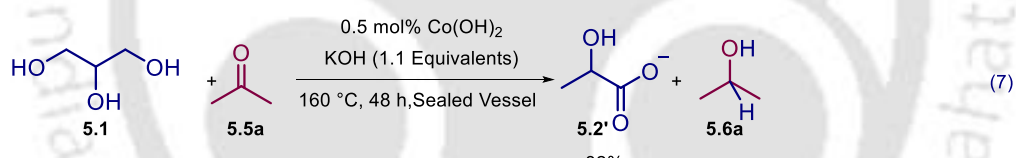
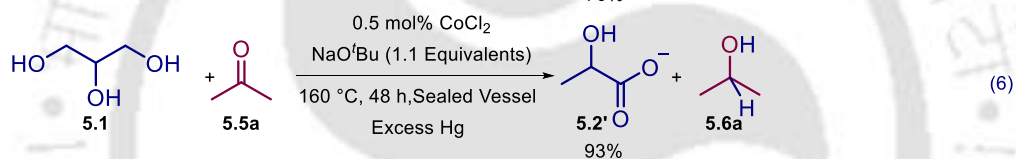
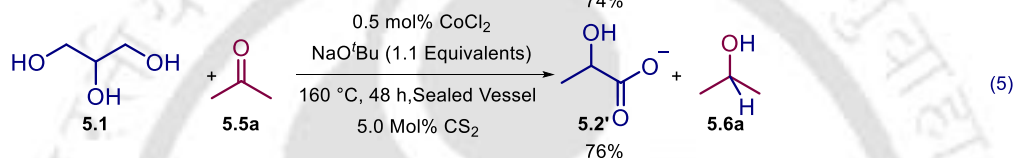
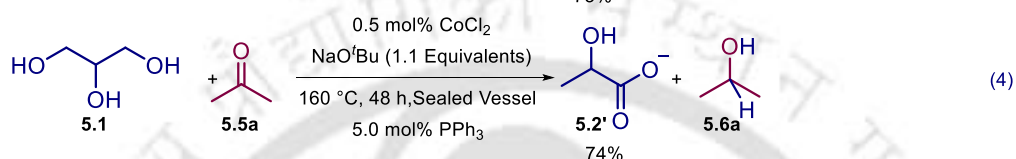
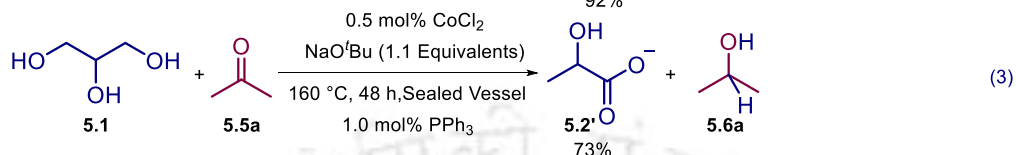
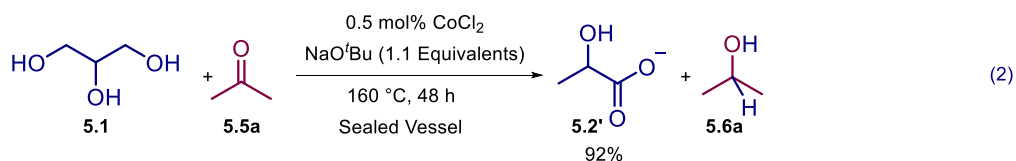
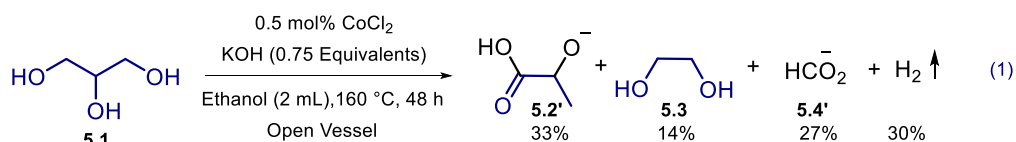
The liberated hydrogen has been independently detected (Figure D49, Appendix D) by GC analysis of the head-space of the vessel containing the reaction mixture corresponding to the

Table 5.2. The transfer dehydrogenative transformation of glycerol to lactic acid catalysed by CoCl_2 .^a

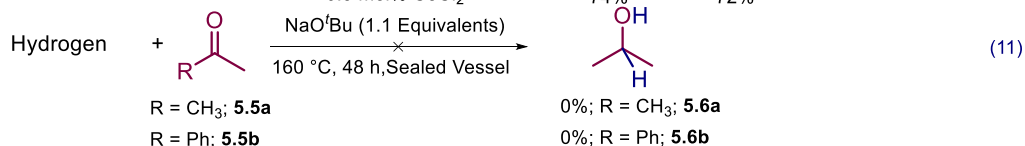
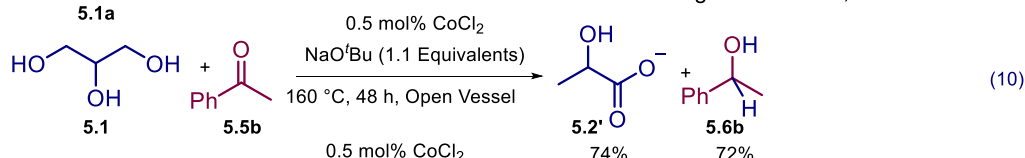
5.1 + 5.5a-c $\xrightarrow[\text{Sealed Vessel}]{\text{X mol\% CoCl}_2, \text{Base (Y Equivalents)}, 160\text{ }^\circ\text{C}, 48\text{ h}}$ 5.2' + 5.6a-c $\xrightarrow{\text{Work-up with Acid}}$ 5.2 $\text{a; R}_1 = \text{R}_2 = \text{Me}$ $\text{b; R}_1 = \text{Ph}, \text{R}_2 = \text{Me}$ $\text{c; R}_1 = \text{Ph}, \text{R}_2 = \text{H}$					
Entry	CoCl_2 Mol%	Base Equivalents	5.5a-c	% Glycerol Conversion ^b	% Yield ^b (% Selectivity) ^c 5.2'
1	0.5	KOH (0.75)	5.5a	52	50 (96)
2	0.5	KOH (1)	5.5a	70	67 (96)
3	0.5	KOH (1.1)	5.5a	81	81 (100)
4	0.75	KOH (1.1)	5.5a	77	70 (91)
5	0.25	KOH (1.1)	5.5a	78	78 (100)
6 ^d	0.5	KOH (1.1)	5.5a	69	67 (97)
7 ^e	0.5	KOH (1.1)	5.5a	59	58 (98)
8	0.5	KOH (1.1)	5.5b	62	60 (97)
9	0.5	KOH (1.1)	5.5c	4	4 (100)
10 ^f	0.5	KOH (1.1)	5.5a	73	72 (99)
11 ^{g,h}	0.5	KOH (1.1)	5.5b	58	57 (98)
12 ^{g,i}	0.5	KOH (1.1)	5.5b	38	37 (98)
13 ^{g,j}	0.5	KOH (1.1)	5.5b	57	55 (96)
14	0.5	NaOH (1.1)	5.5a	64	64 (100)
15 ^{k,l}	0.5	NaO ^t Bu (1.1)	5.5a	97±3	93±4 (96)
16 ^l	0.5	KO ^t Bu (1.1)	5.5a	63±1	62±1 (98)
17	0.5	NaOEt (1.1)	5.5a	76	73 (96)
18	0.5	Na ₂ CO ₃ (1.1)	5.5a	0	0
19	0.5	K ₂ CO ₃ (1.1)	5.5a	Trace	Trace
20	0.5	NaHCO ₃ (1.1)	5.5a	Trace	Trace
21	0.5	KHCO ₃ (1.1)	5.5a	Trace	Trace
22	0.0	KOH (1.1)	5.5a	15	14 (98)
23	0.5	No Base	5.5a	0	-
24	0.5	NaO ^t Bu (0.75)	5.5a	71	70 (98)
25	0.5	NaO ^t Bu (0.5)	5.5a	47	45 (96)
26	0.5	NaO ^t Bu (0.25)	5.5a	18	16 (89)
27	0.005	NaO ^t Bu (1.1)	5.5a	39	38 (97)

^a Reaction conditions: 5 mmol glycerol, X mol% CoCl_2 , KOH (Y equivalents with respect to glycerol), 1 mL acceptor, at 160 °C, in a 20 mL autoclave under air. ^b Determined from ¹H NMR analysis using sodium acetate as a standard. ^c Selectivity of lactic acid = (yield of lactic acid / conversion of glycerol)100. ^d Reaction was done at 140 °C. ^e Reaction was done at 120 °C. ^f Reaction was done with $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$. ^g Reaction was done under microwave conditions: 5 mmol glycerol, 0.5 mol% CoCl_2 , KOH (1.1 equivalent with respect to glycerol), 1 mL **5.5b**, sealed vessel, 50 W microwave power for 2.5 hours. ^h Reaction was done at 160 °C. ⁱ Reaction was done at 140 °C. ^j Reaction was done at 180 °C. ^k LA **5.2** was isolated in the pure form after workup of the reaction with dilute HCl. ^l Average of two runs.

optimized acceptorless dehydrogenation of glycerol (entry 3, Table 5.1). Furthermore, the amount of hydrogen evolved has been determined by burette measurements (see footnote d of



45% Figure D46-D47, Section D3



Scheme 5.6. Control experiments.

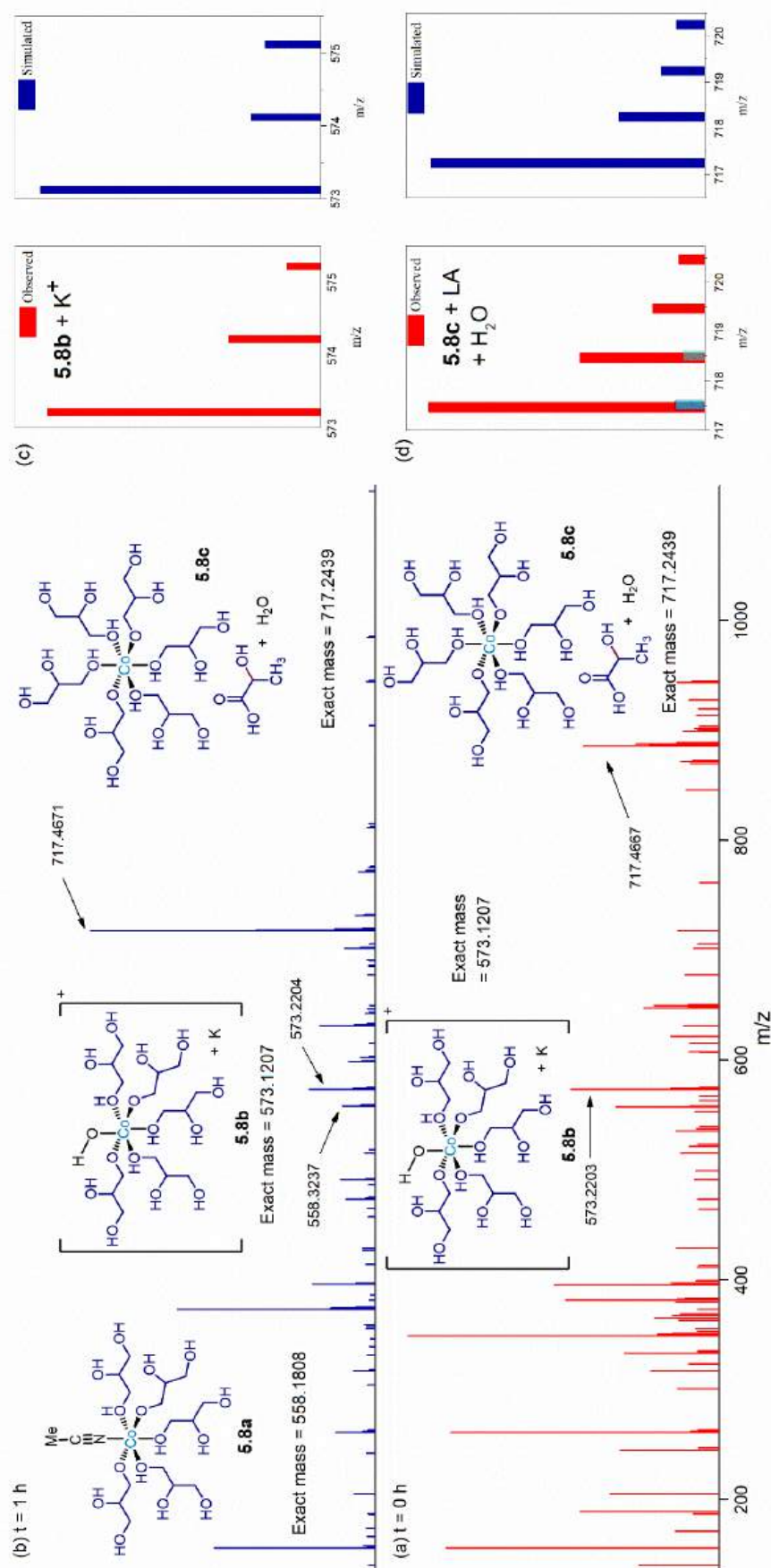


Figure 5.1. HRMS analysis of the reaction mixture obtained from the optimized acceptorless dehydrogenation of glycerol (entry 3, Table 5.1 and equation 1, Scheme 5.6) at (a) $t = 0$ h at room temperature in presence of base and (b) $t = 1$ h at 160°C in presence of base. HRMS (ESI) expanded spectra of $m/z = 573.1207$ (5.8b) (c) observed (red) and simulated (blue). HRMS (ESI) expanded spectra of $m/z = 717.2439$ (5.8c) (d) observed (red) and imulated (blue).

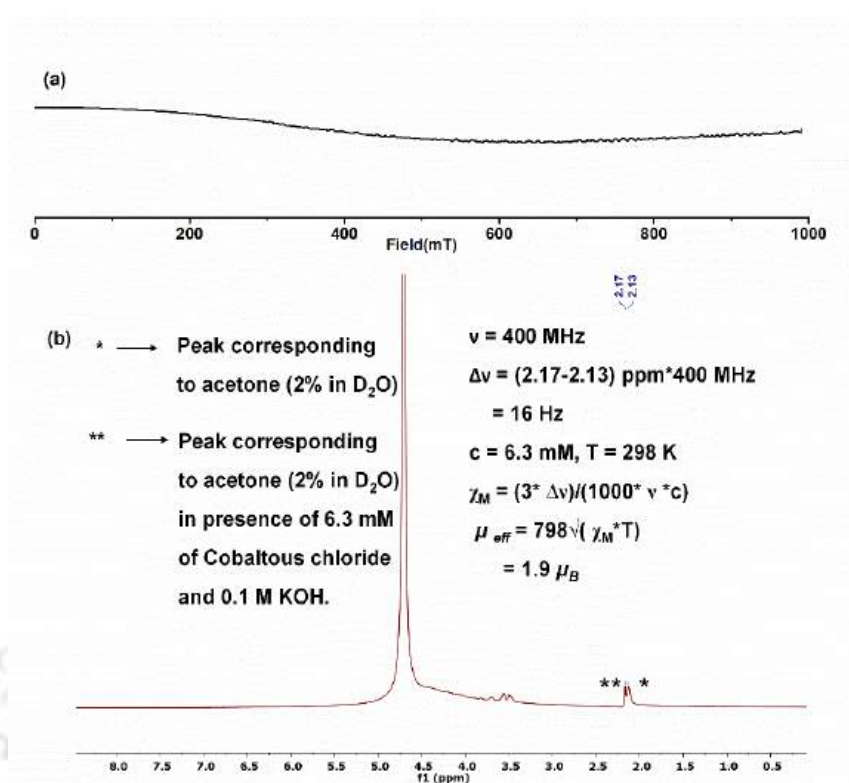
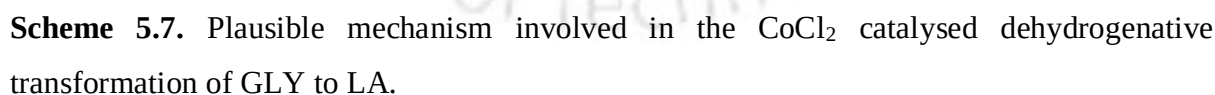


Figure 5.2. (a) EPR analysis of the reaction mixture obtained from the optimized acceptorless dehydrogenation of glycerol (entry 3, Table 5.1 and equation 1, Scheme 5.6). (b) Determination of magnetic moment via Evan's method of the reaction mixture obtained from the optimized acceptorless dehydrogenation of glycerol (entry 3, Table 5.1 and equation 1, Scheme 5.6).

Table 5.1). Upon performing the transfer dehydrogenation of glycerol under the optimized conditions (entry 15, Table 5.2 and equation 2, Scheme 5.6) in the presence of PPh_3 and CS_2 which are well-established⁶¹ poison for heterogeneous catalysts, only a slight decrease in the yield of LA was observed (equations 3,4 and 5, Scheme 5.6). Though PPh_3 or CS_2 can poison both homogeneous and heterogeneous catalysts, one must note the distinct difference in the mode of poisoning. While 1 equivalent of PPh_3 or CS_2 with respect to the catalyst is sufficient to quench the activity of heterogeneous catalyst, more than 1 equivalent of the considered poison is required to inhibit the activity of a homogeneous catalyst.⁶¹ This points to the involvement of molecular Co species in the catalytic cycle. This possibility of the presence of homogeneous catalytic species is further fortified by mercury poisoning test (equation 6, Scheme 5.6) which results in a comparable yield of lactate **5.2'** (yield = 93%, selectivity = 100%) as that obtained under the optimized condition (entry 15, Table 5.2 and equation 2, Scheme 5.6).



Furthermore, HRMS analysis (Figure 5.1) indicates that these molecular octahedral Co(II) species are likely formed *in-situ* by the reaction of CoCl₂ with the reaction mixture. A similar observation was reported by us earlier in the CoCl₂ catalysed β -alkylation of 1-phenyl ethanol with benzyl alcohol.⁵²

A 1:1 mixture of deuterated (D8) glycerol (**5.1a**) and glycerol (**5.1**) when subjected to the optimized transfer dehydrogenation conditions (entry 15, Table 5.2), resulted in 45% yield of LA with a modest KIE of 1.7 (equation 9, Scheme 5.6). This apparent secondary KIE suggests that the catalytic cycle involves a C-H activation step which is not part of the RDS. The inferences obtained from the mechanistic studies (Scheme 5.6, Figure 5.1, Figure 5.2 and discussions *vide-supra*) have been instrumental in elucidating a possible mechanistic path (Scheme 5.7) for the CoCl_2 catalysed dehydrogenation of glycerol to LA.

In the first step, anhydrous CoCl_2 could react with KOH to yield Co(OH)_2 . Comparable yields of lactate **5.2'** in reactions catalysed by CoCl_2 (entry 3, Table 5.2) and Co(OH)_2 (equation 7, Scheme 5.6) fortifies this hypothesis. Simultaneous solvation of Co(OH)_2 by glycerol leads to octahedral Co(II) hydroxide **5.7** which would readily undergo an alcoholysis with glycerol to yield the octahedral Co(II) alkoxide **5.8** along with the loss of water. Similarly, when NaO^tBu , NaOEt , and Na_2CO_3 are used as bases, one can anticipate involvement of $\text{Co(O}^t\text{Bu)}_2$, Co(OEt)_2 , and CoCO_3 that ultimately leads to **5.8** along with the loss of HO^tBu , HOEt and H_2CO_3 respectively. Several derivatives of **5.8** (**5.8a**, **5.8b** and **5.8c**) have been detected by HRMS analysis, Figure 5.1).

A β -hydride elimination from **5.8** would result in the formation of the Co(II) hydride **5.9** and glyceraldehyde **5.11** (Scheme 5.7). A series of uncatalysed reaction involving dehydration of **5.11** to **5.12**, tautomerization of **5.12** to **5.13** and final base mediated intramolecular Cannizzaro in **5.13** leads to the formation of lactate **5.2'** (Scheme 5.7) which upon work-up with dilute HCl leads to LA **5.2**. Under acceptorless dehydrogenation conditions, a σ -bond metathesis between the Co-H bond in **5.9** with the O-H bond of glycerol (Scheme 5.7) could lead to regeneration of **5.8** along with the liberation of hydrogen (detected by GC, Figure D49, Appendix D).

On the other hand, under transfer dehydrogenation conditions, the insertion of carbonyl in **5.5a** into the Co-H bond of **5.9** results in the formation of Co-isopropoxide **5.10** (Scheme 5.7). Subsequent, σ -bond metathesis (hydrogenolysis) of **5.10** with hydrogen can result in the regeneration of **5.9** along with the formation of isopropanol **5.6a** (Scheme 5.7). Alternatively, σ -bond metathesis (alcoholysis) of **5.10** with glycerol can regenerate **5.8** while giving rise to **5.6a** (Scheme 5.7). Considering the fact that the CoCl_2 catalysed reaction of glycerol using high boiling acceptor **5.5b** leading to **5.6b** and LA occurs even in an open vessel (equation 5.10, Scheme 5.6), it can be inferred that both hydrogenolysis (due to any trapped hydrogen in the viscous reaction mixture) and alcoholysis may be contributing to the observed transfer dehydrogenation reactivity. However, the apparent lack of reactivity observed in the

independent reaction of either acetone or acetophenone with hydrogen in the presence of CoCl_2 under standard optimized conditions (equation 11, Scheme 5.6) are indicative of the sole involvement of the alcoholysis step in the CoCl_2 catalysed net transfer dehydrogenation of glycerol to LA. From the mechanism presented (Scheme 5.7), one may note that the salt-metathesis step **5.7**→**5.8** requires only catalytic amounts of base (1 mol%). The rest of the stoichiometric amount (1.1 equivalents) of the base used finds role to play in not only mediating the final intramolecular Cannizzaro step in **5.13** but also in trapping the product LA **5.2** in the form of its Na/K salt (Scheme 5.7). Not surprisingly both the rate and productivity in LA formation increase with increase in concentration of base (entries 24–26, Table 5.2, Figure D50, Appendix D).

5.4. Conclusions

Readily available, inexpensive, environmentally benign and earth-abundant base metal salt cobaltous chloride (0.5 mol%) was successfully used to catalyse the dehydrogenative conversion of glycerol to lactic acid in an acceptorless fashion as well as under transfer dehydrogenation conditions using acetone as a sacrificial acceptor at 160 °C in the presence of various bases. Under the acceptorless conditions, up to 75% conversion of glycerol to lactic acid (33%), ethylene glycol (14%) and formic acid (27%) was observed in addition to hydrogen in the cobaltous chloride (0.5 mol%) catalysed reaction at 160 °C in the presence of 0.75 equivalents of KOH in an open-vessel. Gratifyingly, a maximum of 93% lactic acid with 96% selectivity was obtained when the cobaltous chloride (0.5 mol%) catalysed dehydrogenation of glycerol at 160 °C in the presence of 1.1 equivalents of NaO^tBu was performed with acetone as a sacrificial hydrogen acceptor in a sealed vessel. Isopropanol, a high-value specialty chemical was also obtained as a by-product in these transfer dehydrogenation reactions.

Evidence for the homogeneous nature of the reaction mixture involving molecular Co species was obtained from the transfer dehydrogenation of glycerol at 160 °C in the presence of CoCl_2 (0.5 mol%), NaO^tBu (1.1 equivalents) and excess PPh_3 (10 equivalents with respect to CoCl_2) that demonstrated negligible effect of PPh_3 on the productivity (74%) of the reaction. Further, Hg drop experiment confirmed the homogeneous nature of the reaction mixture. Further, these molecular species in the catalytic cycle appear to be octahedral Co(II) species formed *in-situ* in the reaction mixture as inferred from EPR analysis, HRMS studies and determination of magnetic moment by Evans method. Deuterium labelling studies are indicative of the participation of the C-H bond activation in the catalytic cycle but not in the RDS with a modest

secondary KIE of 1.7. Alcoholysis rather than hydrogenolysis is apparently the sole contributor to the observed net transfer dehydrogenation activity.

5.5. Experimental Section

Materials and methods: All the reactions were carried out in air. All the chemicals were purchased from MERCK or Sigma-Aldrich or Himedia and used as such.

5.5.1. Physical measurements:

^1H , $^{13}\text{C}\{\text{H}\}$ and ^2H NMR was recorded either on a Bruker ASCEND 600 operating at 600 MHz for ^1H and ^2H and 151 MHz for $^{13}\text{C}\{\text{H}\}$ or and 151 MHz for 400 MHz for ^1H . Chemical shifts (δ) are reported in ppm, spin–spin coupling constants (J) are expressed in Hz, and other data are reported as follows: s = singlet, d = doublet and q = quartet. HRMS measurements were recorded using an Agilent Accurate-Mass QTOF ESI-MS 6520. The X-band EPR spectra was recorded on a JESFA200 ESR spectrometer. GC analysis (TCD detection) was performed on an Agilent 7820-GC instrument fitted with Agilent Front SSZ Inlet N2 using a HPLOT Q column (30 m length $\times$ 530 μm $\times$ 40 μm). Agilent 7820-GC back detector TCD Oven temperature: 50 $^\circ\text{C}$, time at starting temp: 0 min, Hold time = 10 min, inlet temperature: 100 $^\circ\text{C}$, detector temperature (TCD): 250 $^\circ\text{C}$, detector temperature (FID): 300 $^\circ\text{C}$, flow rate (carrier): 5 mL/min (N_2), split ratio: 10.

5.5.2. General procedure for the acceptorless dehydrogenation of glycerol under conventional heating: A 50 mL one-necked round bottom flask containing glycerol (0.460 g, 5 mmol), CoCl_2 (0.0032 g, 0.025 mmol), KOH (0.2102 g, 3.747 mmol) and solvent (2 mL) connected to a burette (to determine the amount of gas evolved) through a water-cooled condenser, were added. The reaction mixture was stirred at room temperature for 5–10 minutes to make a homogeneous solution. The resulting homogeneous green solution was then allowed to stir at 160 $^\circ\text{C}$ for 48 h in air. After 48 h, the reaction mixture was brought to room temperature and 1 mL water was added and mixed thoroughly. An aliquot was drawn from the reaction mixture for NMR analysis. The conversion of glycerol as well as the yield of lactate **5.2'**, ethylene glycol **5.3** and formate **5.4'** were determined from ^1H NMR analysis using sodium acetate as standard and D_2O as the NMR solvent. The amount of hydrogen evolved was quantified via measurement of water displacement in a burette after deducting the contribution from a blank experiment done under identical conditions but without any CoCl_2 .

5.5.3. General procedure for the transfer dehydrogenation of glycerol under conventional heating: In a 20 mL stainless steel autoclave containing a teflon liner, glycerol (0.460 g, 5

mmol) followed by CoCl_2 (0.0032 g, 0.025 mmol), NaO^tBu (0.5281 g, 5.4956 mmol) and acetone (1 mL, 13.75 mmol) were added. The reaction mixture was then allowed to stir at 160 °C for 48 h. After 48 h, the reaction mixture was brought to room temperature and 1 mL water was added and mixed thoroughly. An aliquot was drawn from the reaction mixture for NMR analysis. The yield of lactate **5.2'** was determined as 93% from ^1H NMR analysis using sodium acetate as standard and D_2O as the NMR solvent. Solvent was evaporated from the rest of the reaction mixture under reduced pressure. The residue was washed with dilute HCl and extracted with ethyl acetate. The organic portion was separated and dried over anhydrous Na_2SO_4 prior to its removal under reduced pressure to yield pure LA **5.2** as a colorless oil (0.36 g, 80%). ^1H NMR (400 MHz, Deuterium Oxide): δ 4.04 (q, J = 6.3 Hz, 1H), 1.26 (d, J = 6.7 Hz, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (151 MHz, Deuterium Oxide): δ 181.62 (COOH), 67.59 (CH(OH)), 19.14 (CH_3).

5.5.4. General procedure for the transfer dehydrogenation of glycerol under microwave heating: In a 10-mL microwave vial, glycerol (0.460 g, 5 mmol) followed by CoCl_2 (0.0032 g, 0.025), KOH (0.3083 g, 5.4956 mmol) and acetophenone (1 mL, 8.57 mmol) were added. The reaction mixture was then allowed to stir at 160 °C for 2.5 h under microwave conditions (50 W microwave power). After 2.5 h, the reaction mixture was brought to room temperature and 1 mL water was added and mixed thoroughly. An aliquot was drawn from the mixture for NMR analysis. The yield of lactate was determined from ^1H NMR analysis using sodium acetate as standard and D_2O as the NMR solvent.

5.6. References

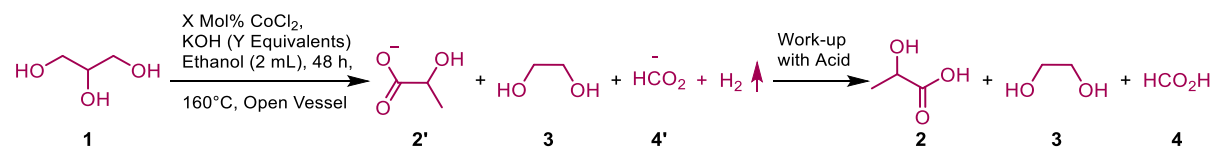
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Appendix D

D1. Optimization Studies

Table D1. Glycerol acceptorless dehydrogenation to lactic acid catalysed by CoCl₂ under varying conditions^a

Entry	CoCl ₂ X mol%	KOH (Y equiv.)	LA yield (%) ^b /LA sel. ^c (%)	Total Vol. of gas evolved (mL)	Vol. of gas Of blank reaction (mL)	Vol. of H ₂ (mL) = (vol of total - vol of blank) (mL)	Yield of H ₂ (%) ^d
1	0.5	0.25	25 (38)	57.7	28.2	29.5	24
2	0.5	0.5	29 (45)	59.2	29.2	30	25
3	0.5	0.75	33 (44)	66.1	29	37.1	30
4	0.5	1	32 (39)	67	30	37	30
5	0.25	0.75	23 (42)	56.2	29	27.2	22
6	0.75	0.75	33 (43)	67	29	38	31
7	1	0.75	34 (44)	65	29	36	29
8 ^e	0.5	0.75	19 (53)	55	35.7	19.3	16
9 ^f	0.5	0.75	5 (42)	-			Not Detected
10	0	0.75	5 (45)	-			Not Detected
11	0.5	0	0				0
12 ^g	0.5	0.75	17±1 (48)	55.7	36.2	19.5	15
13 ^h	0.5	0.75	0				0
14 ⁱ	0.5	0.75	16 (51)	51.2	34	17.2	14
15 ^j	0.5	0.75	22 (55)	56.8	30.3	26.5	22
16 ^k	0.5	0.75	17 (55)	52.5	34.5	18	14
17 ^l	0.5	0.75	18 (51)	57.7	38.5	19.2	16

^a Reaction conditions: 5 mmol glycerol, X mol% CoCl₂, KOH (Y equivalents with respect to glycerol), 2 mL ethanol, 160 °C, 48 h in an open vessel (one neck round bottom flask) under air. ^b Determined from ¹H NMR using sodium acetate as an internal standard. ^c Selectivity of lactic acid = (yield of lactic acid/conversion of glycerol)100. ^d Hydrogen evolution was determined by burette measurements after deducting the blank contribution. Yield of hydrogen was calculated as (moles of H₂(as observed from GC and the amount of gas evolved)/moles of 5.1)100. ^e Reaction performed at 170 °C. ^f Reaction performed at 140 °C. ^g 1 mL dioxane was used. ^h 1 mL DMF was used. ⁱ 1 mL o-xylene was used. ^j 1 mL acetone was used. ^k 1 mL water was used. ^l 1 mL methanol was used.

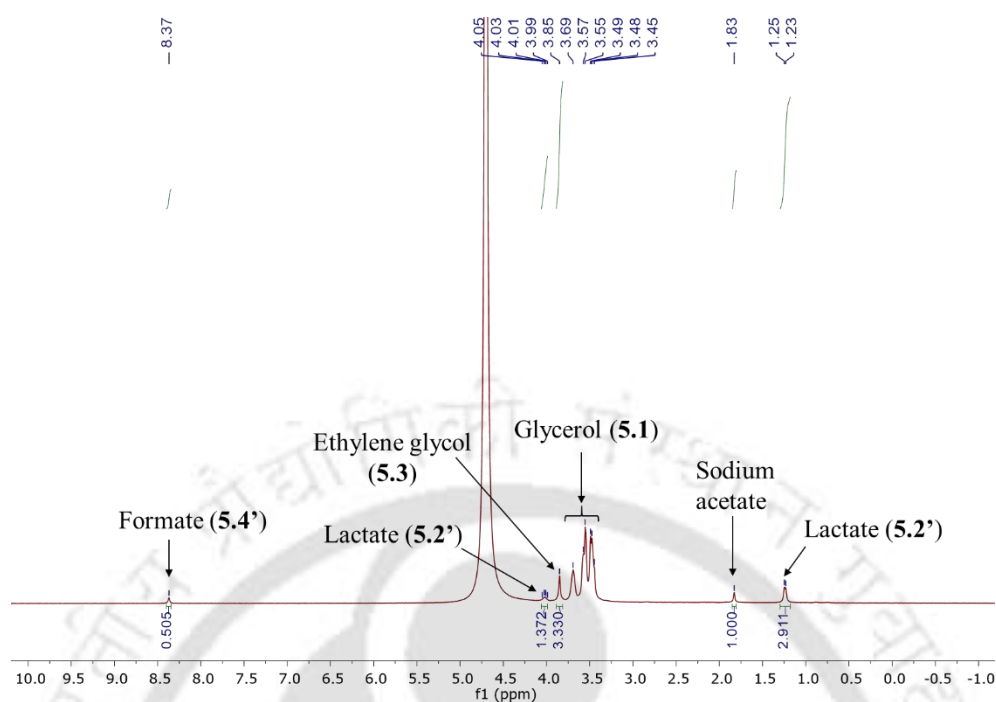
D2. NMR Spectra:

Figure D1: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.25 equivalents KOH , at 160°C . (entry 1, Table 5.1).

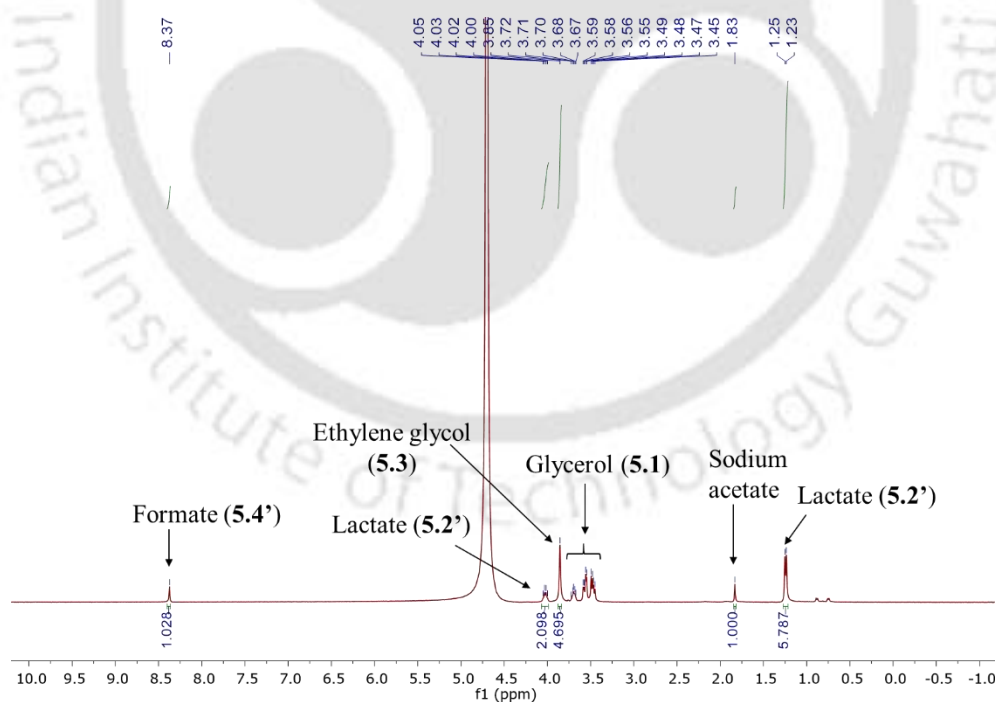


Figure D2: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.5 equivalents KOH , at 160°C . (entry 2, Table 5.1).

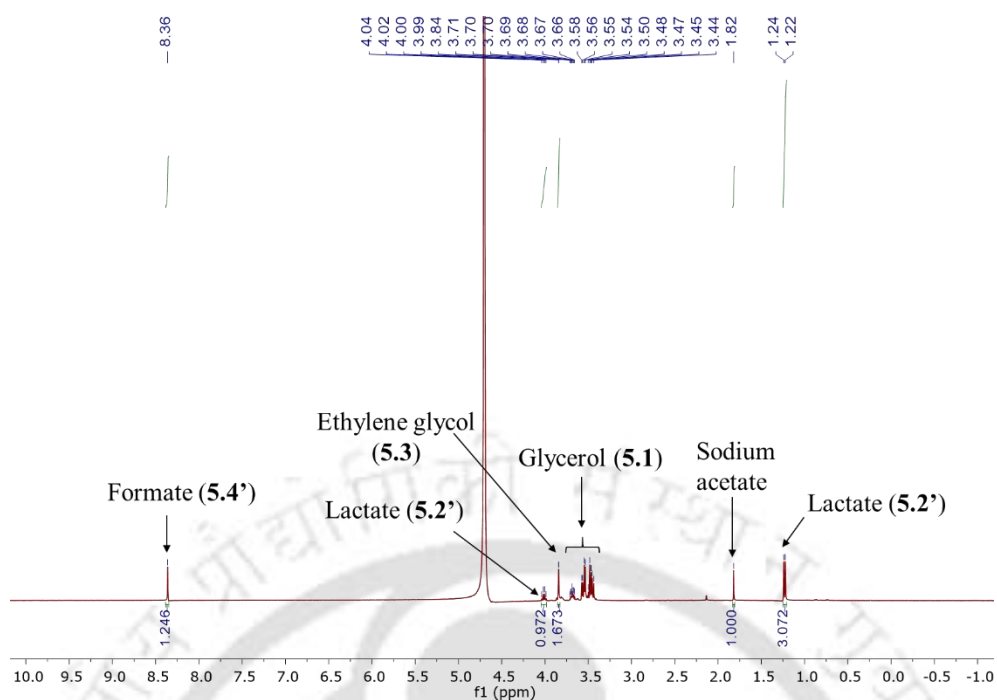


Figure D3: ¹H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 0.75 equivalents KOH, at 160 °C. (entry 3, Table 5.1).

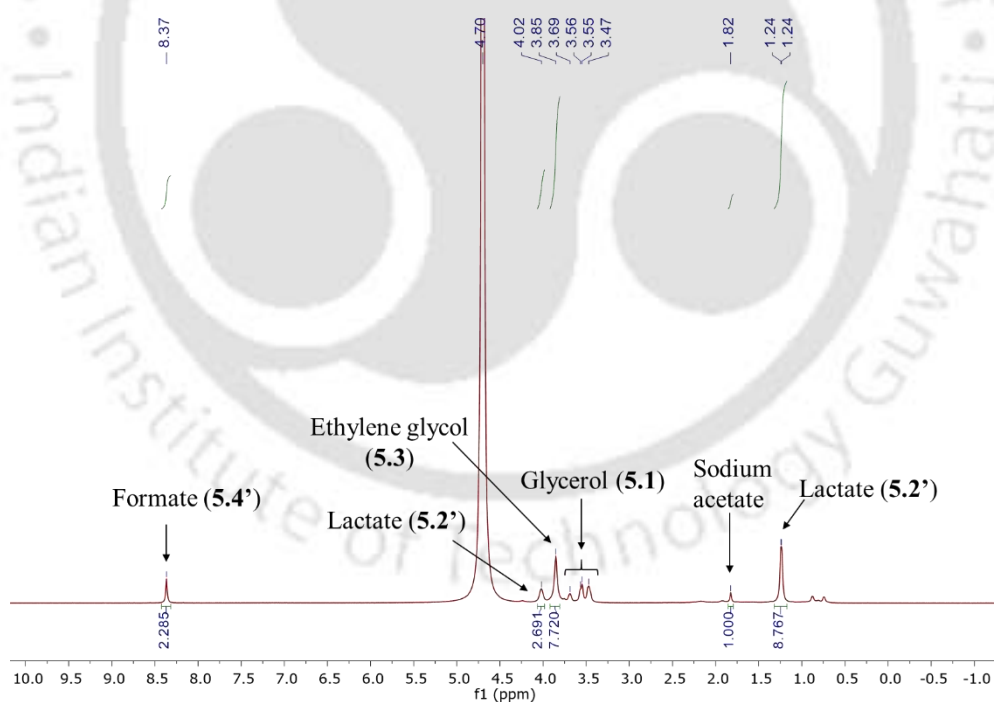


Figure D4: ¹H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1 equivalent KOH, at 160 °C. (entry 4, Table 5.1).

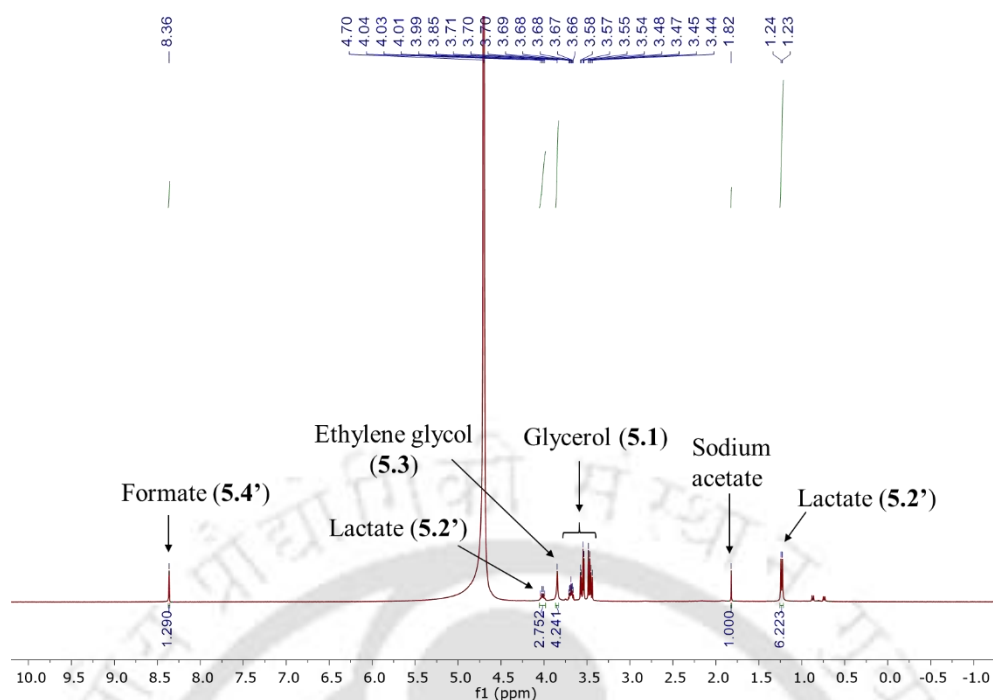


Figure D5: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.25 mol% CoCl_2 , 0.75 equivalents KOH, at 160 $^\circ\text{C}$. (entry 5, Table 5.1).

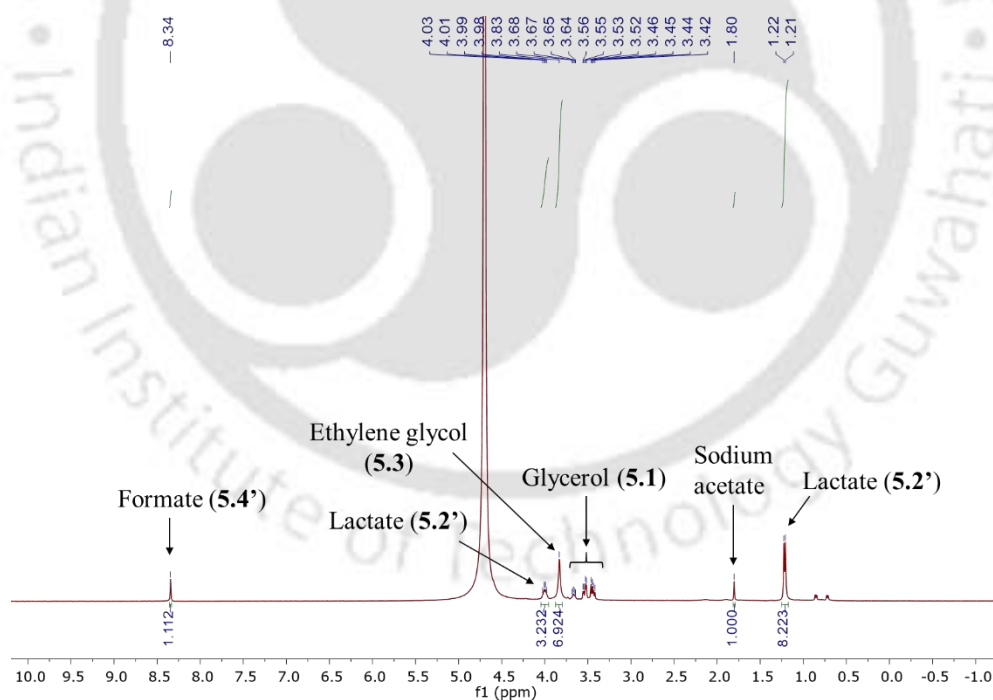


Figure D6: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.75 mol% CoCl_2 , 0.75 equivalents KOH, at 160 $^\circ\text{C}$. (entry 6, Table 5.1).

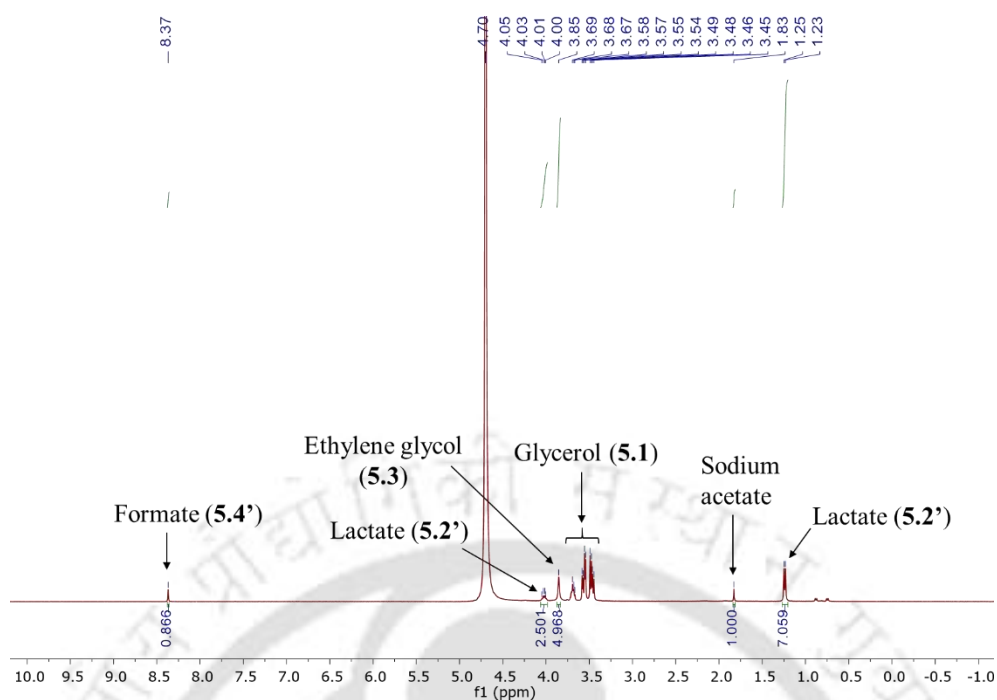


Figure D7: ¹H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 0.75 equivalents KOH, at 170 °C. (entry 8, Table 5.1).

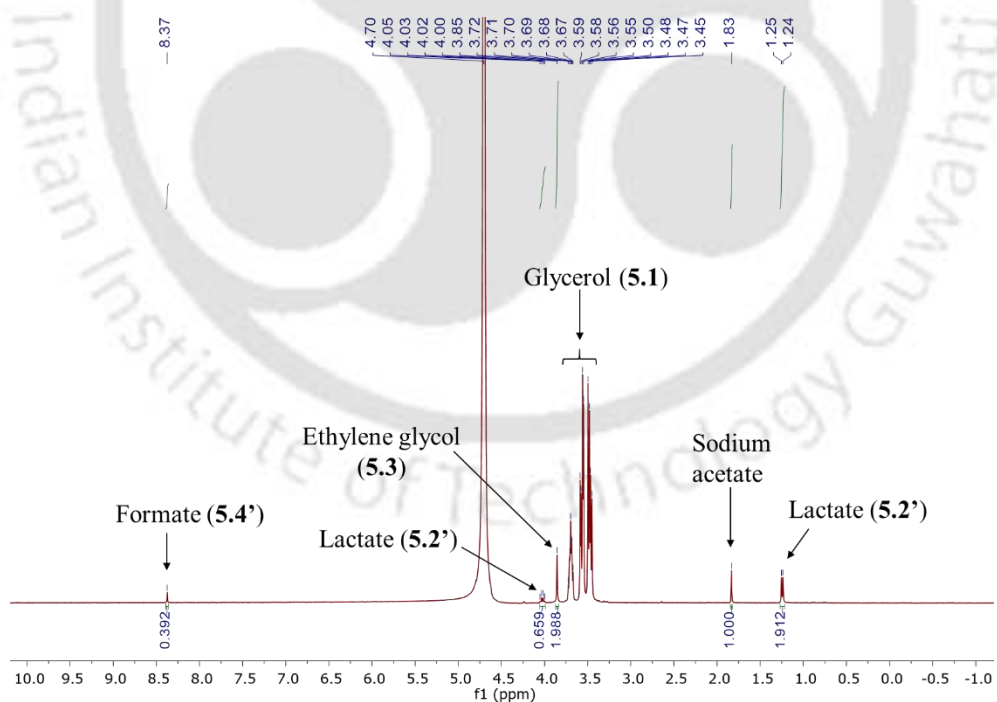


Figure D8: ¹H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 0.75 equivalents KOH, at 140 °C. (entry 9, Table 5.1).

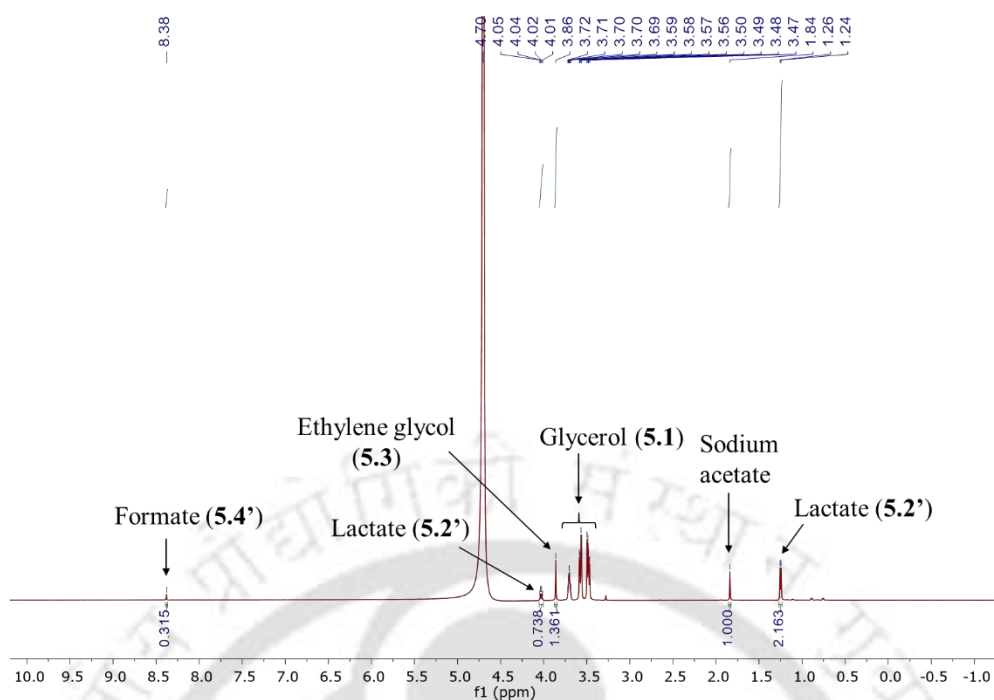


Figure D9: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.75 equivalents KOH , dioxane, at 160 $^\circ\text{C}$. (entry 12, Table 5.1).

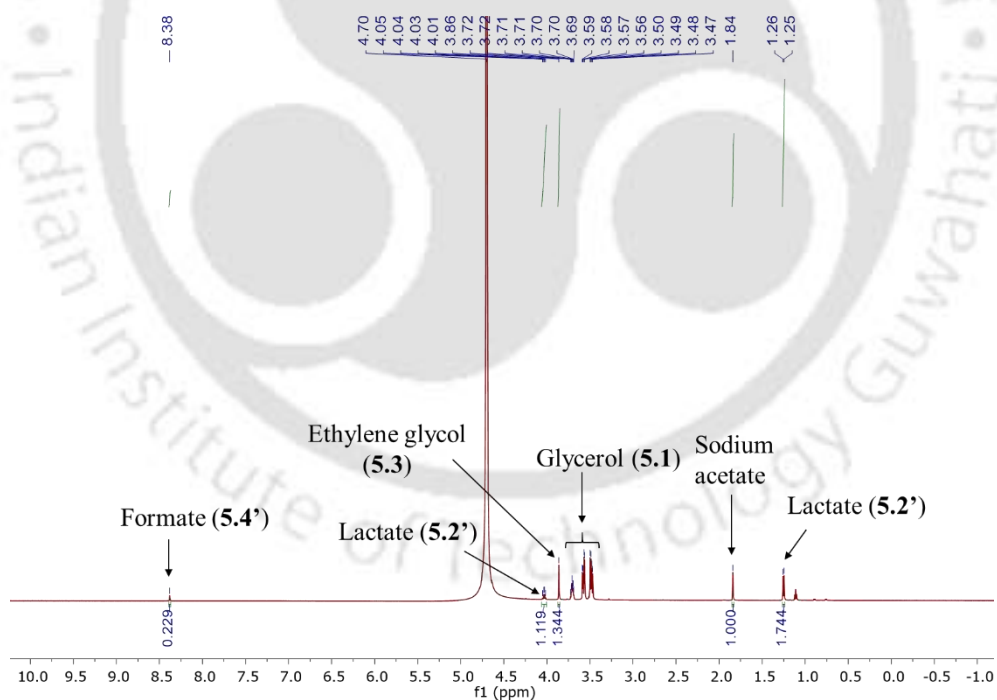


Figure D10: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.75 equivalents KOH , *o*-xylene, at 160 $^\circ\text{C}$. (entry 14, Table 5.1).

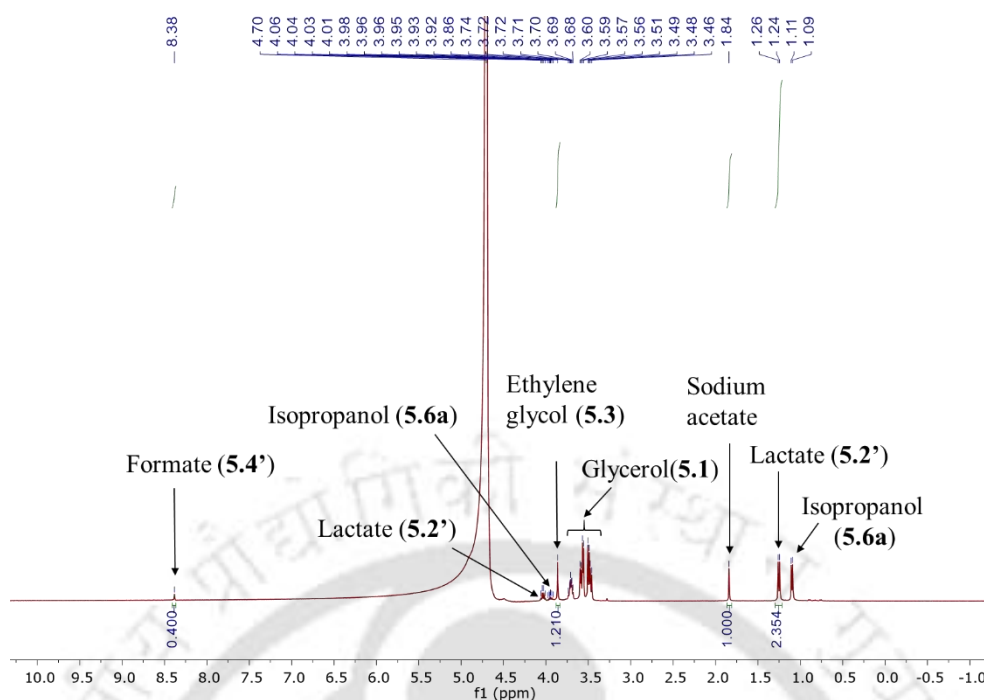


Figure D11: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.75 equivalents KOH, acetone, at 160 °C. (entry 15, Table 5.1).

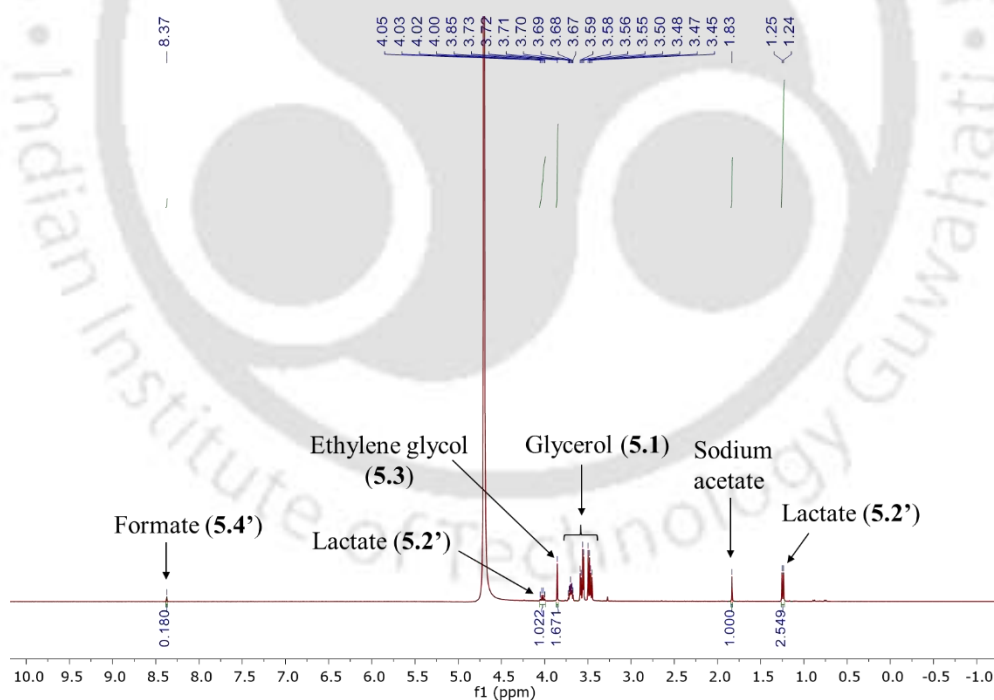


Figure D12: ^1H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.75 equivalents KOH, water, at 160 °C. (entry 16, Table 5.1).

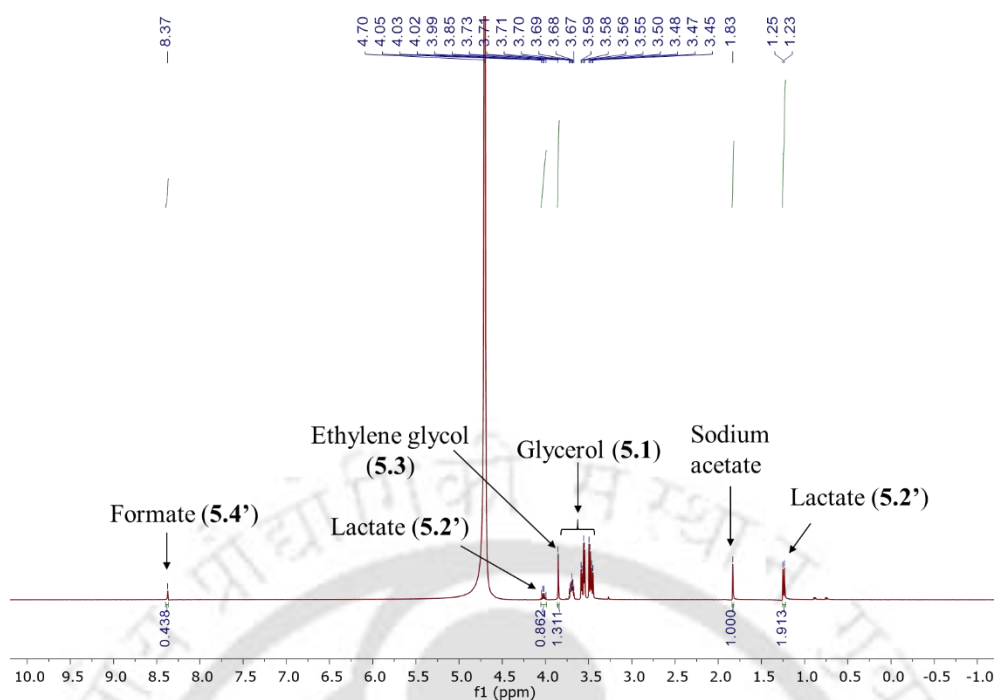


Figure D13: ¹H NMR spectra of glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 0.75 equivalents KOH, methanol, at 160 °C. (entry 17, Table 5.1).

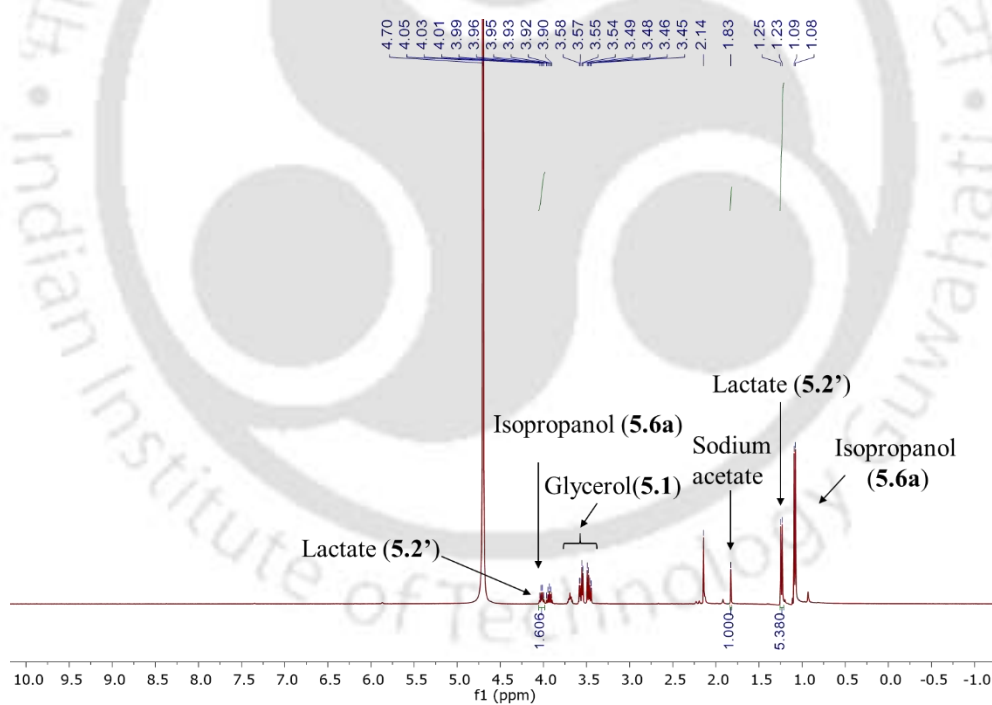


Figure D14: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 0.75 equivalents KOH using acetone as hydrogen acceptor, at 160 °C. (entry 1, Table 5.2).

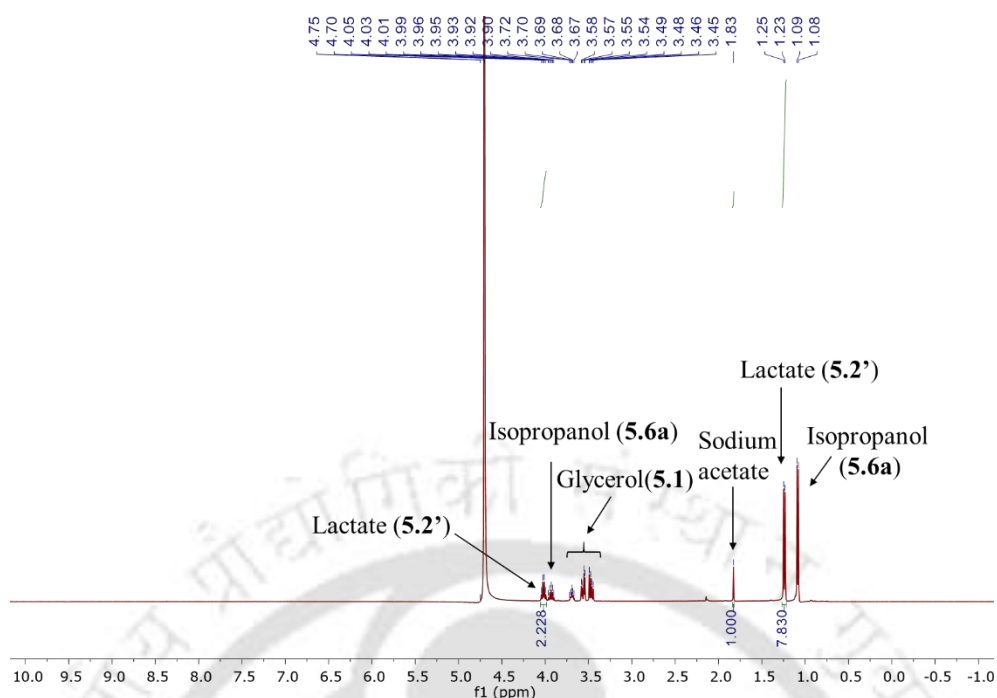


Figure D15: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1 equivalent KOH using acetone as hydrogen acceptor, at 160 °C. (entry 2, Table 5.2).

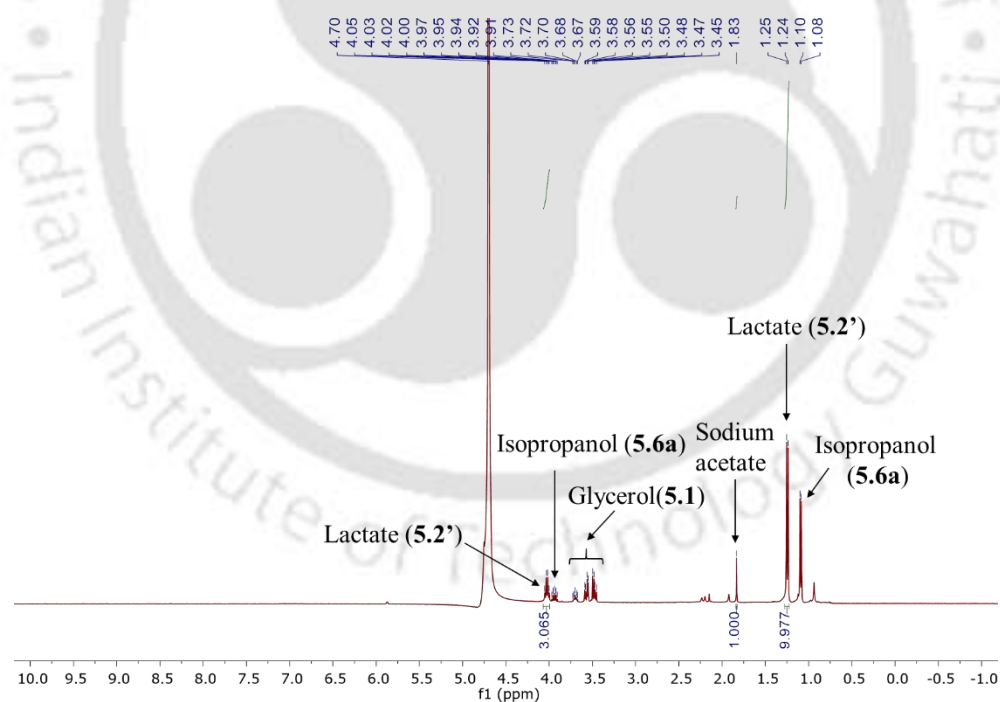


Figure D16: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents KOH using acetone as hydrogen acceptor, at 160 °C. (entry 3, Table 5.2).

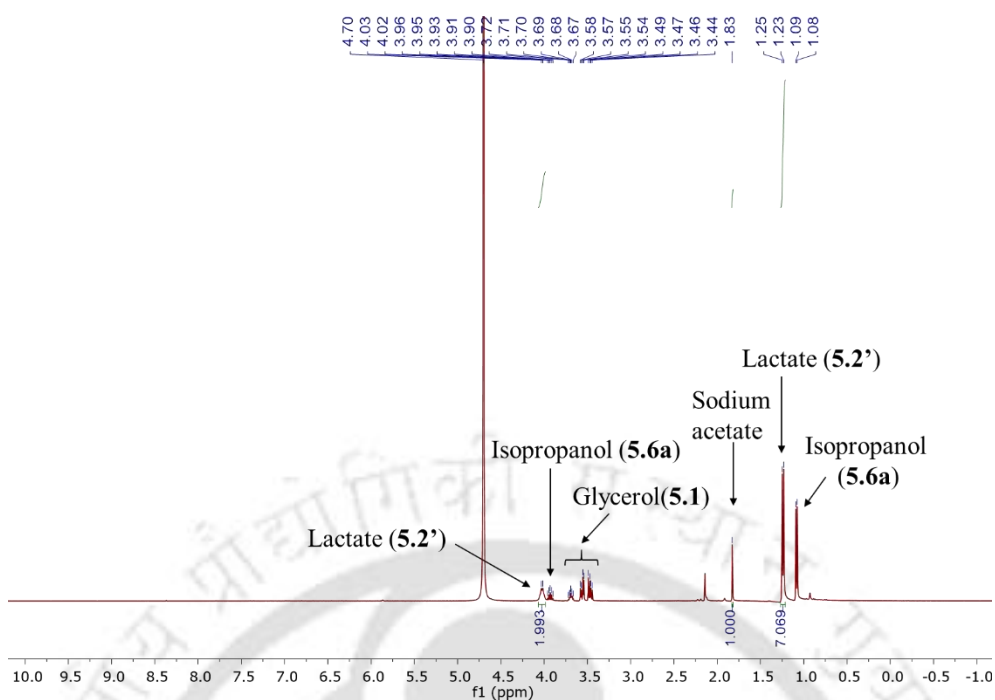


Figure D17: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.75 mol% CoCl_2 , 1.1 equivalents KOH using acetone as hydrogen acceptor, at 160 °C. (entry 4, Table 5.2).

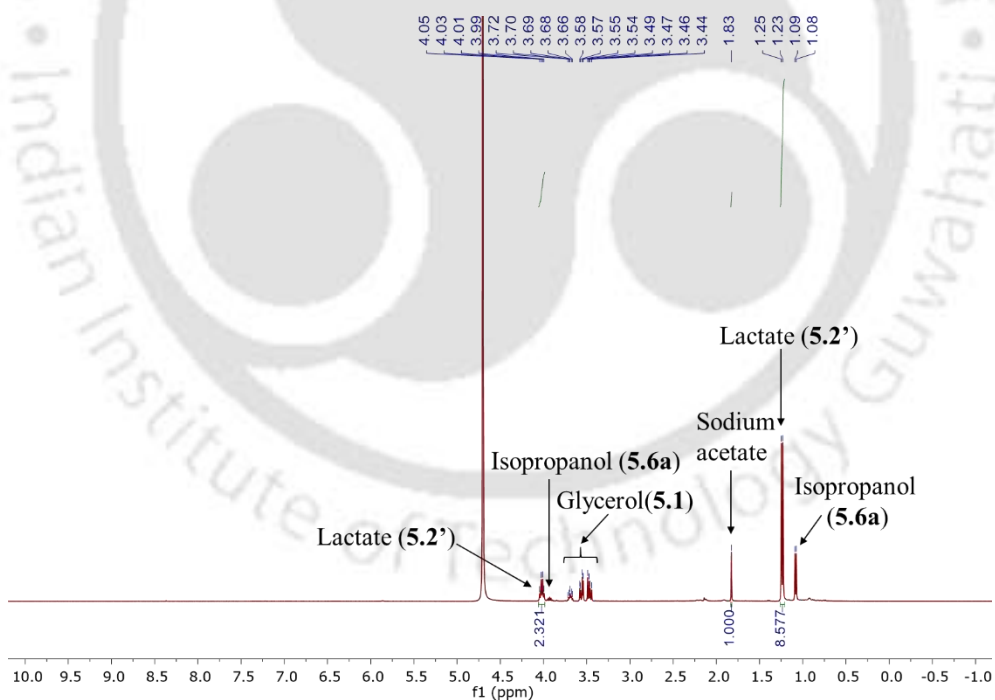


Figure D18: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.25 mol% CoCl_2 , 1.1 equivalents KOH using acetone as hydrogen acceptor, at 160 °C. (entry 5, Table 5.2).

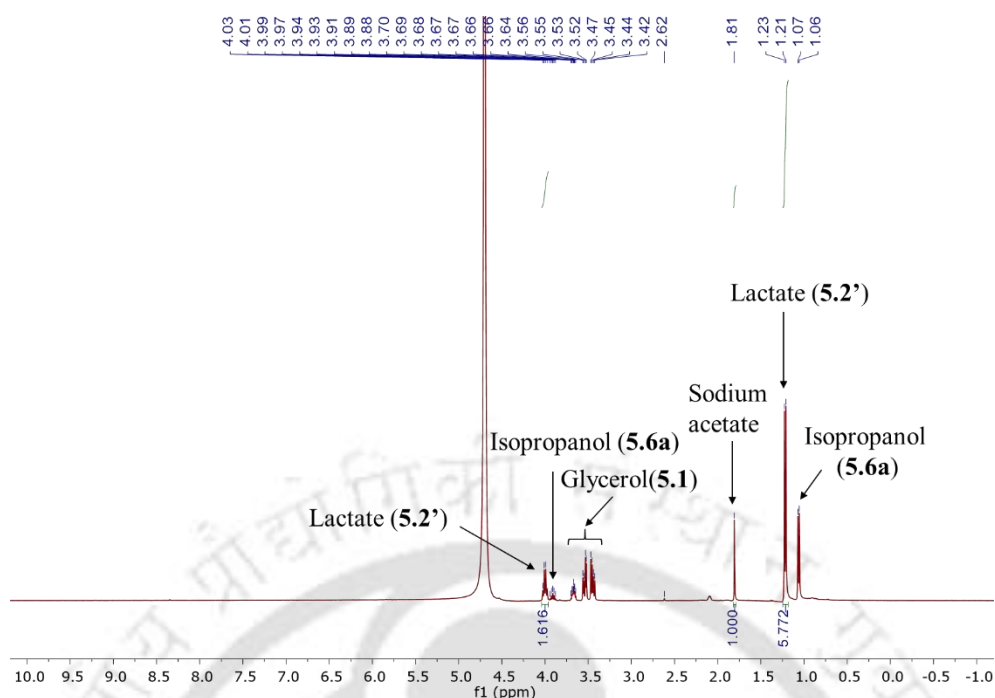


Figure D19: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents KOH using acetone as hydrogen acceptor, at 140 °C. (entry 6, Table 5.2).

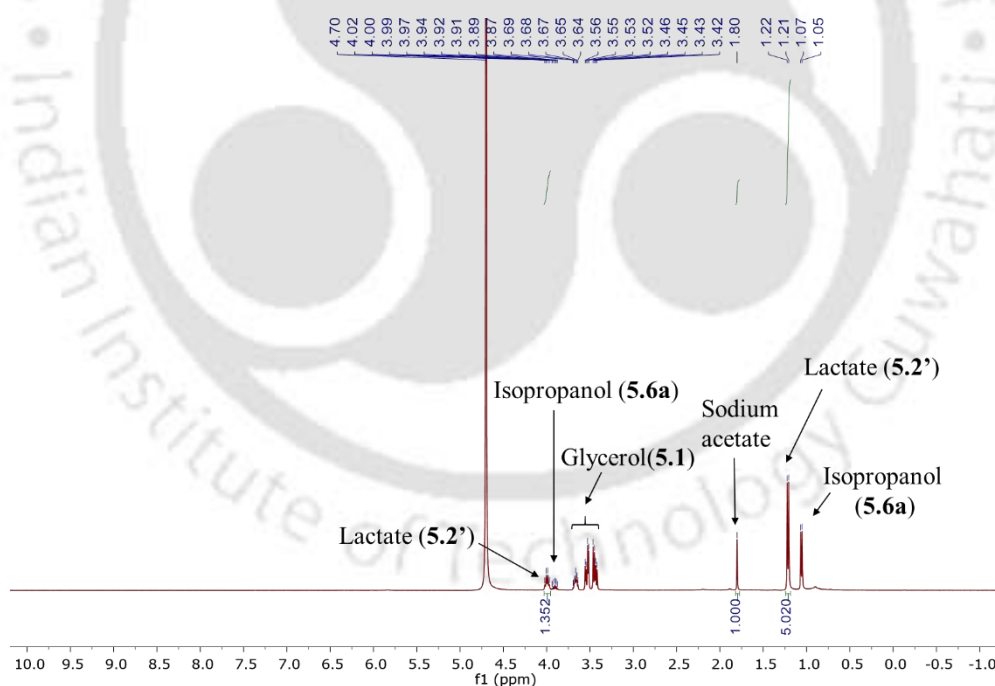


Figure D20: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents KOH using acetone as hydrogen acceptor, at 120 °C. (entry 7, Table 5.2).

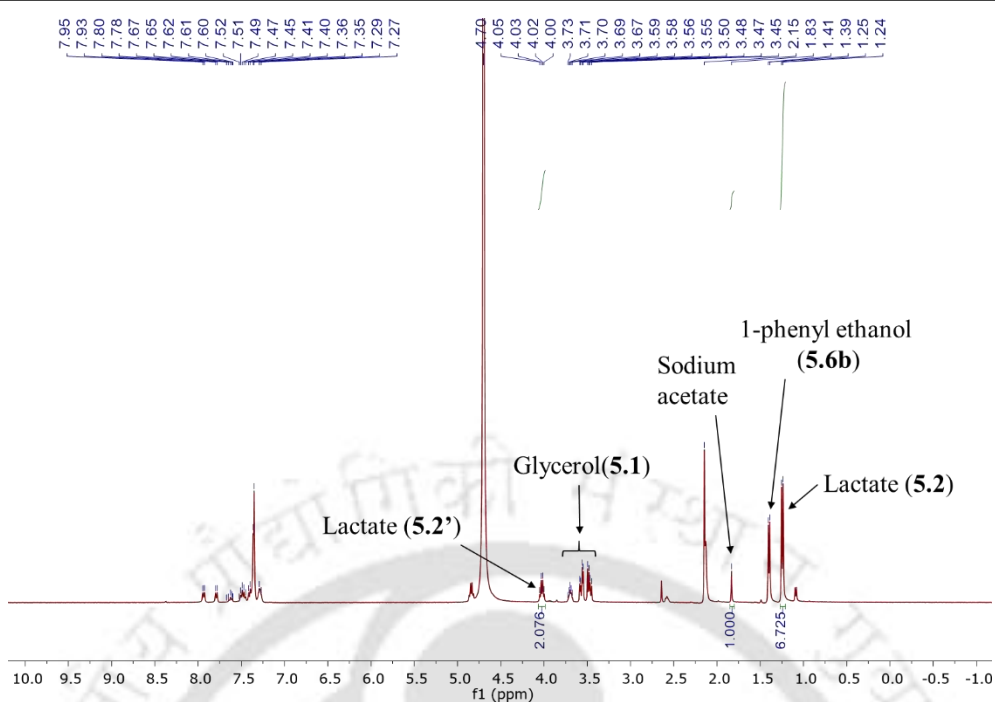


Figure D21: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents KOH using acetophenone as hydrogen acceptor, at 160 °C. (entry 8, Table 5.2).

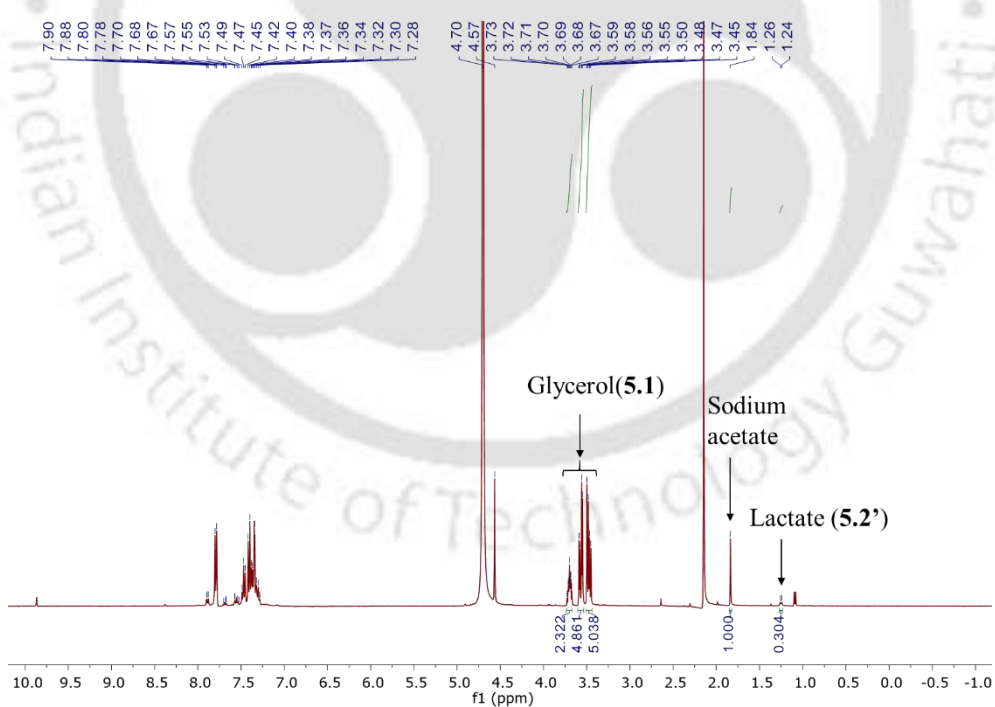


Figure D22: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents KOH using benzaldehyde as hydrogen acceptor, at 160 °C. (entry 9, Table 5.2).

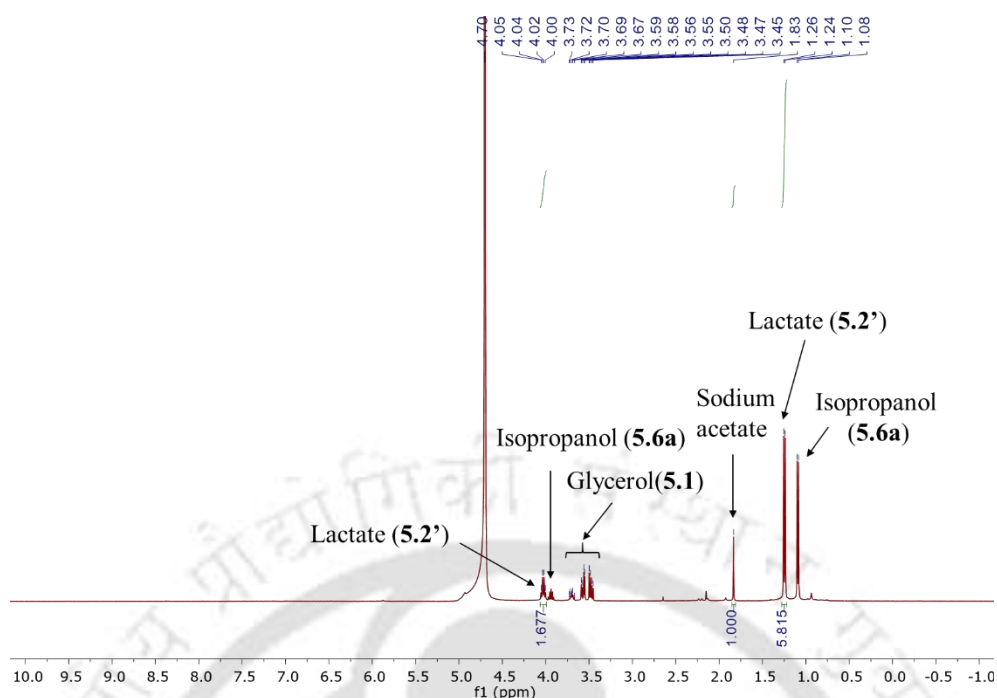


Figure D23: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, 1.1 equivalents KOH using benzaldehyde as hydrogen acceptor, at 160 °C. (entry 10, Table 5.2).

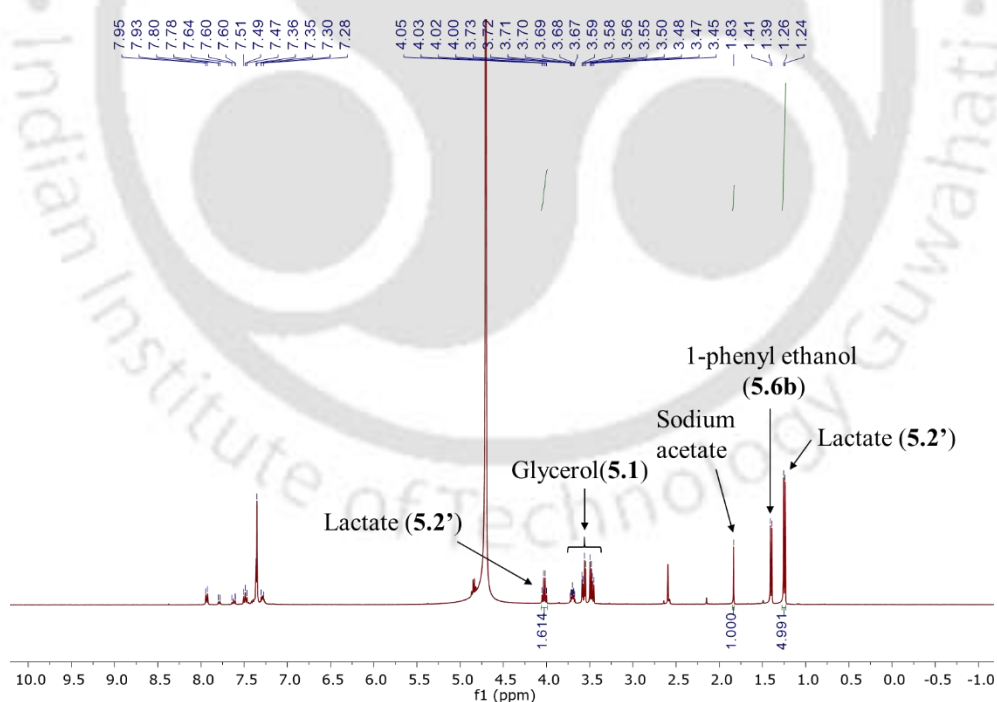


Figure D24: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents KOH using acetophenone as hydrogen acceptor under microwave conditions (50 W microwave power, 160 °C). (entry 11, Table 5.2).

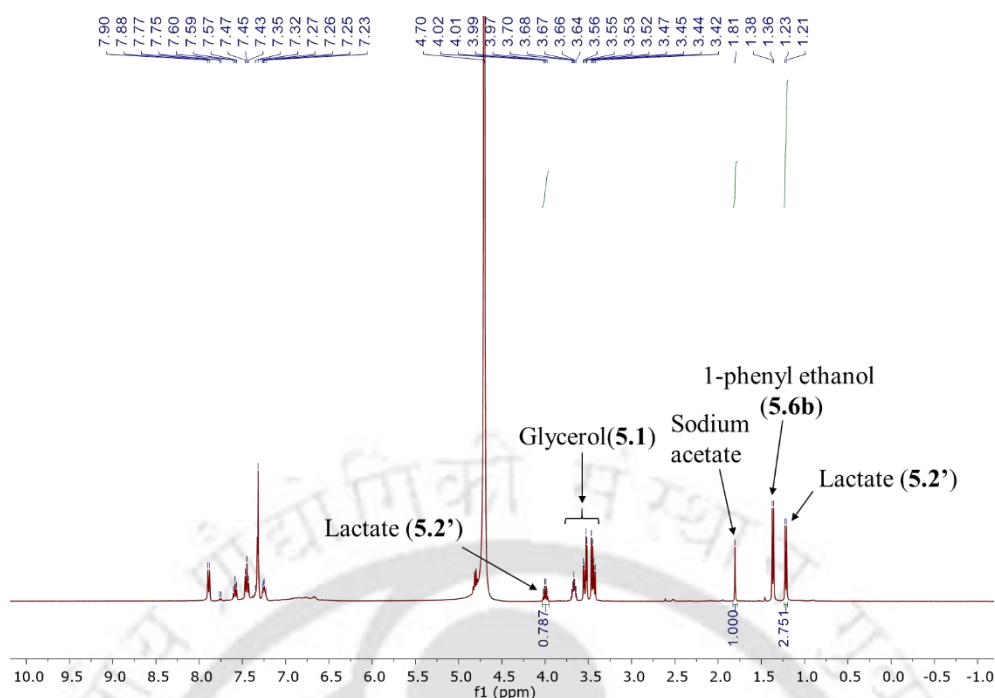


Figure D25: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents KOH using acetophenone as hydrogen acceptor under microwave conditions (50 W microwave power, 140 °C). (entry 12, Table 5.2).

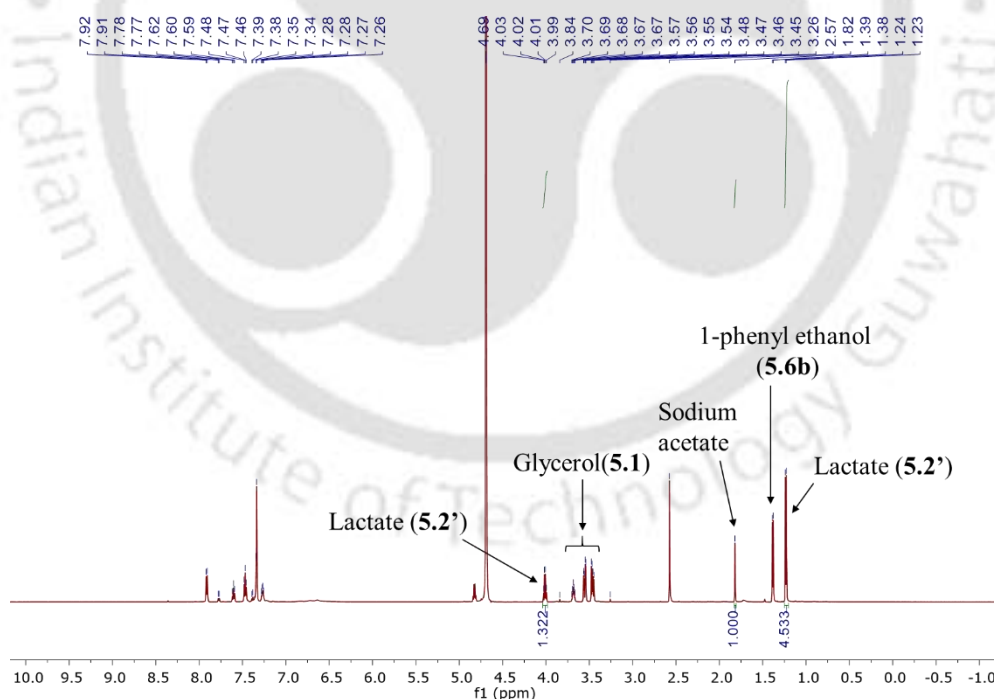


Figure D26: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents KOH using acetophenone as hydrogen acceptor under microwave conditions (50 W microwave power, 180 °C). (entry 13, Table 5.2).

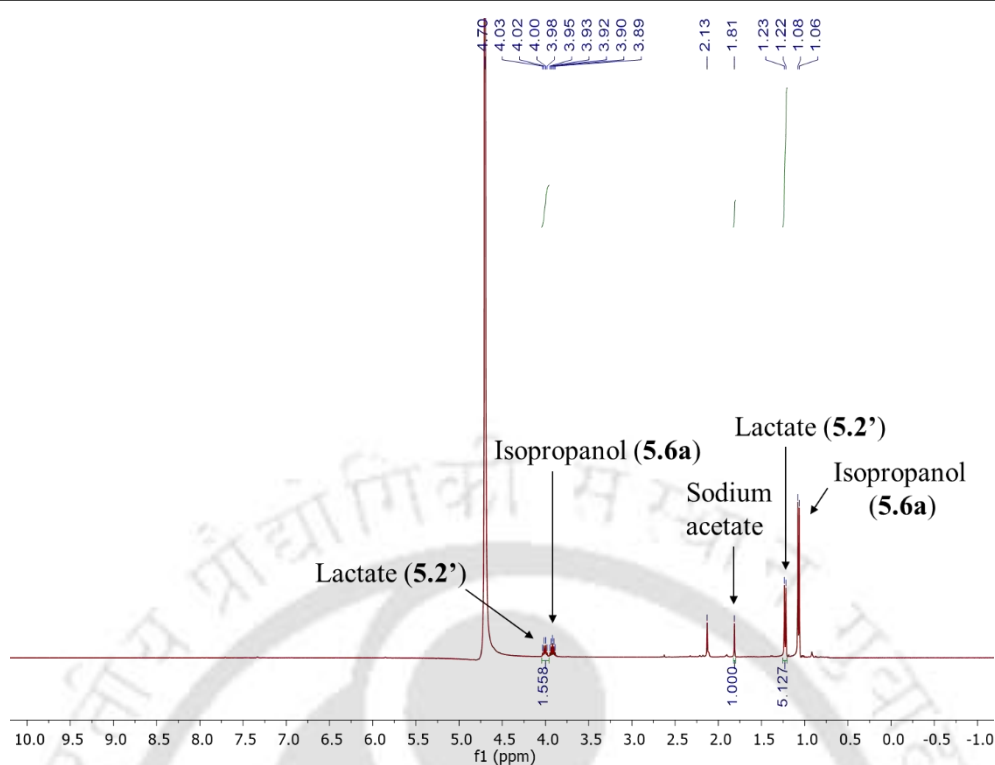


Figure D27: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents NaOH using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 14, Table 5.2).

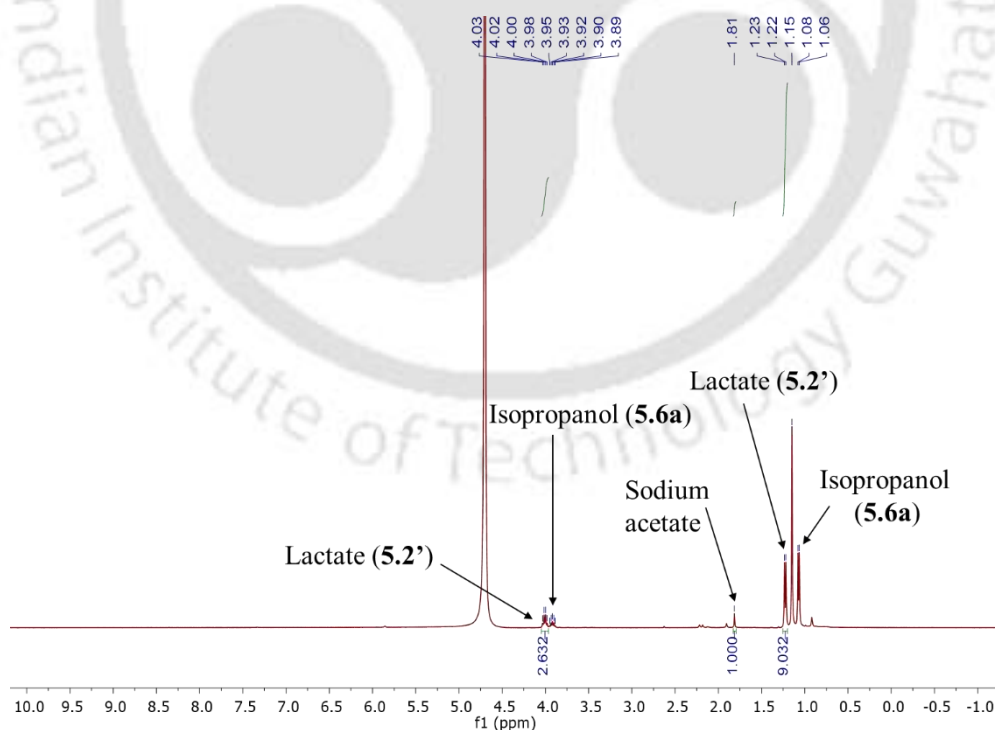


Figure D28: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents NaO^tBu using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 15, Table 5.2).

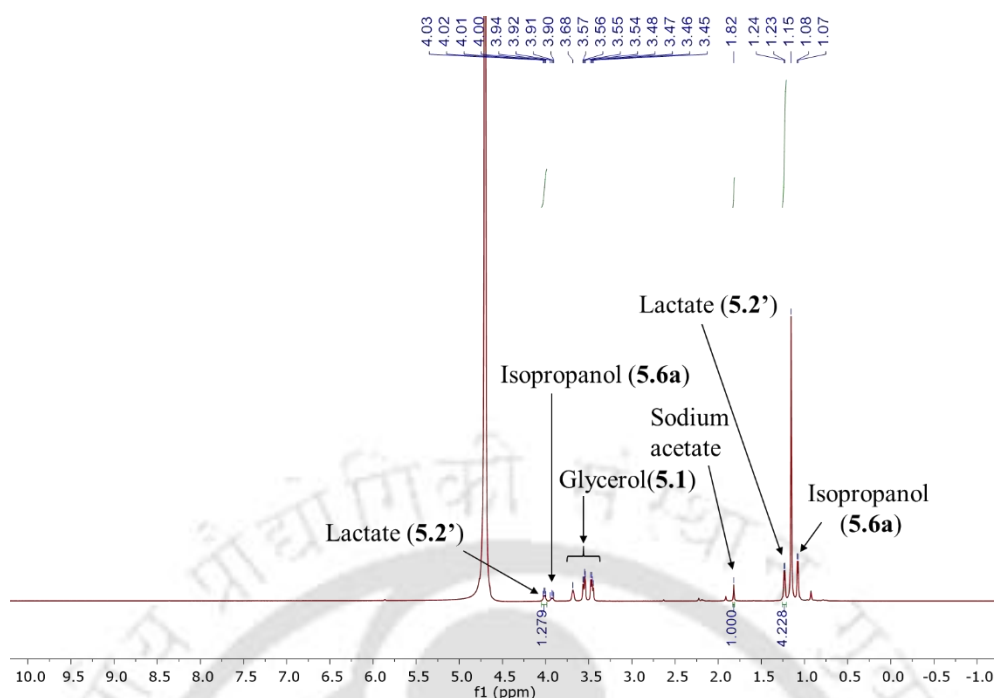


Figure D29: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents KO^tBu using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 16, Table 5.2).

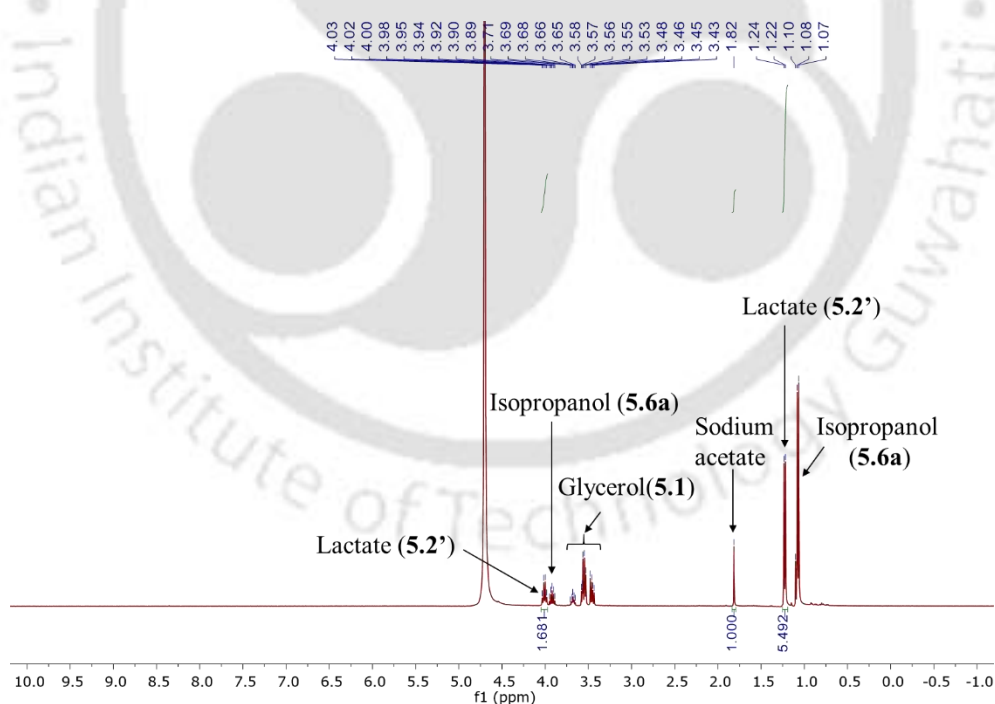


Figure D30: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents NaOEt using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 17, Table 5.2).

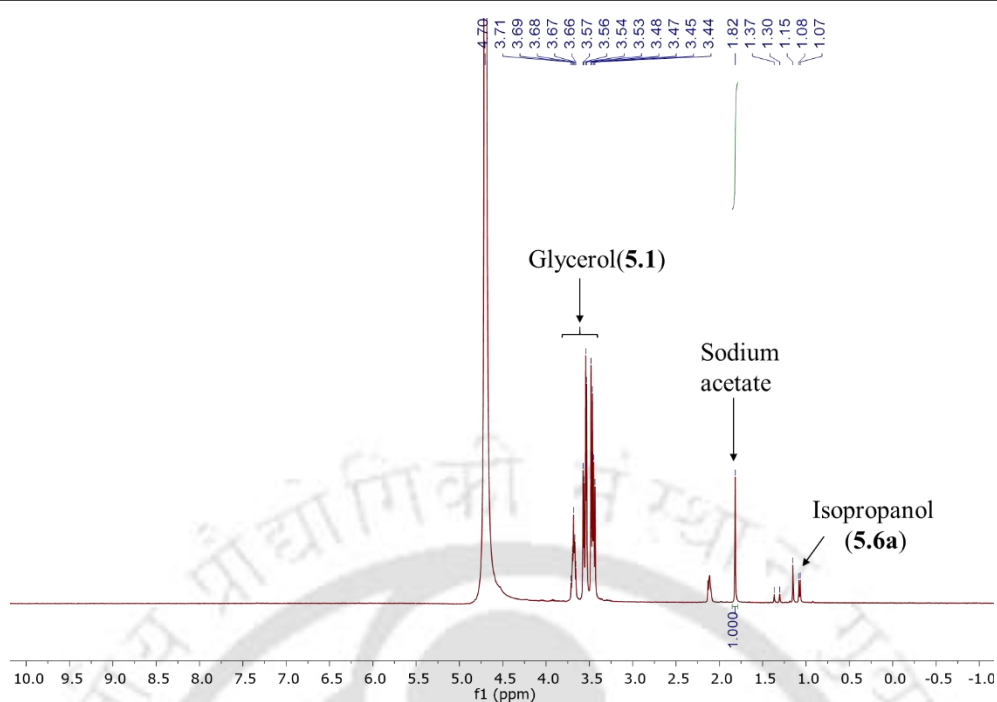


Figure D31: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents Na_2CO_3 using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 18, Table 5.2).

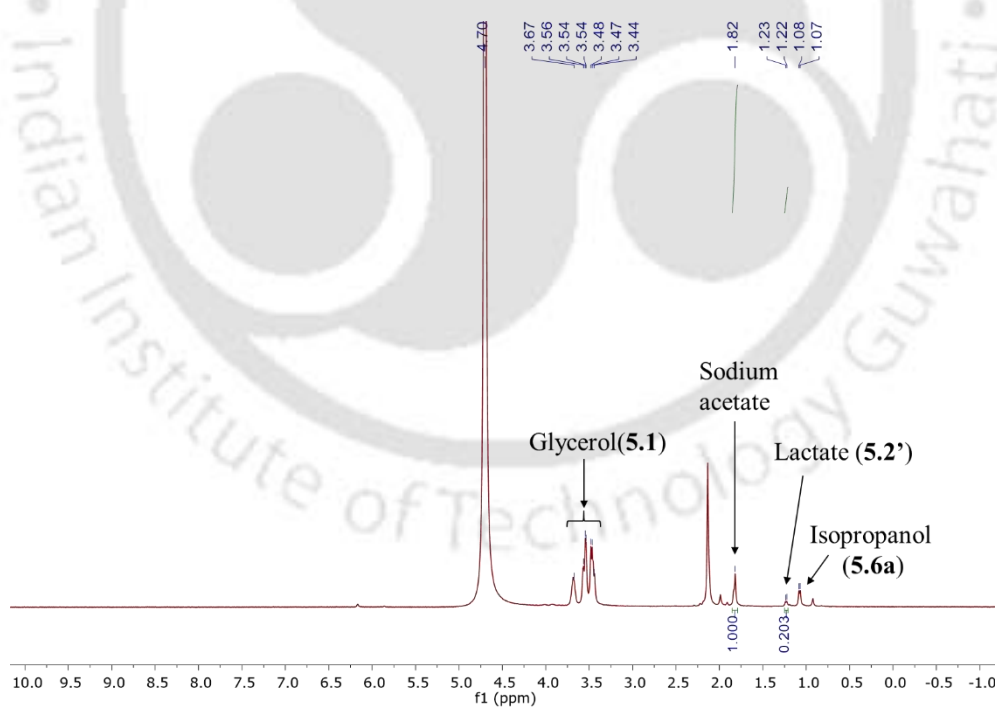


Figure D32: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents K_2CO_3 using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 19, Table 5.2).

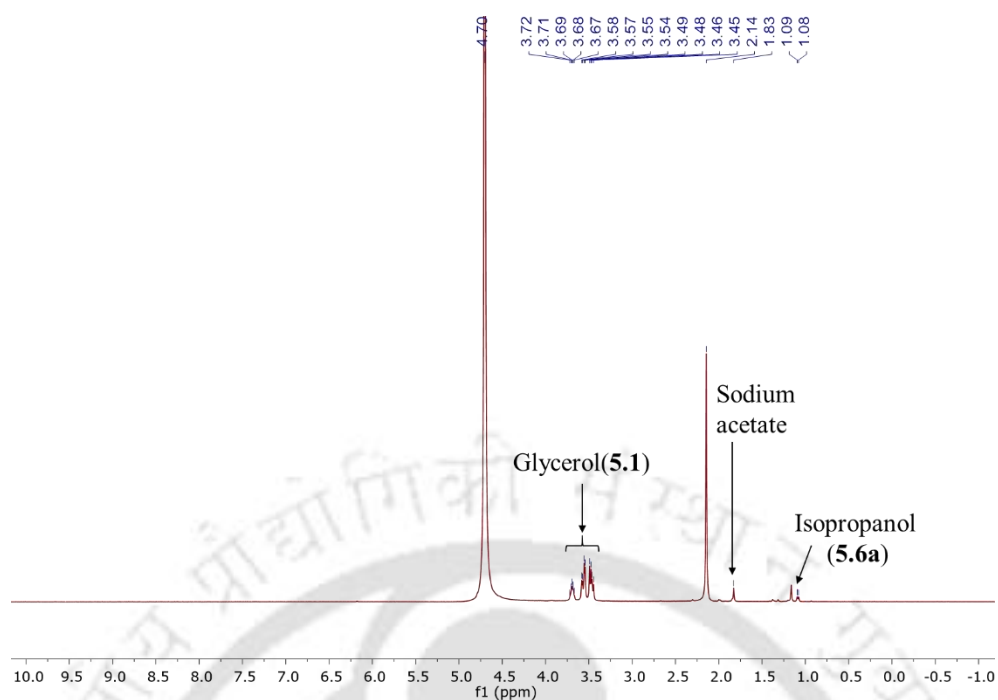


Figure D33: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents NaHCO₃ using acetone as hydrogen acceptor, at 160 °C. (entry 20, Table 5.2).

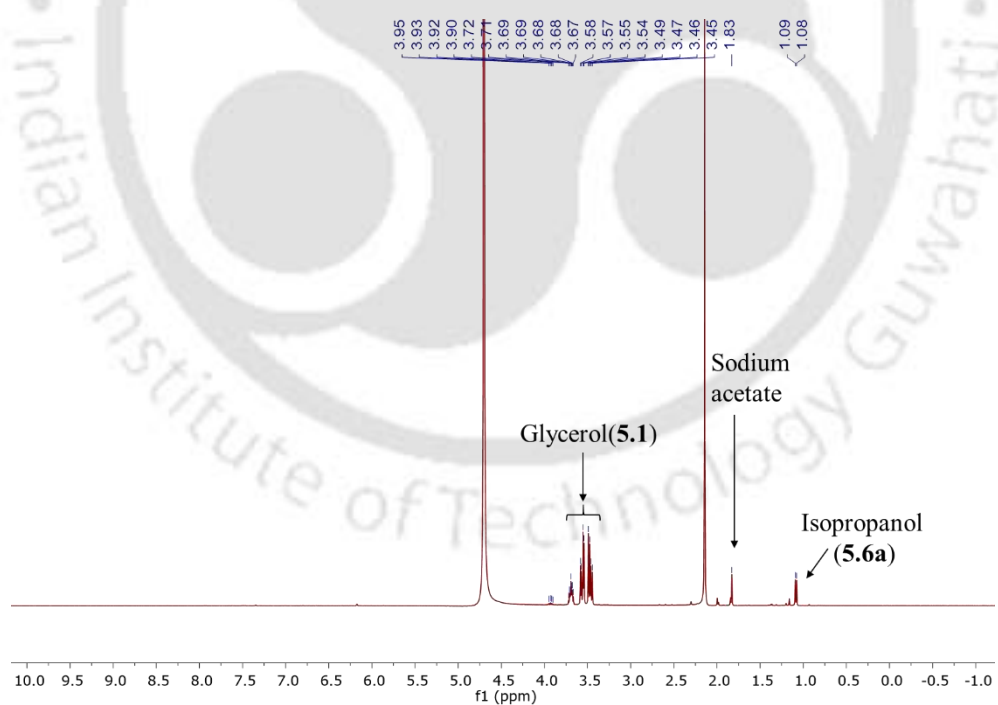


Figure D34: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents KHCO₃ using acetone as hydrogen acceptor, at 160 °C. (entry 21, Table 5.2).

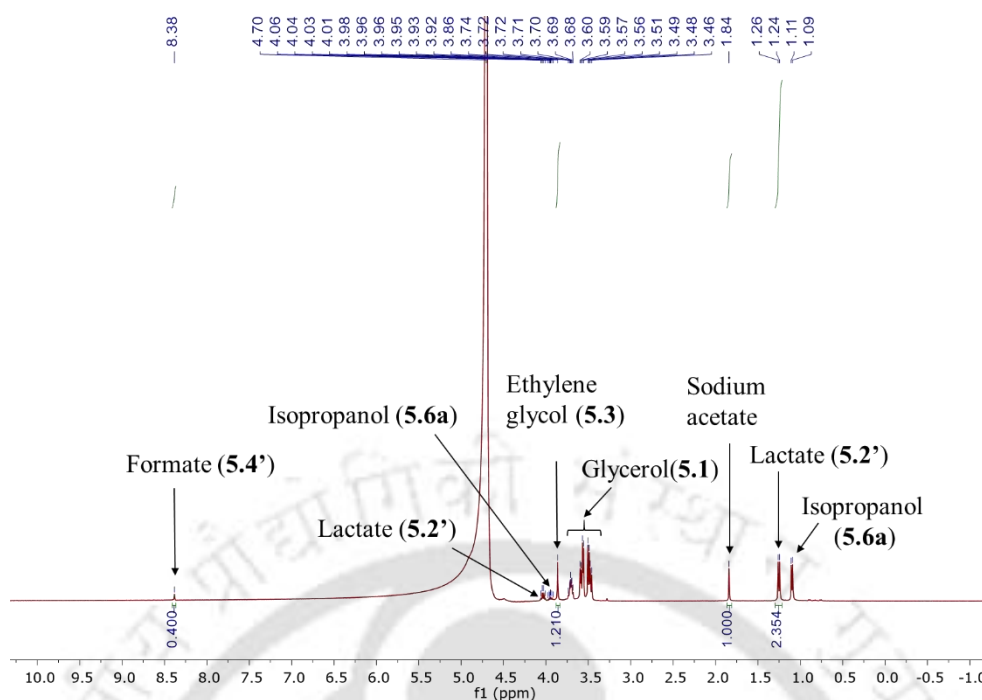


Figure D35: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 1.1 equivalents KOH using acetone as hydrogen acceptor, at 160 °C. (entry 22, Table 5.2).

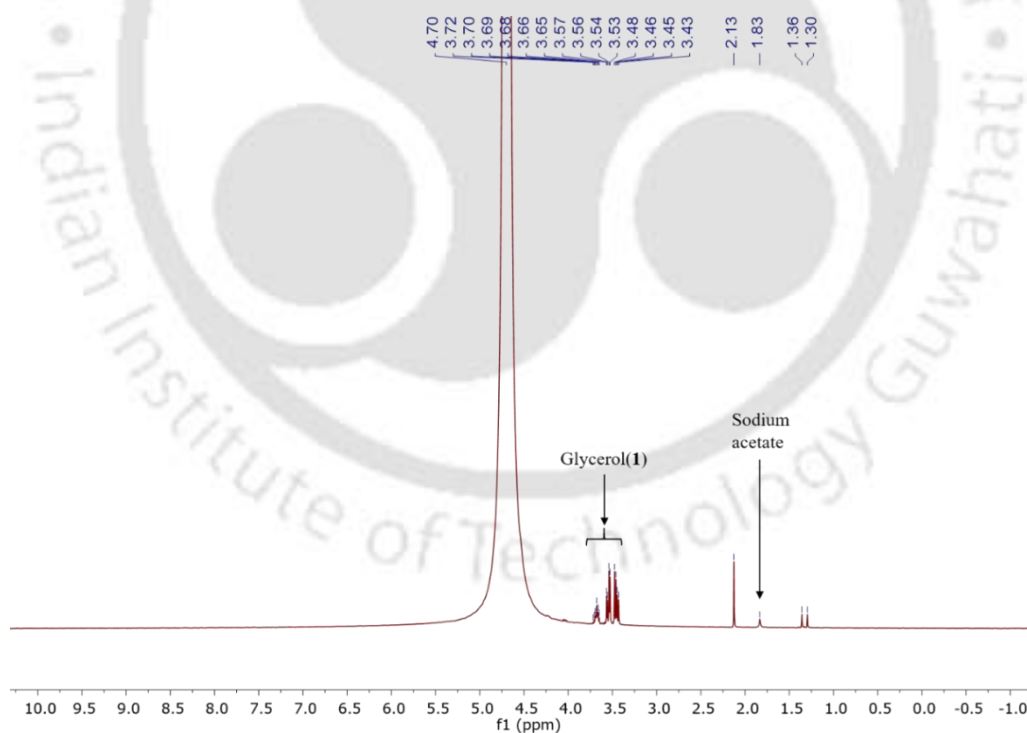


Figure D36: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 using acetone as hydrogen acceptor, at 160 °C. (entry 23, Table 5.2).

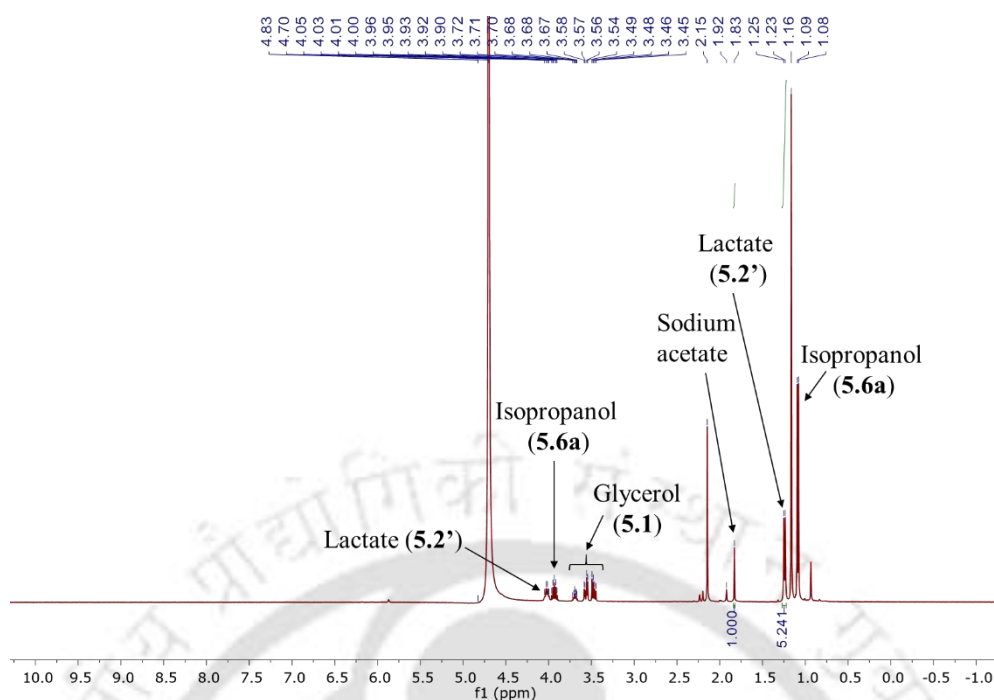


Figure D37: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.75 equivalents NaO^tBu using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 24, Table 5.2).

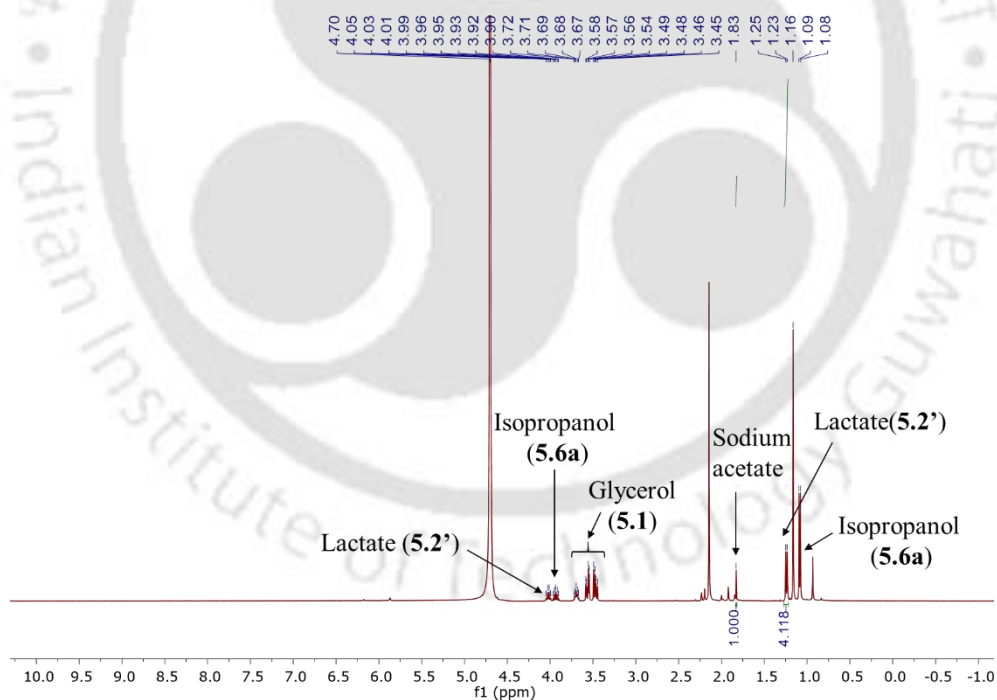


Figure D38: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.5 equivalents NaO^tBu using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 25, Table 5.2).

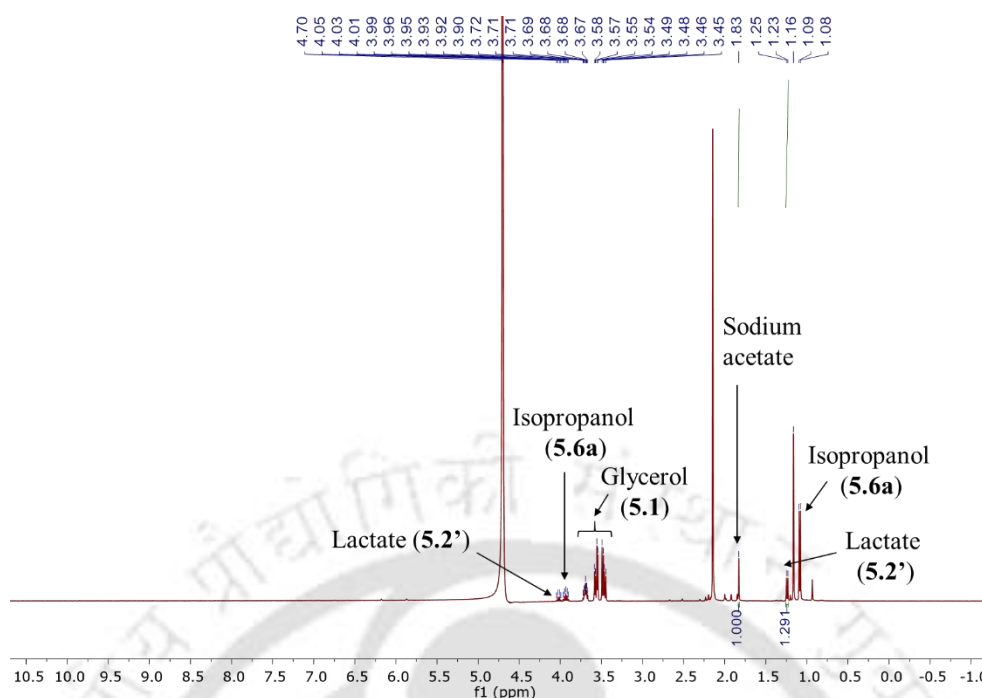


Figure D39: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.25 equivalents NaO^tBu using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (entry 26, Table 5.2).

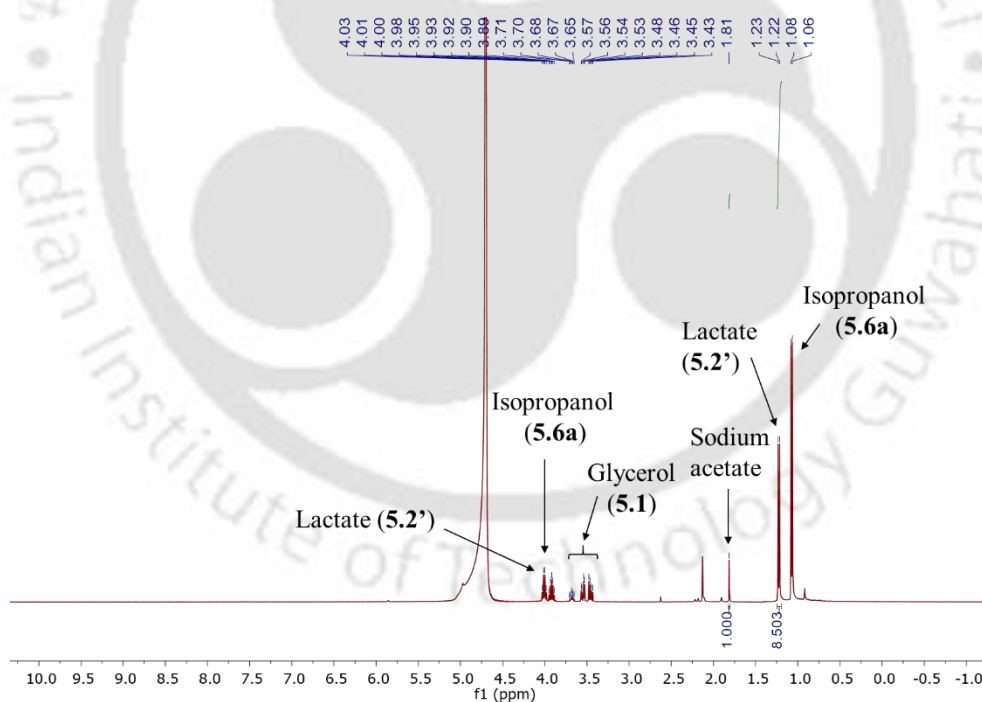


Figure D40: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents NaO^tBu using acetone as hydrogen acceptor, in presence of 1.0 mol% PPh_3 , at 160 $^\circ\text{C}$ (equation 4, Scheme 5.6).

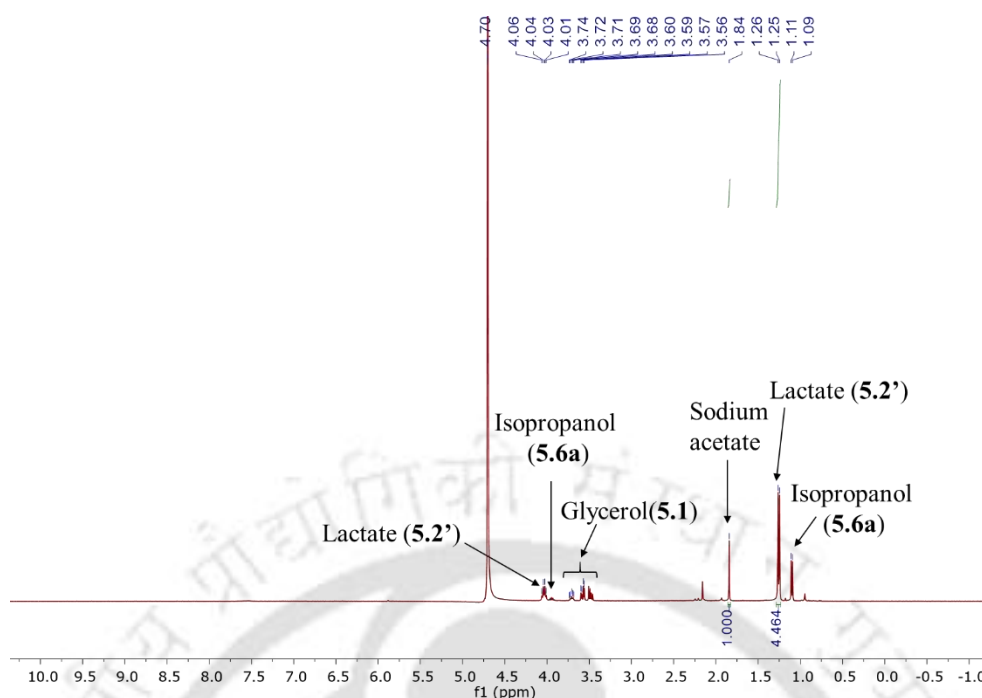


Figure D41: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents NaO'Bu using acetone as hydrogen acceptor, in presence of 5 mol% PPh₃, at 160 °C (equation 5, Scheme 5.6).

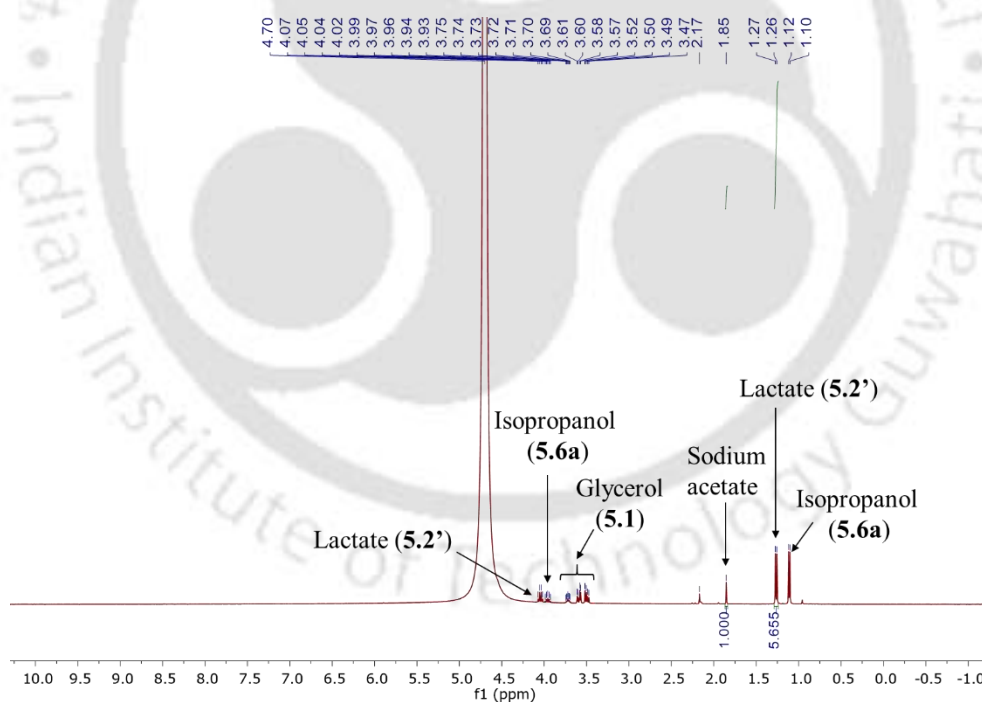


Figure D42: ¹H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents NaO'Bu using acetone as hydrogen acceptor, in presence of 5 mol% CS₂, at 160 °C (equation 6, Scheme 5.6).

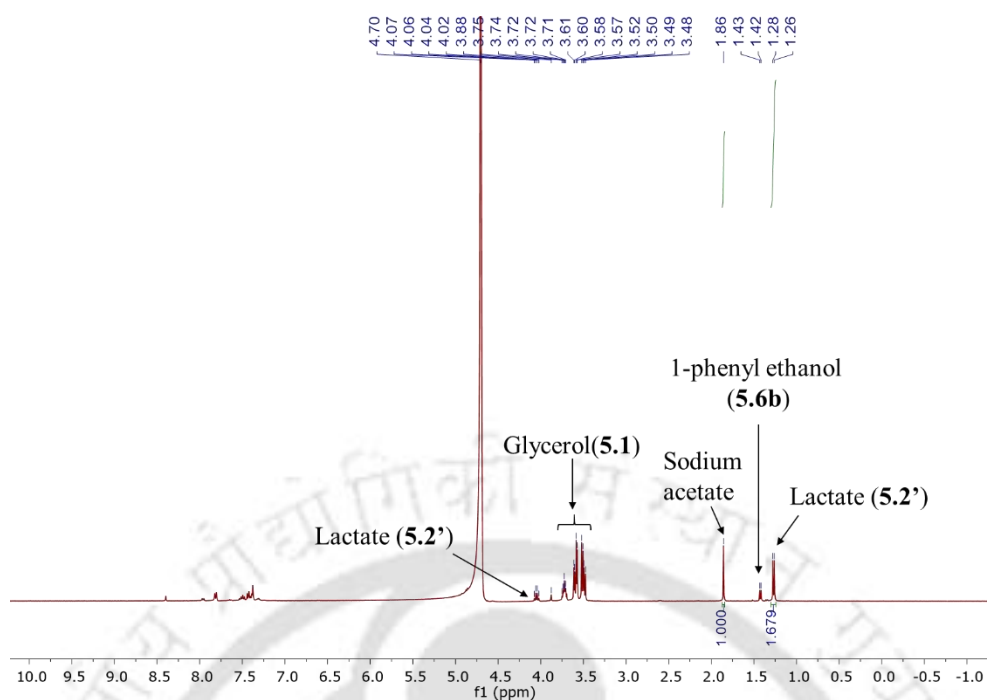


Figure D43: ^1H NMR spectra of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents KOH using acetophenone as hydrogen acceptor in open vessel, at 160°C . (equation 8, Scheme 5.6).

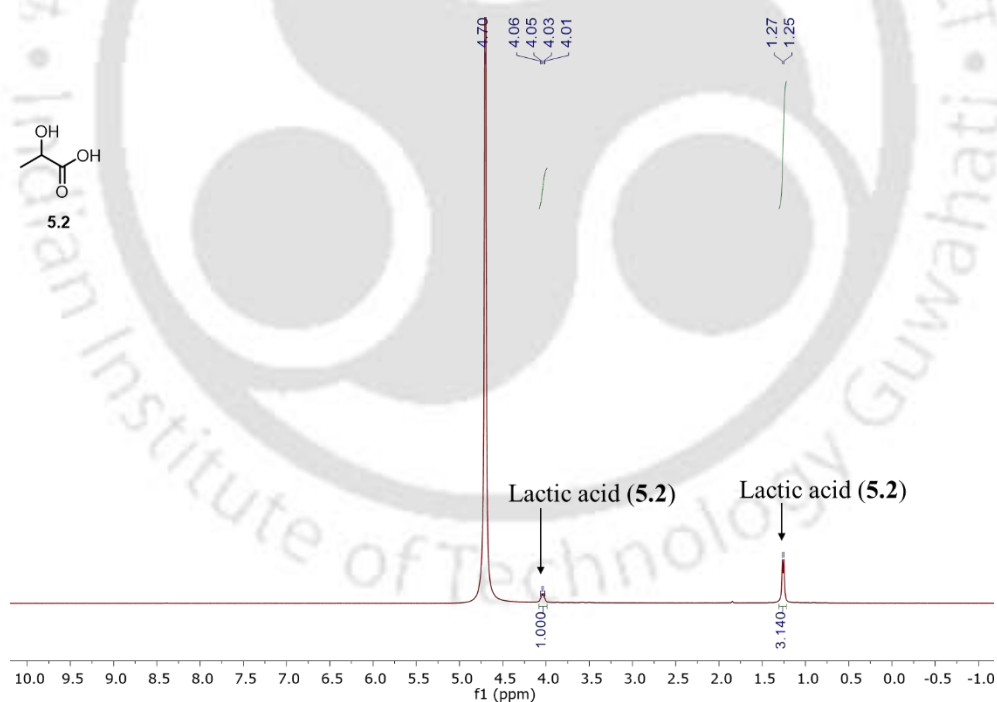


Figure D44: ^1H NMR spectra of lactic acid (5.2).

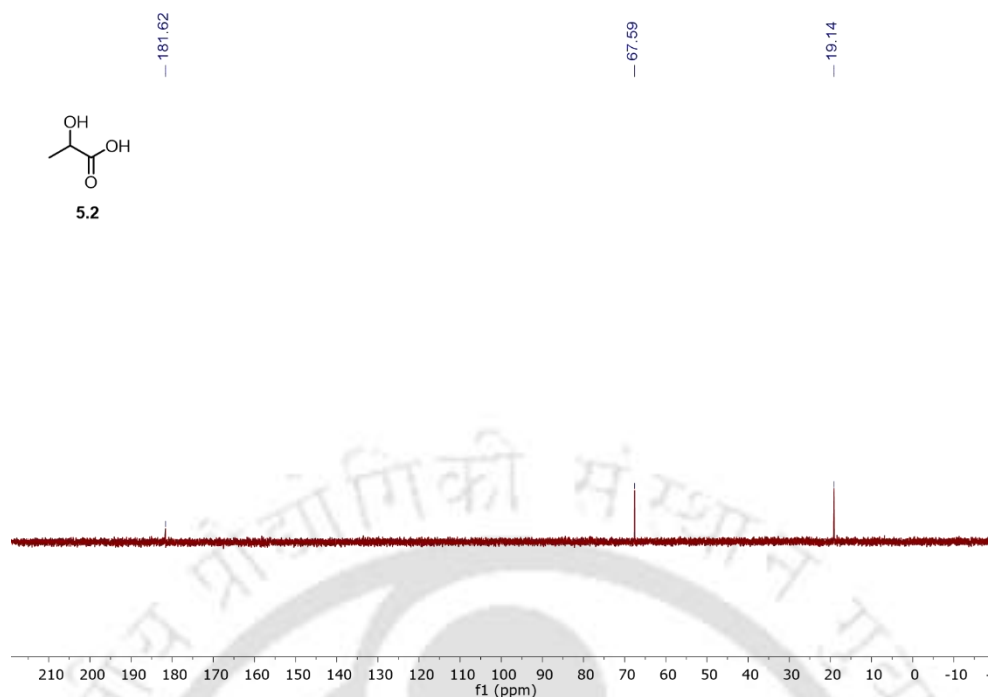


Figure D45: ¹³C {¹H} NMR spectra of lactic acid (5.2).

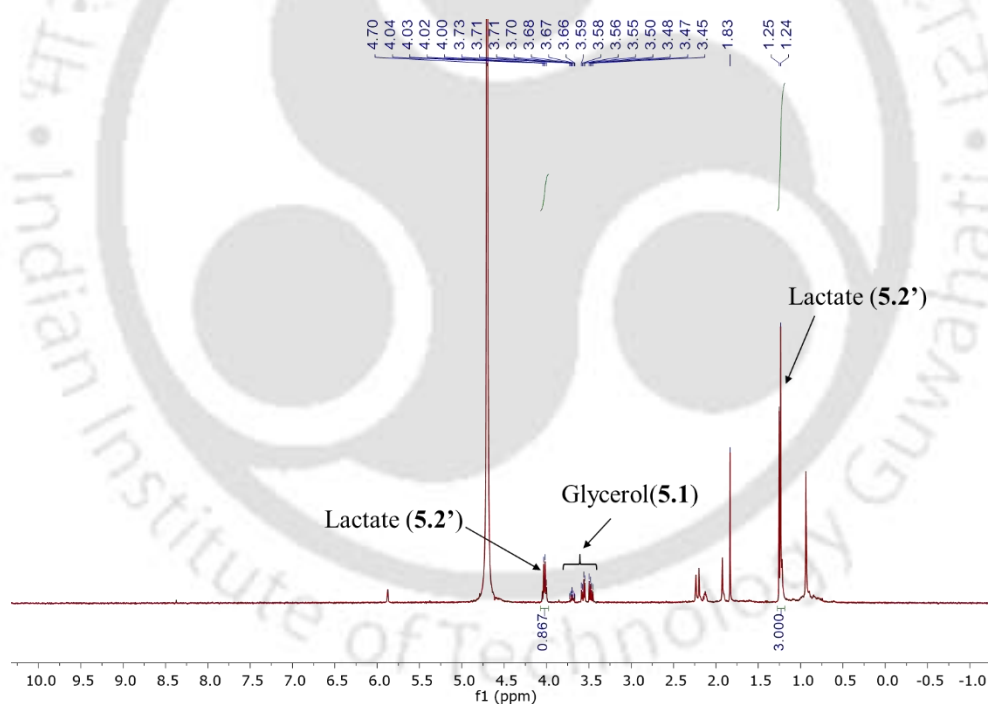


Figure D46: ¹H NMR spectra of deuterium labelling experiment of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl₂, 1.1 equivalents NaO^tBu using acetone as hydrogen acceptor, at 160 °C. (equation 7, Scheme 5.6).

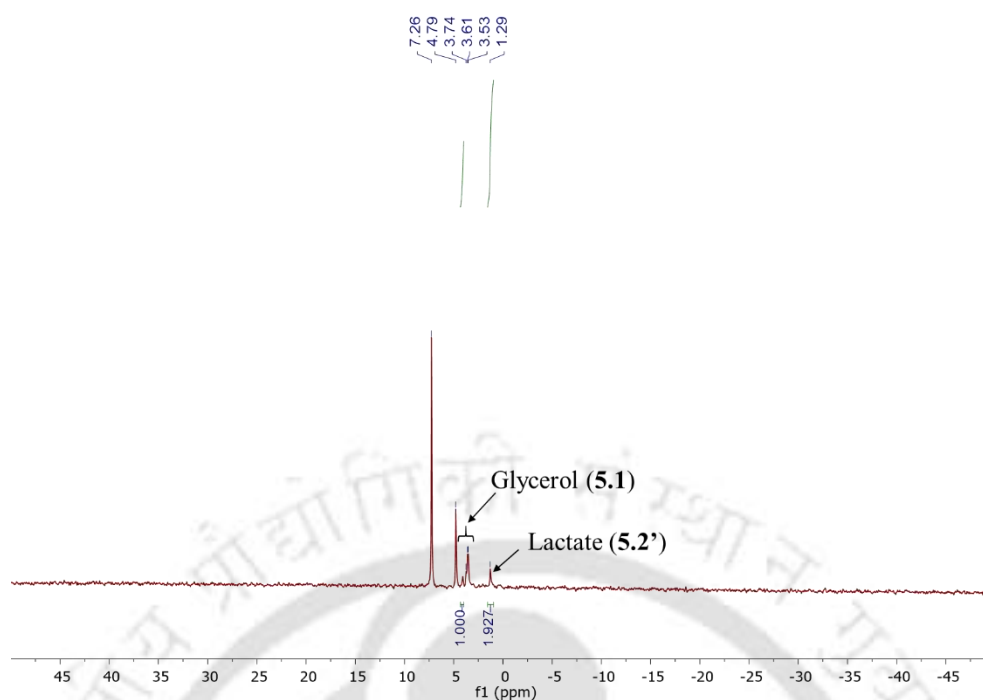
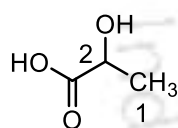


Figure D47: ^2H NMR spectra of deuterium labelling experiment of glycerol (5.1) transfer dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 1.1 equivalents NaO^tBu using acetone as hydrogen acceptor, at 160 $^\circ\text{C}$. (equation 7, Scheme 5.6).

D3. Calculation of K_H/K_D : (Figure D46 and Figure D47)



Considering zero deuteration at C1 in ^1H NMR (Figure D46) and full deuteration at C2 in ^2H NMR (Figure D47)

From Figure D46, integration value of the peak for CH_3 is 3

From Figure D47, integration value of the peak for CD_3 is 1.927

Hence, protonation in CD_3 in Figure D47 = $(3 - 1.927) = 1.073$

From Figure D46, integration value of the peak for CH_3 is 3

From Figure D47, integration value of the peak for CH_3 is 1.073

Total proton retained in C1 considering both from ^1H NMR and ^2H NMR = $(3 + 1.073) = 4.073$

If we normalise 4.073 as 3.

Then, from Figure D46, 0.867 will be normalised to $[(0.867 \times 3)/4.073] = 0.638$

Hence, the revised integrations after normalization are 3 for C1 and 0.638 for C2.

So, the deuterium incorporation in C2 = $(1 - 0.638) = 0.362$

From Figure D46, D incorporation in C2 = $(1 - 0.867) = 0.133$

From Figure D47, D incorporation in C2 = 1

So, the total deuterium incorporation in C2 = $1 + 0.133 = 1.133$

Again, if we normalise 1.133 as 1

Then from Figure D47, 1.927 will be $[(1.927 \times 1)/1.133] = 1.7$

Therefore, deuterium content in C1 = 1.7

KIE = $0.638/0.362 = 1.7$

D4. Reaction profile of acceptorless dehydrogenation of glycerol under optimized condition:

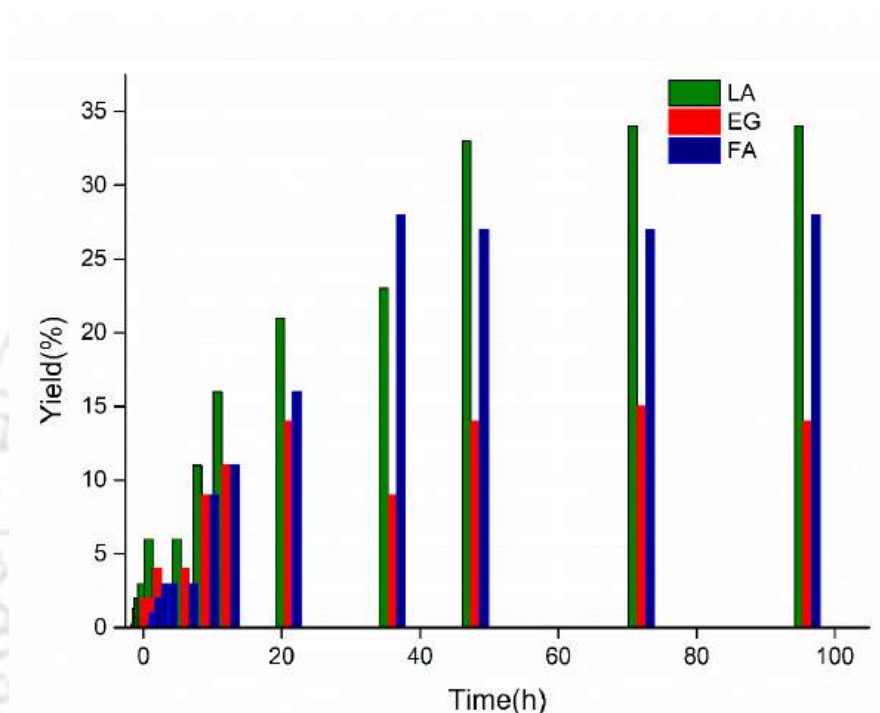


Figure D48: Reaction profile of acceptorless glycerol (5.1) dehydrogenation to lactate catalysed by 0.5 mol% CoCl_2 , 0.75 equivalents KOH using ethanol as solvent, at 160°C . (entry 3, Table 5.1)

D5. Gas Chromatography Analysis:

GC analysis (TCD detection) was performed on an Agilent 7820-GC instrument fitted with Agilent Front SSZ Inlet N_2 HP-PLOT Q column (30 m length x $530\ \mu\text{m}$ x $40\ \mu\text{m}$) using the following method:

Agilent 7820-GC back detector TCD

Oven temperature: 50°C

Time at starting temp: 0 min

Hold time = 10 min

Inlet temperature: 100°C

Detector temperature (TCD): 250°C

Detector temperature (FID): 300°C

Flow rate (carrier): 5 mL/min (N_2)

Split ratio: 10

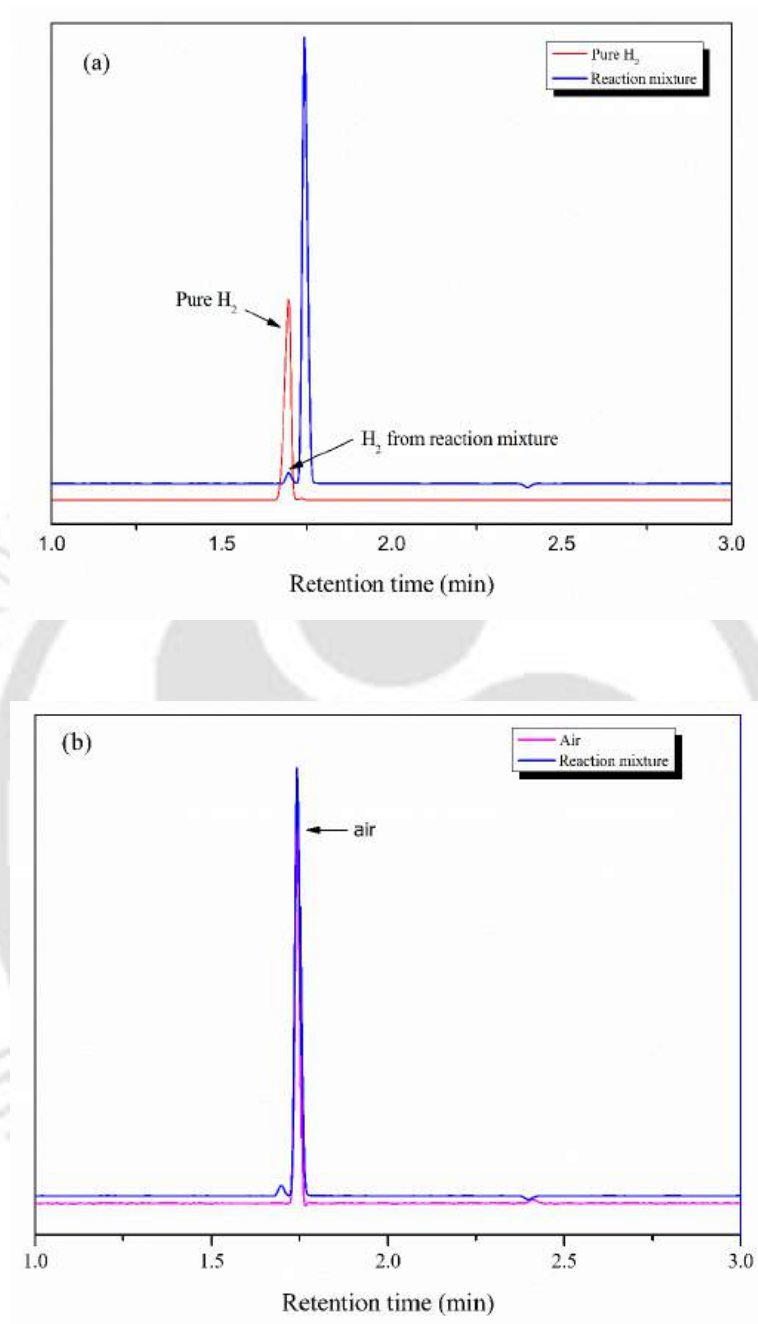


Figure D49. Evidence for H_2 evolution [(a) Pure H_2 and gas from reaction mixture (b) air and gas from reaction mixture] in the acceptorless dehydrogenation of glycerol (5.1) catalysed by $CoCl_2$ (0.5 mol %) and KOH (0.75 equivalents) at 160 °C via GC analysis.

D6. Reaction profile of transfer dehydrogenation at various base concentration:

In a 15 mL pressure tube, glycerol (0.460 g, 5 mmol), anhydrous CoCl_2 (0.0032 g, 0.025 mmol), KOH (0.0701-0.3083 g, 1.25-5.4956 mmol), acetone (0.5 mL, 6.809 mmol), distilled water (0.2 mL, 11.11 mmol) were added. Distilled water was used to ease the solubility in the initial times of the reaction. The reaction mixture was then allowed to stir at 160 °C. Samples were collected at an interval of 0.25h, 0.5h, 1h, 2h, 4h, 6h, 9h, 12h, 18h, 24h. An aliquot was drawn from the collected mixture for NMR analysis. The yield of lactate was determined from ^1H NMR analysis using sodium acetate as an internal standard and D_2O as the NMR solvent.

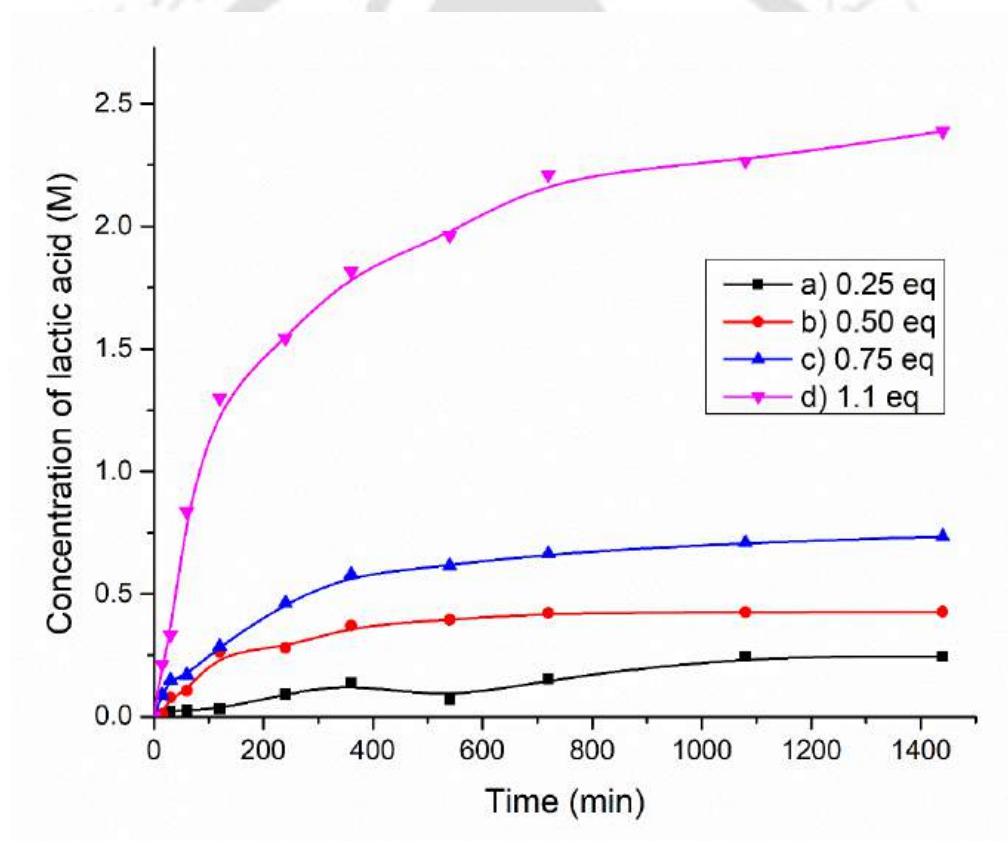


Figure D50: Reaction profile of transfer dehydrogenation of glycerol (5.1) to lactate (5.2) catalysed by 0.5 mol% CoCl_2 , using acetone (0.5 mL, 6.809 mmol) as hydrogen acceptor, distilled water (0.2 mL, 11.11 mmol), at 160 °C and KOH (a) 0.25 equivalents vs glycerol (b) 0.5 equivalents vs glycerol (c) 0.75 equivalents vs glycerol (d) 1.1 equivalents vs glycerol.

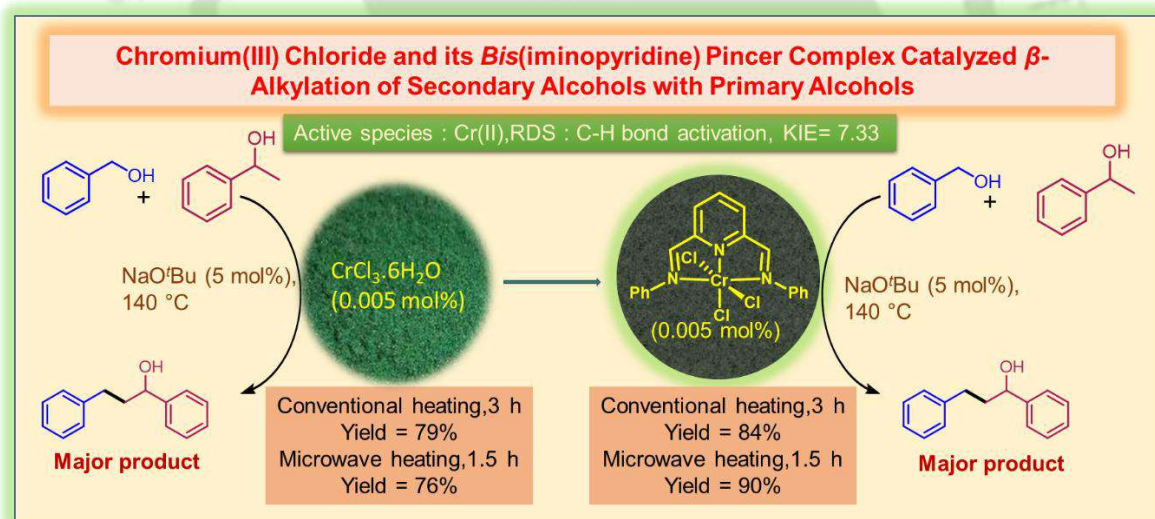
Summary & Outlook





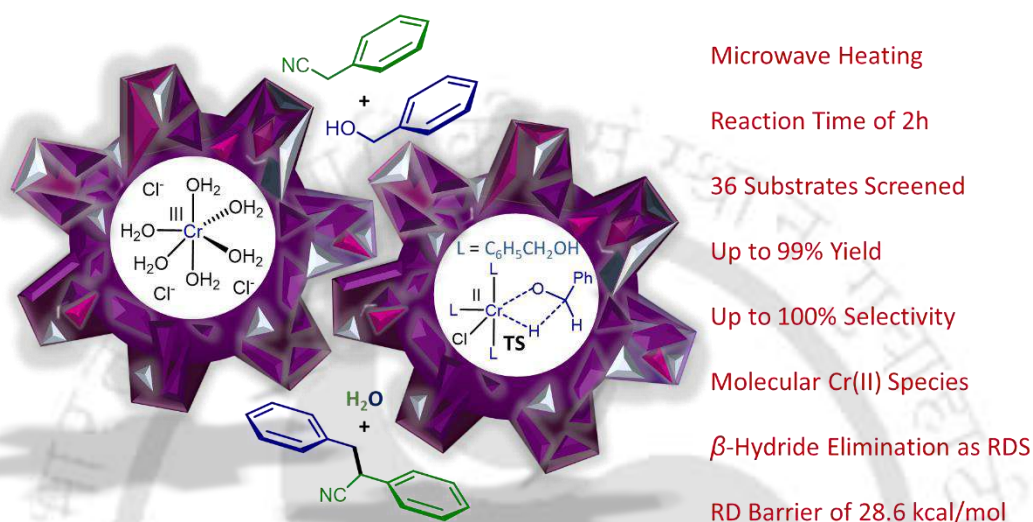
Chapter I provides a brief introduction to transition metal salts, co-ordination compound, organometallic compounds and pincer complex (a special class of organometallic compounds), their application in the field of catalysis. The chapter ends with a section that discusses the objectives of the current thesis.

Chapter II deals with the chromium catalysed β -alkylation of secondary alcohols with primary alcohols. High yields (ca. 90%) of the β -alkylated product was obtained with a selectivity of 91% at very low loadings (0.005 mol%) of the pincer-chromium catalyst based on *bis*(iminopyridine) under microwave conditions in the presence of 5 mol% NaO^tBu. The molecular nature of the catalyst was determined by HRMS, EPR, hot filtration and mercury-drop studies. A KIE of 7.33 and detection of resting-state species in the HRMS analysis are suggestive of the involvement of the insertion of the β -alkylated ketone into the Cr-H bond as the most probable rate determining step. CrCl₃.6H₂O being an active catalyst, opens up an exciting possibilities of utilizing readily available, abundant and inexpensive 3d-metals as catalysts in related organic transformations.

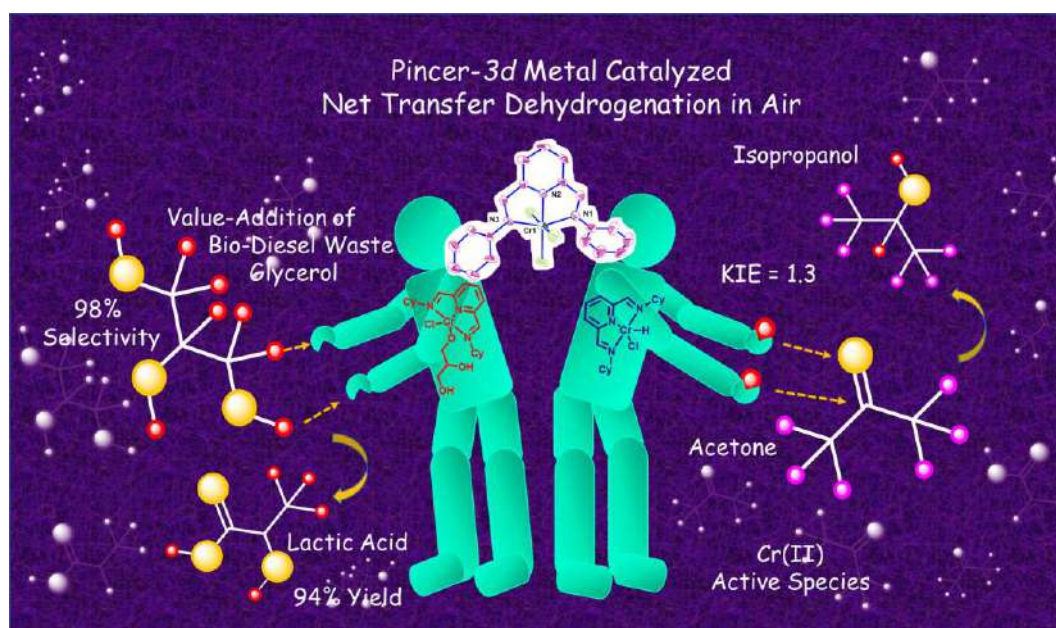


Chapter III discusses the catalytic activity of commercially available first-row 3d transition metal salt Chromium (III) chloride in dehydrogenative coupling of benzyl alcohol and benzyl nitrile. 0.4 mol% of CrCl₃.6H₂O was sufficient for catalysing the selective α -alkylation of nitriles with benzyl alcohol in excellent yields (ca. 99%) in the presence of 30 mol% KO^tBu at 140 °C in 24 h using conventional heating in air. The same reaction when performed under microwave heating conditions, comparable yields (ca. 93%) of the α -alkylated nitrile was obtained within 2 h of reaction in air. The formulated synthetic protocol was utilized to bring about the selective

α -alkylation of a range of benzyl nitriles with various benzyl alcohols. Catalyst poisoning experiments revealed the homogeneous molecular nature of the Cr species. Detailed mechanistic investigations are suggestive of the Cr(II) as the active species. A KIE of 4.7 points out, Cr-benzyloxide species undergoing β -hydride elimination to be the RDS of the catalytic cycle with a barrier of 28.6 kcal/mol.



Chapter IV demonstrates how a commercially available first-row transition metal salt $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and its corresponding pincer complexes were successful in accomplishing the transfer dehydrogenation of glycerol to lactic acid in the presence of a sacrificial hydrogen acceptor, acetone. In particular, the pincer-Cr complex, $(\text{Cy}^2\text{NNN})\text{CrCl}_3$ (0.5 mol%) was found to efficiently bring about the catalytic net transfer dehydrogenation of glycerol in presence of 1.1 equivalents of NaOH, at 160 °C to afford 94% lactic acid at 98% selectivity along with another value added product isopropanol (IPA). Mercury drop experiment revealed the homogeneous molecular nature of the Cr(II) active catalyst. Detailed mechanistic studies are indicative of the sole contribution of the alcoholysis path towards the observed reactivity with a KIE of 1.3.



Chapter V in line with the above chapter, a more environmentally benign commercially available 3d-metal salt CoCl_2 was utilised to accomplish the dehydrogenation of glycerol to lactic acid in an acceptorless fashion as well as under transfer dehydrogenation conditions using acetone as a sacrificial acceptor. Under the acceptorless conditions, up to 75% conversion of glycerol to lactic acid (33%), ethylene glycol (14%) and formic acid (27%) was observed in addition to hydrogen in the cobaltous chloride (0.5 mol%) catalysed reaction at 160 °C in the presence of 0.75 equivalents of KOH in an open-vessel. Delightfully, a maximum of 93% lactic acid with 96% selectivity along with isopropanol was obtained when the cobaltous chloride (0.5 mol%) catalysed dehydrogenation of glycerol at 160 °C in the presence of 1.1 equivalents of NaO^tBu was performed with acetone as a sacrificial hydrogen acceptor in a sealed vessel. Detailed mechanistic investigation confirmed the molecular nature of the Co(II) active catalyst. Deuterium labelling studies are indicative of the participation of the C-H bond activation in the catalytic cycle but not in the RDS with a modest secondary KIE of 1.68. Alcoholysis rather than hydrogenolysis is apparently the sole contributor to the observed net transfer dehydrogenation activity.



The current thesis has explored various organic transformations with a special emphasis towards the transformation of alcohols to value-added chemicals catalysed by 3d-metal salts and their corresponding pincer complexes based on *bis(imino)pyridine* ligands. Attempts have been made to shed light on the reaction mechanism wherever possible. The finding of the thesis could open new route for the synthesis of value-added chemicals, speciality chemicals and organic reaction intermediates from readily available alcohols. Apart from the various catalytic transformations discussed in the thesis, following challenges still remain unaddressed that could be taken up during future studies,

1. Can one develop a protocol to accomplish the coupling of aliphatic alcohols using the most effective and efficient pincer-Cr catalyst based on *bis(imino)pyridine* or *bis(benzimidazole-2-yl)pyridine* ligand system?
2. Can one utilise these pincer-Cr complexes to generate hydrogen from abundantly available LOHCs like methanol, ethanol and ethylene glycol?
3. Is it possible to design better catalyst to activate CO₂ via transfer dehydrogenation of alcohols?

In general, there is a requirement of developing protocols and catalytic systems based on earth abundant 3d-metals which is inexpensive environmentally benign, and which is highly active towards catalytic value-addition of alcohols under mild reaction conditions.





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Academic Background

Doctor of Philosophy (PhD) in Chemistry from Indian Institute of Technology, Guwahati, (2019-2025), Assam, India under the supervision of Dr. Akshai Kumar A.S.

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Research Interest

1. Catalysis
2. Organometallics chemistry

Conferences Attended

- **Narjinari, H.;** Dhole, S; Kumar, A. Poster presentation during 3rd International Conference on Main-group Molecules to Materials MMM III, IIT Hyderabad, University of Hyderabad, Telangana, December 2023. “Base Metal Catalyzed Glycerol Dehydrogenation to Lactic Acid” Bagged the Best Poster Award.
- **Narjinari, H.;** Tanwar, N.; Kathuria, L.; Kumar, A. Poster presentation during Modern Trends in Inorganic Chemistry MTIC-XIX, Banaras Hindu University, Varanasi. December 2022. “Guerbet-type β -alkylation of secondary alcohols catalyzed by chromium chloride and its corresponding NNN pincer complex.”
- **Narjinari, H.;** Dutta, M.; Srivastava, H. K.; Kumar, A. Poster presentation during 2021#Catalysis Science & Technology 10th anniversary symposium 2021, Nov 2021. “NNN pincer ruthenium catalyzed one pot transformation of glycerol to lactic acid”.

Publications

- **Narjinari, H.;** Tanwar, N.; Kathuria, L.; Jasra, R. V.; Kumar, A. Guerbet-Type β -Alkylation of Secondary Alcohols Catalyzed by Chromium Chloride and its Corresponding NNN Pincer Complex. *Catal. Sci. Technol.* **2022**, 12, 4753–4762.
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Book Chapters and Review Articles

- **Narjinari, H.**; Bisarya, A.; Arora, V.; Nandi, P. G.; Das, K.; Kumar, A., Current State of-Art in the Guerbet-Type β -Alkylation of Secondary Alcohols with Primary Alcohols Catalyzed by Complexes Based on 3d Metals. In *Dehydrogenation Reactions with 3d Metals*, Sundararaju, B., Ed. Springer Nature Switzerland: Cham, 2024; pp 93-127.
- Arora, V.; **Narjinari, H.**; Nandi, P. G.; Kumar, A., Recent advances in pincer–nickel catalyzed reactions. *Dalton Trans.* **2021**, *50*, 3394-3428.
- Islam, K.; **Narjinari, H.**; Kumar, A. Polycyclic Aromatic Hydrocarbons Bearing Polyethynyl Bridges; Synthesis, Photophysical Properties and their Applications *Asian J. Org. Chem.* **2021**, *10*, 1544-1566.
- Bisarya, A.; Karim, S.; **Narjinari, H.**; Banerjee, A.; Arora, V.; Dhole, S.; Dutta, A.; Kumar, A. Production of hydrogen from alcohols via homogeneous catalytic transformations mediated by molecular transition-metal complexes *Chem. Commun.* **2024**, *60*, 4148–4169.

