Development of new bio-based solvents *via* dialkyl carbonate chemistry

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Abstract

This work aimed to synthesise new bio-based solvents from bio-based platform molecules and dimethyl carbonate (DMC) as alternatives for traditional solvents. This work extended the scope of the DMC chemistry to including acid catalysts. Hansen Solubility Parameters in Practice (HSPiP) software was utilised as an effective tool to identify suitable bio-based solvents candidates.

3-Methoxybutan-2-one (MO) was synthesised from acetoin and DMC, in a yield of 95%. Solvent properties, including the Kamlet-Taft (KT) and Hansen solubility parameters (HSPs), demonstrate that MO is a suitable candidate for the replacement of halogenated solvents such as dichloromethane (DCM). MO did not exhibit mutagenicity in an initial Ames tests. MO also proved to have similar performance to DCM when applied in Friedel-Crafts acylation.

Methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC) was synthesised from glycerol and DMC. KT and HSPs demonstrate MMC could be a replacement solvent for a wide range of different conventional solvents, and MMC is proved to be a suitable solvent in both Friedel-Crafts and Diels-Alder reactions. However, Ames tests demonstrated MMC to be mutagenic, and as such is unlikely to accord with regulatory controls and not be considered as a green medium. The methodology of solvent testing described here is a broadly applicable protocol that indicates new solvents are functionally proficient, but also highlights any potential health risk of these candidates.

p-Toluenesulfonic acid (PTSA), sulphuric acid, aluminium chloride and iron (III) chloride have been observed to assist carboxymethylation for primary aliphatic alcohols at catalytic loadings with >99% conversion and selectivity. For carboxymethylation of secondary alcohols, stoichiometric PTSA and catalytic aluminium chloride both provide quantitative conversion and selectivity. Stoichiometric iron (III) chloride and sulphuric acid promote dehydration of linear aliphatic alcohols. Iron (III) chloride assists methylation of cyclohexanol, whilst aluminium chloride aids the methylation of phenolic compounds.

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Declaration

Some of the results presented in this thesis were obtained through collaboration with others, details as follows:

1. Chapter 2 – The optimisation reactions were carried out under the assistance of Dr. Con Robert McElroy. Ames test was carried out with the assistance of Fergal Byrne.
2. Chapter 3 – Ames test was carried out with the assistance of Fergal Byrne.
3. Chapter 4 – Gas phase GC-MS analysis of butene was carried out by Karl Heaton and Julia Sarju.

All other results are the work of the author. Aspects of work presented in this thesis have been included in publications, references as follows:

1. S. Jin, A. J. Hunt, J. H. Clark and C. R. McElroy, Acid-catalysed carboxymethylation, methylation and dehydration of alcohols and phenols with dimethyl carbonate under mild conditions, *Green Chem*., 2016, **18**, 5839-5844.
2. F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. R. McElroy and J. Sherwood, Tools and techniques for solvent selection: green solvent selection guides, *Sustain. Chem. Process*., 2016, **4**, 7.
3. F. P. Byrne, S. Jin, C. R. McElroy, T. J. Farmer, J. H. Clark and A. J. Hunt "*Chapter 5 Solvent from Waste"*, in Bio-based Solvents, F. Jerome (Ed.), Willey, 2017.

The work presented in this thesis has not previously been submitted for a degree at this or any other university.

Chapter 1 Introduction

Part of the work presented in this chapter has appeared in:

F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. R. McElroy and J. Sherwood, Tools and techniques for solvent selection: green solvent selection guides, *Sustain. Chem. Process*., 2016, 4, 7

F. P. Byrne, S. Jin, C. R. McElroy, T. J. Farmer, J. H. Clark and A. J. Hunt "*Chapter 5 Solvent from Waste"*, in Bio-based Solvents, F. Jerome (Ed.), Willey, 2017

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1.1 Scope of this project

The preliminary scope of this project is to synthesise and purify new solvents, as replacements for traditional solvents, from bio-derived platform molecules and dimethyl carbonate (DMC). Candidate platform molecules were selected based on the calculation of Hansen Solubility Parameters in Practice (HSPiP) software. Properties of these novel bio-based solvents were experimentally determined and applied to test reactions to evaluate their performances compared to conventional organic media. In addition, acid-catalysed DMC chemistry was developed in order to further expand the application of DMC in terms of green chemistry. Therefore, the work conducted in this thesis may be split into three main areas as shown below:

(1) Acetoin derived bio-based solvents: on the basis of predicted Hansen solubility parameters by HSPiP software, acetoin was used as a platform molecule to synthesise the new bio-based solvent 3-methoxybutan-2-one, with DMC utilised as a green methylation agent. After optimisation of synthetic conditions followed by multi-gram synthesis and purification, Kamlet-Taft parameters, mutagenicity and other properties of 3-methoxybutan-2-one were measured. Finally, Friedel–Crafts and Diels-Alder reactions were utilised to test the solvent performance of this novel bio-based solvent in comparison with other common solvents.

(2) Solketal derived bio-based solvents: according to the modelling of Hansen solubility parameters by HSPiP, glycerol derived solketal was employed to synthesise the novel bio-based solvent methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate, with DMC as a green carboxymethylation agent. After optimisation of synthetic conditions followed by multi-gram synthesis and purification, Kamlet-Taft parameters, mutagenicity and other properties of methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate were investigated. Finally, Friedel–Crafts and Diels-Alder reactions were employed to assess the solvent performance of this new bio-based solvent compared to other traditional solvents.

(3) Acid-catalysed DMC chemistry: in order to expand DMC mediated carboxymethylation, methylation and dehydration chemistry *via* acid catalysis, primary, secondary and tertiary alcohols and phenols were reacted with DMC under various conditions in the presence of Brønsted or Lewis acids.

1.2 Green chemistry

The concept of green chemistry is defined as the ‘‘design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances.’’[1,2] Generally, the chemical industry defines the risk of a process by:

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

Risk is traditionally controlled by reducing the exposure of chemicals to the operators. However, green chemistry takes a different approach, whereby the intrinsic hazard is decreased *via* the application of alternative methods. Green chemistry nowadays plays a vital role in all areas of the chemical industry as a result of increasing public awareness and regulation concerns pertaining to the hazards and sustainability of a chemical process. Many types of research have been implemented to develop new green chemistry technology by universities, institutions, industries and governments all over the world,[2] and sustainable development is now generally accepted as an imperative goal for realising social, economic and environmental objectives.[3] To provide a guiding framework for the design of greener products and processes, the Twelve Principles of Green Chemistry were then introduced by P. Anastas and J. Warner:[4]

(1) Prevention

It is better to prevent waste than to treat or clean up waste after it has been created.

(2) Atom Economy

Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.

(3) Less Hazardous Chemical Syntheses

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

(4) Designing Safer Chemicals

Chemical products should be designed to affect their desired function while minimising their

toxicity.

(5) Safer Solvents and Auxiliaries

The use of auxiliary substances (*e.g.*, solvents, separation agents, *etc*.) should be made unnecessary wherever possible and innocuous when used.

(6) Design for Energy Efficiency

Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.

(7) Use of Renewable Feedstocks

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

(8) Reduce Derivatives

Unnecessary derivatisation (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimised or avoided if possible, because such steps require additional reagents and can generate waste.

(9) Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

(10) Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

(11) Real-time analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

(12) Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions, and fires.

This thesis will focus on employing the Twelve Principles of Green Chemistry as a methodology to lead the development of novel bio-based solvent from renewable resources, which has reduced hazards of chemical processes and increased sustainability.

1.3 Traditional solvents

1.3.1 The conception and classification of solvents

A solvent is a medium used to dissolve the solute to form a solution.[5] Solvents are commonly applied in industrial and lab-based procedures as diluters and reaction media, which aim to bring substrates and/or catalysts together as well as deliver heat, or a carrier for extraction, separation and purification.[5,6] Solvents are also employed for recrystallisation, as coating removers, chromatography mobile phases, cleaning, *etc*. Currently, a large number of solvents are in daily use in the fine chemical and pharmaceutical industry. For example, in 2012, almost 28 million metric tonnes of solvent were consumed around the world.[7]

Table 1.1 The classification of solvents and the examples

Protic solvents	Dipolar aprotic solvents	Non-polar solvents
Water	Acetone	Dichloromethane
Liquid ammonia	Acetonitrile	Ethyl acetate
Ethanol	Nitromethane	Cyclohexane
Benzyl alcohol	Dimethyl sulfoxide (DMSO)	Tetrahydrofuran (THF)
Acetic acid	Pyridine	Benzene

In general, a solvent can be classified into three different categories (Table 1.1),[8] *viz*., protic solvents, dipolar aprotic solvents and non-polar solvents:

(1) A protic solvent is a solvent which can form hydrogen bonds. Protic solvents donate labile protons and are better for the unimolecular nucleophilic substitution reactions (S_N1).

(2) A dipolar aprotic solvent is a solvent which has a permanent dipole but does not contain

labile protons. In comparison with protic solvents, dipolar aprotic solvents are better for the bimolecular nucleophilic substitution reactions (S_N2).

(3) A non-polar solvent is defined as a solvent with a low dielectric constant (<15). Non-polar solvents are not a proton source and only exhibit weak intermolecular forces.

1.3.2 The problems and REACH regulations for traditional organic solvents

Nowadays, although organic solvents are used ubiquitously throughout chemistry, there are still many challenges and problems relating to their application, including environmental issues, health and safety (EHS) issues and sustainability. Firstly, many organic solvents are volatile organic compounds (VOCs) and are highly toxic, which is not only harmful to human health but is also a threat to the environment. Previous research demonstrated that many traditional solvents are highly mutagenic and suspected to be carcinogenic.[9,10] Some of the halogenated hydrocarbon solvents, such as chlorofluoromethanes,[11] are found to deplete the ozone layer which increases the levels of ultraviolet (UV) radiation reaching the surface of the earth. Worse still, the vast majority of traditional organic solvents are inherently non-renewable due to their synthesis from petroleum feedstock, which does not comply with the principle of sustainable development.

At present, stricter legislations and regulations concerning the use of organic solvents are being implemented. From 2006, Registration, Evaluation, Authorisation and restriction of CHemicals (REACH)[12] has been executed by the European Union (EU). REACH is one of the most rigorous regulations ever adopted. It forces companies to register every chemical (manufactured or imported at more than one tonne per year) and evaluate its health and environmental risks. It is deemed 'illegal' when companies supply unregistered substances (so called 'no data, no market'). REACH proposed a candidate list of substances of very high concerns (SVHCs) for authorisation,[13] including common organic solvents (Table 1.2) such as 1,2-dichloroethane, 1-methyl-2-pyrrolidone (NMP), *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMAc), nitrobenzene and 1,2-diethoxyethane. These SVHCs will be banned for sale or use after a set date, with further use only permitted by authorisation, with REACH urging manufacturers to

search for alternative substances or procedures. REACH also limits the industrial use of the most hazardous materials, and these restricted hazardous compounds[14] include typical widely used organic solvents (Table 1.2) such as dichloromethane (DCM), 1,1,2,2-tetrachloroethane, chloroform, cyclohexane, benzene and toluene. REACH is currently playing a vital role in the import and use of various chemicals in the EU. Any product which does not comply with REACH regulations is eliminated from the market *via* 'Rapid Alert System for Dangerous Non-food Products' (RAPEX) information scheme.[15]

Table 1.2 List of limited conventional solvents according to REACH regulation

SVHCs for authorisation	Restricted usage
1,2-Dichloroethane	DCM
NMP	1,1,2,2-Tetrachloroethane
DMF	Chloroform
DMAc	Cyclohexane
Nitrobenzene	Benzene
1,2-Diethoxyethane	Toluene

Apart from REACH, some other strict laws also have been implemented. In 1999, Canada implemented Schedule I of the Canadian Environmental Protection Act that focuses on the regulation of the use and release of toxic substances.[16] The United States also has the "Code of Federal Regulation Title 40" to protect human health and the environment.[17]

As a consequence, in order to avoid these existing problems of conventional solvents and comply with relevant legislation requirements, it is important to develop new green alternatives while retaining similar properties to traditional solvents.

1.4 DCM as an organic solvent

1.4.1 Advantages of DCM

DCM (as shown in Fig. 1.1), also known as methylene chloride, is a significant chlorinated organic

solvent which has been widely utilised for many applications such as extractions, photochemistry,[18] electrochemistry[19] and homogeneous chemistry.[20] As a petroleum-based compound, DCM is generally produced from chloromethane or methane by reacting with chlorine gas at an elevated temperature of 360-380 °C.[21] DCM has many advantages as a solvent resulting from its excellent physical and chemical properties. Firstly, DCM can dissolve numerous organic compounds, and it is also a non-flammable organic solvent. Furthermore, DCM remains inert in most organic reactions, and also possesses low melting point (-94.9 °C) and boiling point (39.6 °C), which makes DCM a good solvent at low temperatures and can be removed easily from the product mixture after synthesis.[22] Moreover, DCM is only slightly soluble in water and hence it can easily be separated from water.

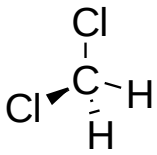


Fig. 1.1 The structure of DCM

1.4.2 Applications of DCM

DCM has been used extensively as a reaction medium and also in many other applications. For example, (a) DCM is used in pharmaceutical industries as a reaction solvent for the production of antibiotics such as ampicillin,[23] amoxicillin derivative[24] and cephalosporins;[25] (b) DCM is employed as a propellant for aerosol gel,[26] a paint remover[27] and a blowing agent in foams;[28] (c) DCM also has been used in cellulose triacetate based film production;[29] (d) DCM is commonly utilised as an extraction agent in the food industry, such as decaffeinating for coffee;[30] (e) DCM has been used as a refrigerant.[31]

1.4.3 Problems of DCM

Although DCM exhibits many advantageous properties, there are still some problems relating to its use. During the 1970s, the initial concern about exposure to DCM was the formation of

carboxyhemoglobin, which is a compound produced by carbon monoxide and hemoglobin, in the human body.[32] This causes the oxygen-carrying capacity in the blood to decline. In addition, the U.S. National Toxicology Program (NTP) reported that DCM exposure could lead to a dose-dependent increase in the incidence of lung and liver cancer in mice.[33] The United States Environmental Protection Agency (EPA) has classified DCM as a B2 carcinogen (probable human carcinogen).[34] DCM also has acute toxicity to human beings and its adverse effect on the central nervous system has been reported as playing a critical role in a number of fatalities.[35] Consequently, it is necessary to find a new less toxic green solvent produced from renewable materials to replace DCM.

1.5 Bio-based solvents

1.5.1 Green solvent

As discussed in Section 1.3 and Section 1.4, many traditional solvents have various issues such as sustainability, toxicity to human health and damaging the environment. One simple method to overcome these problems is to eliminate the need of a solvent, with solvent-free processes having already been applied in many reactions such as cycloaddition and polymerisation.[36] However, there are still many problems relating to its application on a large-scale production such as limited mass transfer, high viscosity, low reaction rate and low selectivity for the product.[37,38] Overall, application of solvent-free reactions are currently still very limited. Therefore, development and application of green solvents as replacements for conventional organic solvents is more feasible and of greater interest.

Although to date, there is not a clear universal definition of a “green solvent”, it is commonly accepted that their production, usage and disposal comply with the Twelve Principles of Green Chemistry to as great an extent as possible. Y. Gu and F. Jérôme suggested a twelve assessment criterion of green solvents inspired by the Twelve Principles of Green Chemistry (Table 1.3).[37]

Table 1.3 The twelve criteria of green solvent proposed by Y. Gu and F. Jérôme[37]

Available on a large scale and produced stably in the market
Competitive and stable prices
Fully recycled by eco-efficient process
Technical grade solvents are needed for preventing the energy-intensive purification procedures
Synthesised *via* high atom economy reaction and energy efficiency processes
Negligible toxicities
Biodegradable and producing non-toxic metabolites
Similar or even better performances than the traditional solvents
Stable regarding thermostability and electrochemistry
Preferred to be not flammable
Stored easily and transported safety with satisfied all of the legislations
Preferred to be produced from the renewable materials

This green solvent criterion is over-detailed and covers almost every aspect of EHS and lifecycle assessment (LCA) of a solvent. Although these criterions can be considered as a guide to develop a green solvent, it is not an efficient model as it is practically impossible to find a single solvent simultaneously satisfying all these twelve points. Moreover, a solvent may be considered to be green in a certain reaction while it may not be defined as such in another reaction due to, for example, a different separation method employed. Therefore, it is very challenging to find a philosophically unique definition of what is a 'green solvent'.

Capello *et al*. proposed a relative definition of a green solvent, which can be summarised as follows: A green solvent is a solvent having a lower EHS impact and energy demand during its LCA compared to conventional solvents.[39] This definition rationally explains the profound meaning of green solvents. In this work, this definition is cited as the implication of green solvents. Currently, there are four main research areas of green solvents:[39,40] supercritical fluids,[41,42] room temperature ionic liquids,[43] fluorous solvents[44,45] and bio-based solvents.

1.5.2 The introduction of bio-based solvents

The term *bio-based solvent*, covering the terms *bio-solvent* and *bio-derived solvent*, is defined as a solvent in which at least 20% of the carbon is bio-sourced.[46,47] Bio-based solvents, derived directly (bio-solvent) or synthesised (bio-derived solvent) from natural materials, are being developed to become benign replacements for petroleum-based solvents.[48]

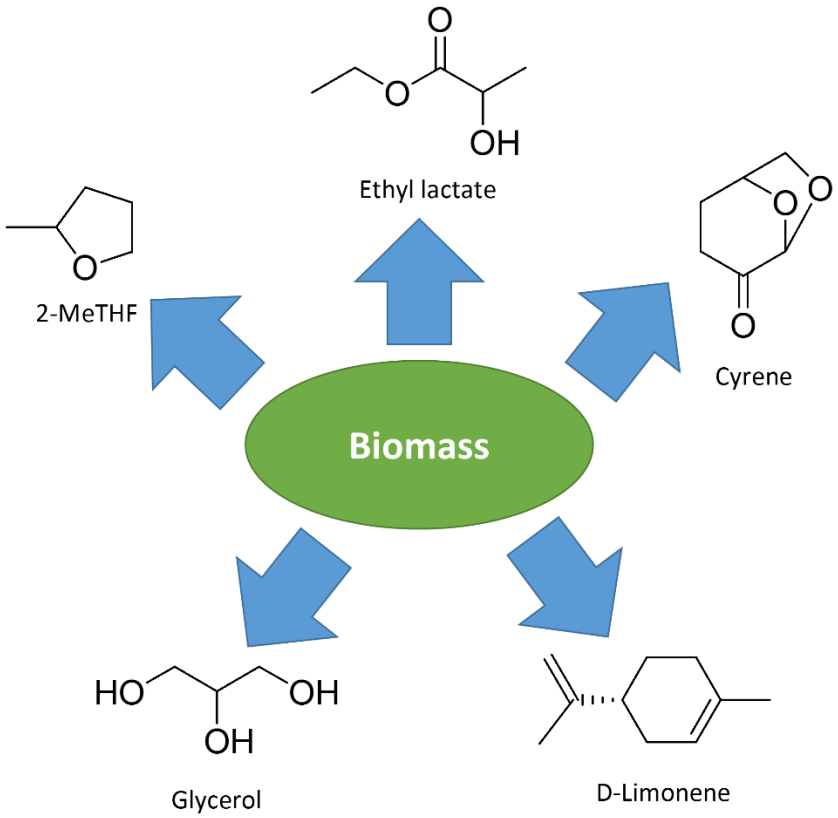


Fig. 1.2 Bio-based solvents

Recently, efforts to expand the range and number of bio-based solvents have increased dramatically. The reason for this is that: (a) known petroleum resources are becoming exhausted; (b) sustainable manufacture has the potential to raise public confidence in the chemical industry; (c) new standards for labelling compounds as "bio-based" results in solvent synthesis being more transparent and promoting higher values.[37,49] Specifically, when a bio-based solvent is used, the cycle of bio-based carbon is closed: at the end of life, these bio-based compounds are usually incinerated or lost to the atmosphere as carbon dioxide, which in turn is fixed during photosynthesis, allowing for the carbon to be reincorporated back into bio-based solvents. The

utilisation of biomass in this process ensures more sustainable life cycle and reduces the carbon footprint of the solvent. Some of the representational bio-based solvents are shown in Fig. 1.2.

1.5.2.1 2-Methyl tetrahydrofuran as a bio-based solvent

2-Methyl tetrahydrofuran (2-MeTHF), synthesised from a furfural platform (Scheme 1.1),[50-53] which can be produced from lignocellulosic biomass (Fig 1.3),[54,55] is an outstanding commercially available bio-based solvent thanks to its wide range of solubility and physical properties as well as non-mutagenicity.[56]

2-MeTHF can substitute many conventional solvents such as THF,[57,58] diethyl ether[58] and toluene[59] in organometallic reactions and DCM in biphasic reactions.[60] Previous research also reported that 2-MeTHF could increase the chemoselectivity and enantioselectivity of organometallic reactions.[61-63] Based on its low miscibility with water, it has already been used as a medium to extract organic compounds from the aqueous phase.[64] 2-MeTHF was also found to be a good solvent for biochemical reactions.[65-67]

Recently, 2-MeTHF was reported to be utilised as a green reaction medium for Suzuki-Miyaura coupling of arylboronic acids to aromatic ketones promoted by oxime-palladacycle.[68]

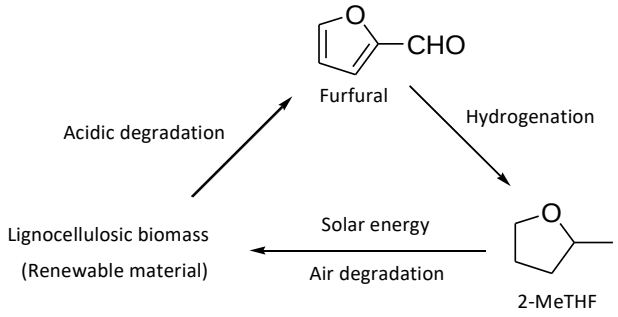
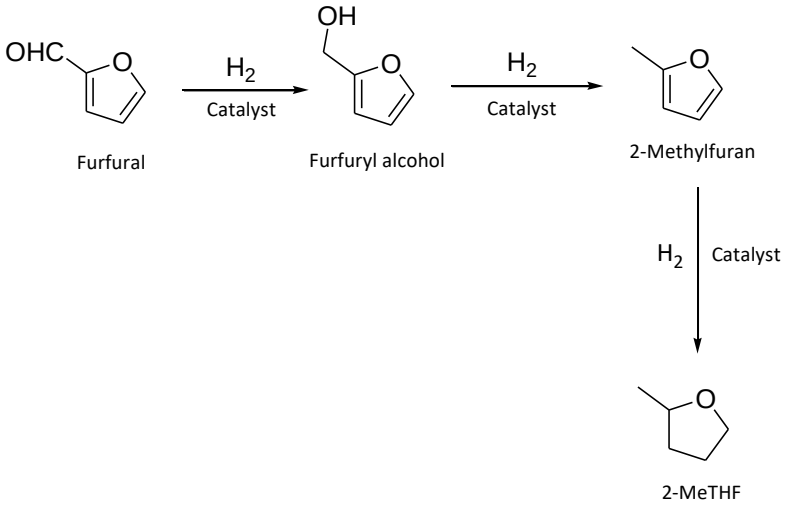


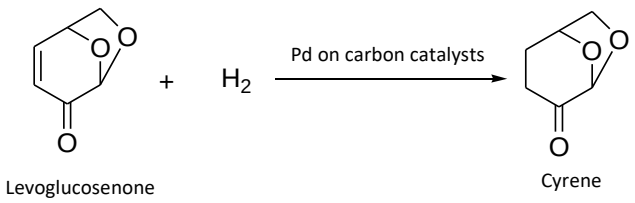
Fig. 1.3 The lifecycle of 2-MeTHF



Scheme 1.1 The hydrogenation process of production of 2-MeTHF from furfural platform

1.5.2.2 Cyrene as a bio-based solvent

Levoglucosenone is one of the most substantial pyrolysis products from cellulose biomass, and it has already been employed as a chiral building block for the synthesis of a wide range of new compounds.[69-71] Sherwood *et al*. synthesised a novel commercialised bio-based solvent named Cyrene (dihydrolevoglucosenone) from levoglucosenone *via* hydrogenation (Scheme 1.2).[72,73] Cyrene can be used to replace the conventional dipolar aprotic solvents such as NMP, DMF and sulpholane.[72,74]



Scheme 1.2 The synthesis of Cyrene from levoglucosenone

1.5.2.3 D-Limonene as a bio-based solvent

D-Limonene is a monocyclic monoterpene compound possessing a lemon-like odour and is a major ingredient in some of the citrus oils such as orange, lime, lemon, grapefruit and

mandarin.[75] D-Limonene can be produced from organic peel biomass (Fig. 1.4).[76-78] It is considered to be the only bio-based solvent which can be used as a substitute for petroleum-based non-polar solvents, such as hexane.[79-81] Moreover, D-Limonene was found as an efficient solvent for the synthesis of esters and amides.[82] Recently, Zhu *et al*. employed D-Limonene as a bio-based medium for the fabrication of high-performance polymer light-emitting diodes and field-effect transistors.[83]

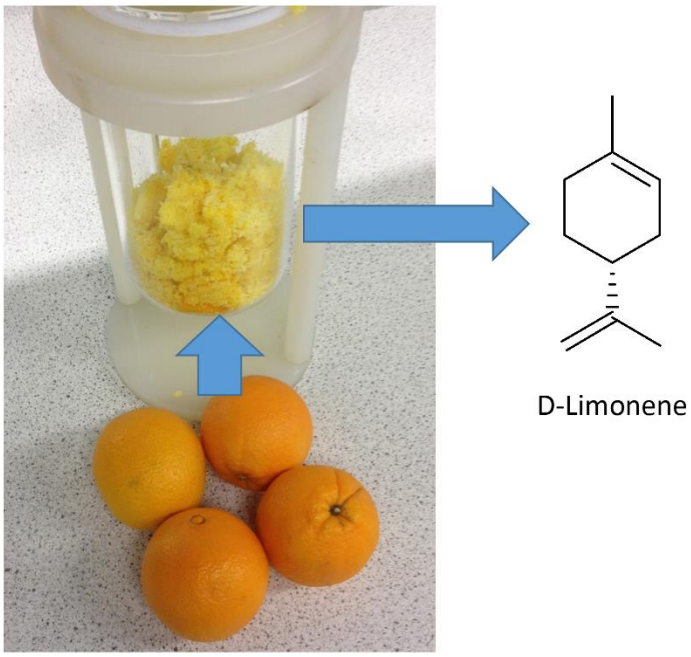
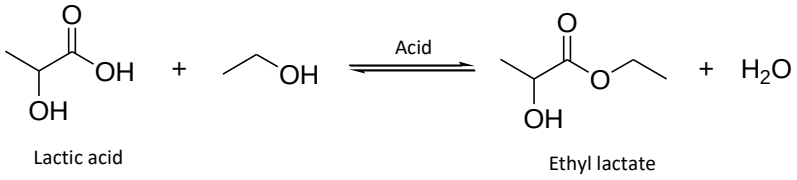


Fig. 1.4 D-Limonene obtained from orange peel

1.5.2.4 Ethyl lactate as a bio-based solvent

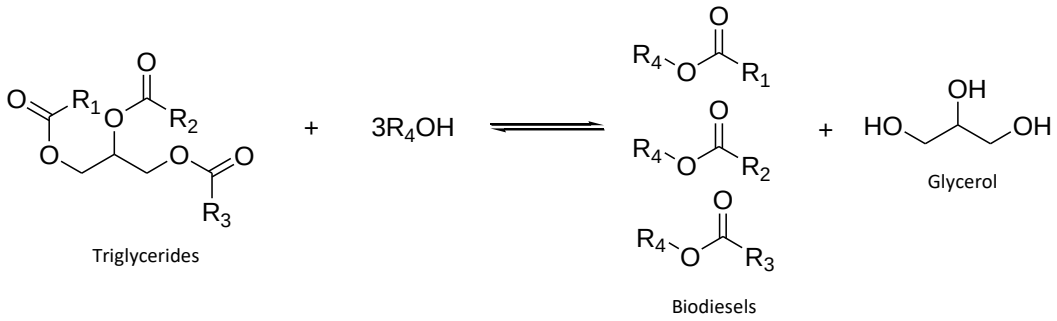
Ethyl lactate is a bio-based solvent which is mainly produced by the esterification reaction between renewable substrates ethanol and lactic acid under acidic catalysis (Scheme 1.3).[84] Ethyl lactate exhibits many excellent properties such as a strong solubility for organic compounds, non-toxicity, biodegradability, non-ozone depleting and low production costs.[37] In the last decade, many efforts focusing on its production and application have been explored. Currently, many new applications of ethyl lactate as a green solvent can be found in the literature.[85-93]



Scheme 1.3 The production of ethyl lactate from lactic acid and ethanol

1.5.2.5 Glycerol as a bio-based solvent

Glycerol is a versatile green compound which has many merits such as bio-based,[94] renewable,[94] non-toxic,[95] non-hazardous, non-volatile, biodegradable,[96] very low price and easy storage.



Scheme 1.4 The production of biodiesels from triglycerides

Glycerol is the by-product of the biodiesel production, and approximately 10 Kg crude glycerol can be obtained from the production of per 100 Kg biodiesel by the transesterification of triglycerides (from vegetable oil or fat).[97,98] Since the output of biodiesel has increased dramatically in the recent years,[99] the utilisation of surplus glycerol is attracting much interest. Glycerol has already been used as a valuable bio-based solvent for many organic syntheses such as nucleophilic substitution, oxidation, reduction, catalytic reduction, Heck coupling, asymmetric reduction, trans-esterification and some other reactions.[100-103] Recently, glycerol was utilised as a solvent for the ampicillin synthesis.[104]

However, its high reactivity with three hydroxyl groups limited its application in many organic reactions.

1.5.2.6 Some other bio-based solvents

In addition to these bio-based solvents mentioned above, there are some other bio-based solvents discussed in the literature (Fig. 1.5). *p*-Cymene is a new bio-based solvent which can be produced from D-limonene by isomerisation and dehydrogenation, and it has been found to be a viable medium for the synthesis of esters and amides.[83] *α*-Pinene is a bio-based solvent derived from turpentine oil[105] and has already been employed as a green extraction medium.[106]

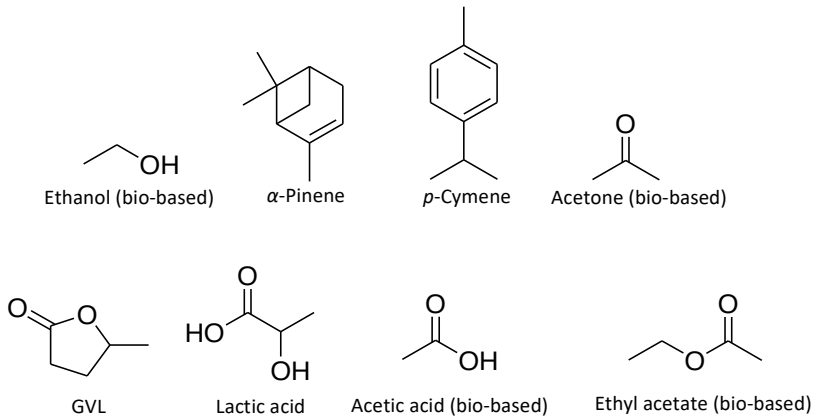


Fig. 1.5 Some other bio-based solvents

Some other common solvents such as ethanol, acetic acid, acetone[107] and ethyl acetate[108] can also be derived from bio-based platforms. Renewable and non-toxic *γ*-valerolactone (GVL) is also accepted as a new bio-based solvent,[109,110] and it currently has many applications as a green medium.[111-113] Lactic acid, which is the starting material for the production of ethyl lactate, was found by Yang *et al*. to be a good bio-based solvent for a series of organic reactions.[114]

Overall, bio-based solvents have excellent prospects, and it is one of the leading research fields in green chemistry. Despite traditional petroleum-based solvents have some advantages compared to bio-based solvents, such as well-established, economically viable processes and lower reactivity,[115] developing new bio-based solvents is still becoming a significant trend and requirement as a result of the increasing concerns about depleting fossil resources, problems of EHS and more rigorous legislations. The work in this thesis focuses on the utilisation of solvent parameters to search for novel bio-based solvents as direct replacements for conventional

organic solvents as well as further investigate the solvent performance of the current bio-based solvents. It was found that Kamlet-Taft solvatochromic parameters and Hansen solubility parameters were two efficient tools for this.

1.6 Kamlet-Taft solvatochromic parameters

1.6.1 The conception of Kamlet-Taft parameters

Polarity is widely accepted as one of the basic methods for demonstrating the physical properties of solvents.[116] All possible interactions between a solvent and solute are included in polarity except for chemical transformations.[117] The Kamlet-Taft (KT) solvatochromic parameter is a widely used solvent tool, to aid in understanding and predicting the behaviours of a solvent.[118-124] KT parameters describe solvent polarity based on three different parameters: hydrogen bond donating (HBD) ability (α), hydrogen bond accepting (HBA) ability (β) and a combination of dipolarity and polarisability (π^*).[122] π^* is used to measure the ability of a solvent to stabilise a dipole or a neighbouring charge by the function of nonspecific dielectric interactions.[122] When the three Kamlet-Taft parameters α, β and π^* are used in linear solvation energy relationship (LSER), they can be utilised to explain extensive phenomena of solvents.[123] One of the common forms of LSER is given by Equation 1.1:[122]

$$XYZ = \ln(K) = XYZ_0 + s(\pi^* + d\delta_0) + a\alpha + b\beta \quad (1.1)$$

In Equation 1.1, *XYZ* stands for a solvent-dependent physicochemical property or represents a reactivity parameter in a specific solvent. *XYZ* is usually equal to ln (K), where K is the reaction rate constant. $XYZ_0 = XYZ$ is when *XYZ* is in an inert solvent or under gas phase conditions. δ_0 is the polarisability correction term. XYZ_0, a, b, s and d are coefficients which are constants under specific conditions of the investigation. Therefore, the mathematic relation between reaction rate constant and KT parameters α, β and π^* of a solvent can be established, which demonstrates that KT parameters of a solvent have a profound influence on the chemical reaction kinetics.

KT parameters and LSER have already been utilised to understand the effects of solvents on many types of reactivity parameters as well as physicochemical properties in organic reactions.[82,125-131]

1.6.2 Kamlet-Taft parameters of conventional and bio-based solvents

The intimate connection between KT parameters and rate constant suggests that when two solvents have similar KT parameters, they will also have similar solvent performance in terms of kinetics for a given reaction. Jessop[132] proposed that a KT solvent map can be established with β and π^* as vertical and horizontal coordinates, respectively. Solvent maps can be separated in two different plots based on the value of α. One is used for the protic solvents (with $\alpha > 0.5$), another one is used for aprotic solvents (with $\alpha < 0.5$). If two solvents are adjacent on the solvent map,

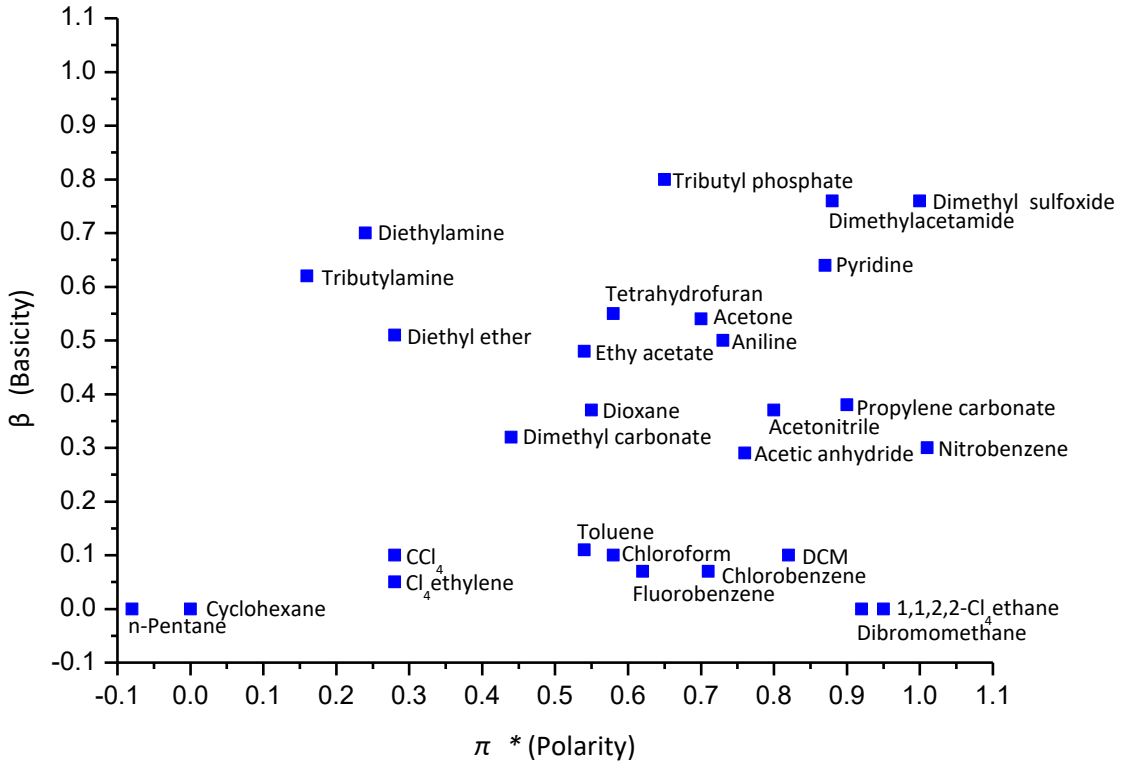


Fig. 1.6 The KT map of conventional aprotic solvents; KT data of DMC is derived from Ref. 133; KT data of ethyl acetate and diethyl ether is derived from Ref. 119 and Ref. 134; KT data of acetonitrile and acetone is obtained from Ref. 135; KT data of propylene carbonate derived from Ref. 136; KT data of other conventional solvents is obtained from Ref. 137

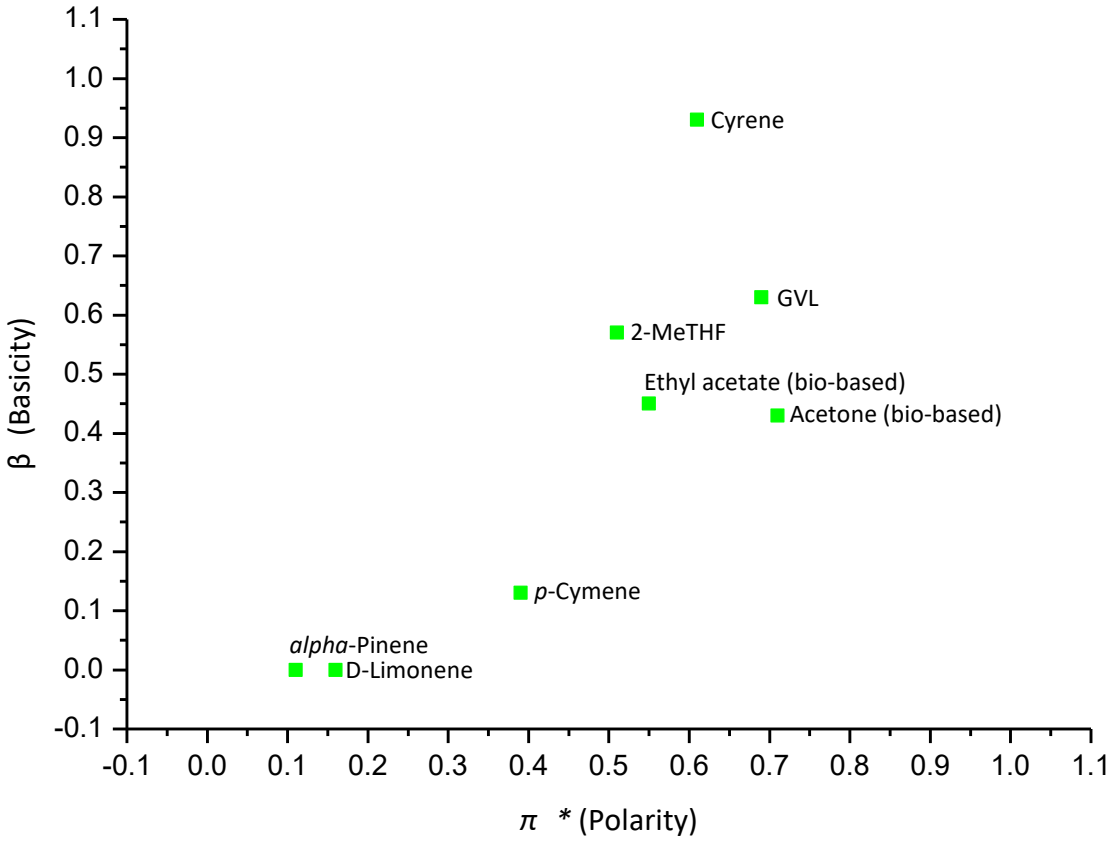


Fig. 1.7 The KT map of aprotic bio-based solvents; KT data of D-limonene,[82] 2-MeTHF,[133] acetone,[137] ethyl acetate,[137] *α*-pinene,[138] GVL,[138] *p*-cymene[82] and Cyrene[72] is obtained from literature

they will possibly have similar solvent performance. The solvent map provides a visual comprehension of KT parameters and is a convenient tool for solvent selection as well as the exploration of new green solvents.

In this work, aprotic solvents are the main research objectives. Fig. 1.6 and Fig. 1.7 illustrate the aprotic KT maps for conventional solvents and bio-based solvents, respectively. When comparing these two maps, it is evident that there is no bio-based solvent in Fig. 1.7 occupying the area populated by aromatic hydrocarbon and halogenated hydrocarbon solvents in Fig. 1.6, *i.e.* solvents with high polarity ($\pi^* > 0.5$) and low basicity ($\beta < 0.3$).

Since numerous organic reactions are carried out in these petroleum based solvents, it is vital to search for new bio-based alternatives with similar KT parameters to aid in the sustainable

development of the chemical industry.

1.7 Hansen solubility parameters

The universal principle of "like dissolves like" is widely employed for solubility parameters. In some cases, solubility parameters are also defined as "cohesion energy parameters" since they are obtained from the energy needed to transform a liquid into a gas.[139] The energy of vaporisation can be a direct measure of the total cohesion energy as all types of bonds assembling the liquid together can be broken by evaporation. Therefore, the total cohesive energy is identical to the energy of vaporisation.[139] Historically, the term *Solubility parameter* was first proposed by Hildebrand and Scott.[140,141] The Hildebrand solubility parameter (δ) is defined as the square root of the cohesive energy density (see Equation 1.2) which is the energy required to remove a unit volume of molecules from their neighbours to be separated infinitely and is equal to E/V:

$$\delta = (E/V)^{1/2} \qquad (1.2)$$

In Equation 1.2, V stands for the molar volume of pure solvents, while E is its energy of vaporisation. Based on Equation 1.2, the unit of solubility parameters is $MPa^{0.5}$. Equation 1.3 can be obtained easily from Equation 1.2:

$$\delta^2 = E/V \qquad (1.3)$$

Hansen proposed that the total energy of vaporisation (E) can be separated into at least three different parts:[142] E_D, E_P and E_H. E_D is dispersion cohesive energy which comes from the nonpolar (dispersion) atomic forces, and E_P is the polar cohesive energy which is produced by the permanent dipole-permanent dipole molecular forces, while E_H represents the electron exchange energy which is obtained from the hydrogen bonding molecular forces.[139] Consequently, Equation 1.4 is then proposed as the core equation of Hansen solubility parameters (HSPs) theory:

$$E = E_D + E_P + E_H \quad (1.4)$$

Equation 1.5 can be attained *via* dividing Equation 1.4 by the molar volume V:

$$E/V = E_D/V + E_P/V + E_H/V \quad (1.5)$$

And then combining Equation 1.3 and Equation 1.5 can get Equation 1.6:

$$\delta^2 = \delta^2_D + \delta^2_P + \delta^2_H \quad (1.6)$$

In Equation 1.6, δ is the Hildebrand solubility parameter, and HSPs δ_D, δ_P, and δ_H stand for Hansen dispersion cohesion solubility parameter, Hansen polar cohesion solubility parameter and Hansen hydrogen bonding cohesion solubility parameter, respectively, and can be calculated from the interactions of identical molecules in a pure liquid. Equation 1.6 clearly shows a mathematical relationship between Hildebrand solubility parameter and HSPs.

These three HSPs can be used as coordinates to establish a three dimension (3D) Hansen space. Equation 1.7 defined the Hansen distance (Ra) in Hansen space:

$$Ra = \sqrt{4(\delta_{D2} - \delta_{D1})^2 + (\delta_{P2} - \delta_{P1})^2 + (\delta_{H2} - \delta_{H1})^2} \quad (1.7)$$

In general, the lower the value of Ra the two chemicals have, the more similar solubility they will possess. R_0 is defined as “interaction radius”. If the solubility of the solvent for the solute needs to be retained, Ra cannot exceed R_0. The units of Ra and R_0 are both $MPa^{0.5}$. To compare Ra and R_0, the relative energy difference (RED) was proposed as shown in Equation 1.8:

$$RED = Ra/R_0 \quad (1.8)$$

When the number of RED is 0, it indicates that the solvent and solute do not have any difference in energy, and their solubility is identical. If the value of RED is less than 1, it demonstrates that the solvent and solute have high affinities, and they will dissolve into each other. If the number

of RED is equal to 1 (the boundary condition), the molecules are only partially dissolved. If the value of RED is higher than 1, then the molecules will have lower affinities, and the solvent/solute, in this case, will not dissolve with each other.

HSPs are extensively used to predict solubility, select appropriate solvents and search for solvent alternatives. HSPs have been ubiquitously used for the research of polymer solubility in solvents and surface science for several decades.[143-145] HSPs are also utilised for the research of coatings.[146] Recently, HSPs were used to study the encapsulation of caffeine in metal-organic frameworks (MOFs),[147] to predict the dispersion of nanoparticles in polymeric films,[148] to predict drug-nail interactions[149] and to predict solubility behaviour of globular plant proteins.[150]

Overall, HSPs can be used as a powerful tool to predict solvent properties and investigate the similarity of solvency between the bio-based solvent and the traditional solvents.

1.8 Platform molecules

Bio-based platform molecules (bio-based building block or biomass derivatives), referred to hereafter simply as platform molecules, are molecules derived from biomass with multiple functional groups which possess the potential to construct new useful compounds.[151,152] In 2004, the National Renewable Energy Laboratory (NREL) in the United States proposed a list of top 30 platform molecules (Fig. 1.8).[152] These platform molecules include the following features: (a) they have multiple functionalities which can be used as a platform to convert to various derivatives, (b) they are derived from renewable starch and lignocellulosic materials, which adheres to the inherent virtues of green chemistry; (c) they are compounds with carbon numbers in the range of 1 to 6, many of which are potential monomers for the synthesis of bio-derived polymers.

Apart from these top 30 platform molecules listed by NREL, GVL was also recognised as a platform molecule and can be utilised for the synthesis of a wide range of chemicals such as polymers and jet fuel.[153] Isosorbide (Fig. 1.9) was proposed as a potential platform molecule for the synthesis of new polymers.[154] Recently, methyl vinyl glycolate was also reported to be a novel

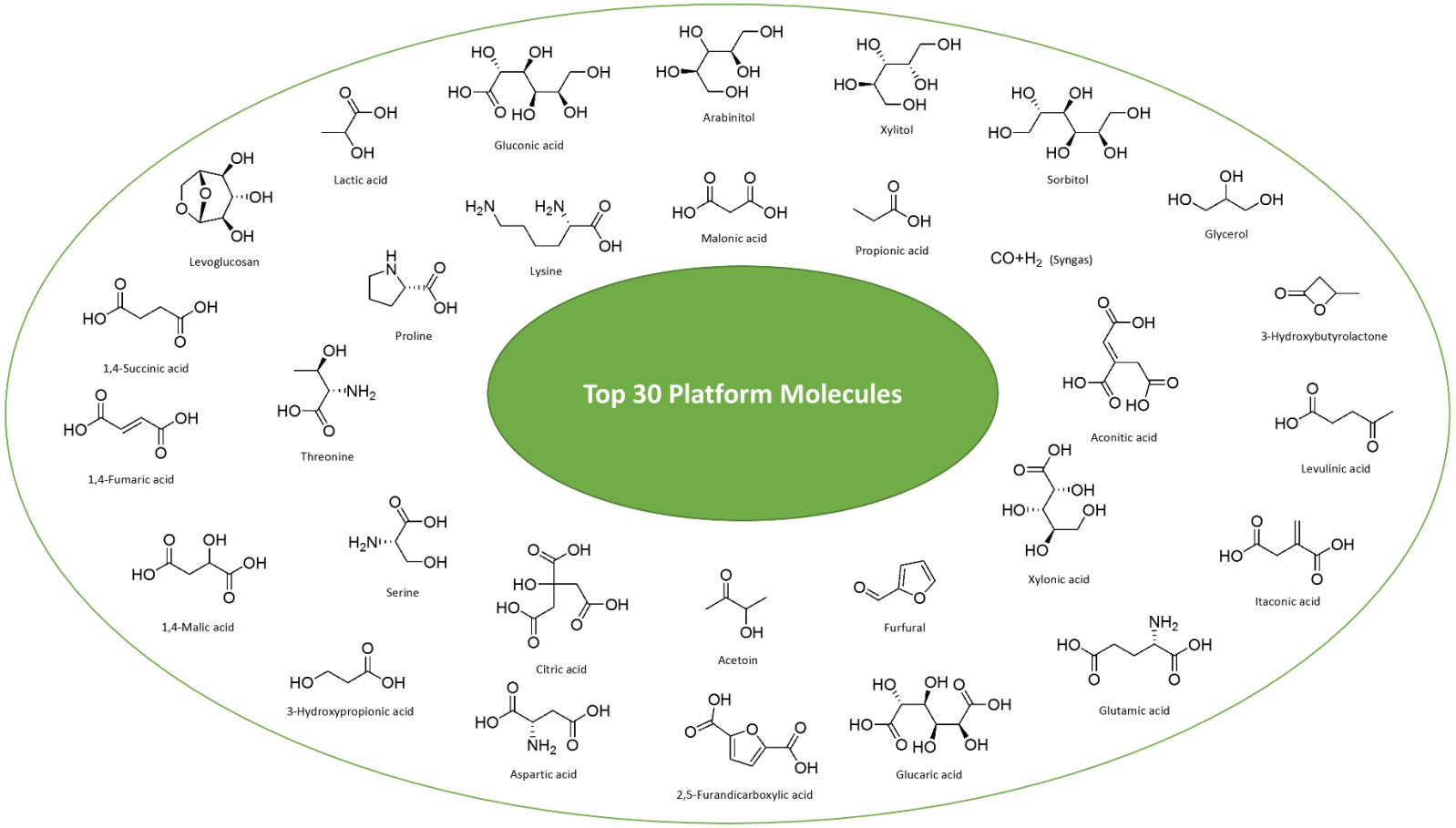
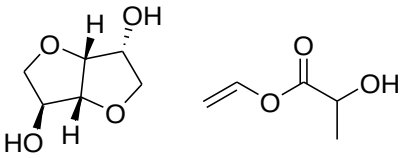


Fig. 1.8 The top 30 platform molecules selected by NREL in 2004

renewable platform molecule which can be produced *via* zeolite catalysed degradation of mono- and disaccharides.[155]



D-isosorbide Methyl vinyl glycolate

Fig. 1.9 Platform molecules: isosorbide and methyl vinyl glycolate

In comparison to the petroleum-based chemicals, renewable building blocks contain various functionalities and heteroatoms making them excellent and easy starting points to construct valuable new chemicals.[151]

In summary, platform molecules are in accordance with the principle of sustainable development and have the potential to become feedstock for the synthesis of a vast number of chemicals as replacements for petroleum-derived compounds. Most relevant to this work, platform molecules offer a route to develop greener bio-based solvents as replacements for conventional solvents.

1.9 Dimethyl carbonate chemistry

1.9.1 The introduction of DMC

DMC (Fig. 1.10) is an established green solvent and a green reagent which has attracted significant attention. It readily biodegrades in the atmosphere[156] and is a non-toxic compound.[157] DMC has shown extensive applications as a solvent,[158] including in pharmaceutically relevant synthesis[159] as well as in biocatalysis.[160]

In fact, as a result of its properties, a recent solvent guide classified DMC in the greenest "recommended" bracket.[161] Additionally, supercritical DMC has been shown to provide a catalyst-free route to biodiesel and glycerol carbonate.[162]

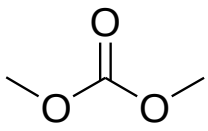


Fig. 1.10 The structure of DMC

Significantly, DMC is a green replacement for highly toxic and hazardous compounds such as (a) dimethyl sulphate (DMS) and halohydrocarbons (CH_3X, X = I, Br, Cl) in methylation reactions and (b) phosgene ($COCl_2$) in carboxymethylation (methoxycarbonylation) reactions.[163] Table 1.4 lists the advantages of DMC in comparison to phosgene and DMS.[164] Hence, significant interest has been given in utilising DMC in organic chemistry.

Table 1.4 The advantages of DMC comparing to phosgene and DMS

Phosgene and DMS	DMC
Hazardous reactants	Innocuous reactant
Solvent used	No other solvent used except for itself
Waste water disposal	No treatment of waste water
Sodium hydroxide consumption	Catalytic amount of base
By-products: sodium chloride and Na_2SO_4	By-products: methanol and CO_2
Exotherm	Little or no exothermic

1.9.2 The synthesis and manufacture of DMC

Currently, there are six main procedures for the synthesis of DMC. They are (a) phosgene synthesis, (b) oxidative carbonylation of methanol, (c) transesterification process, (d) carbonylation of methyl nitrite, (e) direct synthesis process of CO_2 and methanol and (f) alcoholysis of urea (Fig. 1.11).

1.9.2.1 Phosgene synthesis

DMC was first prepared from methanol and phosgene as a side product of diphosgene, a toxic

material used in gas shells during the First World War.[165,166] This synthesis has been used to produce DMC over an extensive period. However, due to the extremely toxic starting material phosgene and the production of hydrochloric acid as an undesired by-product, it is now obsolete.

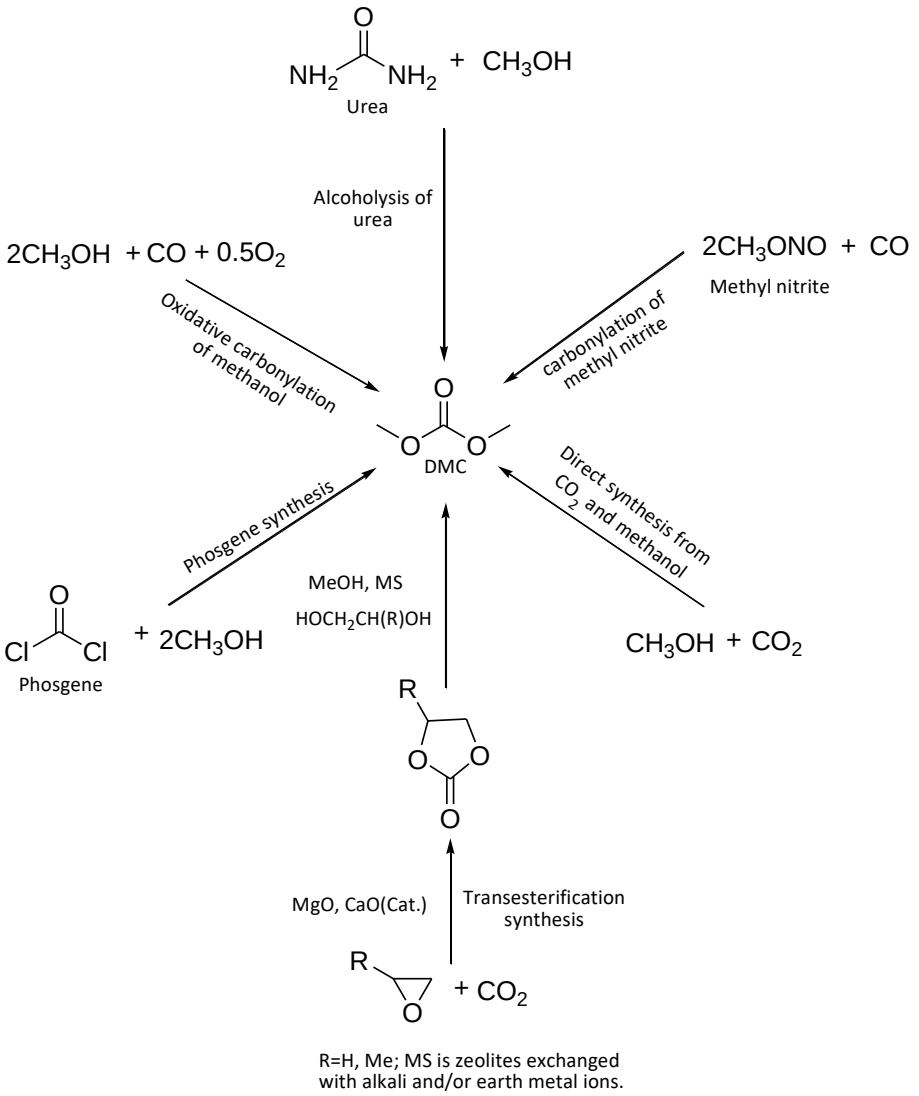


Fig. 1.11 The six main procedures for the synthesis of DMC

1.9.2.2 Oxidative carbonylation synthesis

DMC can be produced from the oxidative carbonylation of methanol.[167,168] Compared to the historic industrial synthesis using phosgene, this method has many advantages: widely available and low-cost raw materials, high production rates, no corrosive reactants used, only water and

carbon dioxide as by-products. Nevertheless, the disadvantages of this process include the hazard of the explosion of methanol and oxygen as well as the toxic starting material carbon monoxide.

1.9.2.3 Transesterification synthesis

China has developed a method of DMC synthesis which is known as the transesterification process.[169] It has already been industrialised for the production of DMC from cyclic carbonates, where these cyclic carbonates can be generated from carbon dioxide and epoxides (See Fig 1.11).[169] In particular, this procedure does not utilise any chlorine-containing reagents.

Recently, Li *et al*. published a method of a one-step synthesis of DMC from carbon dioxide, propylene oxide and methanol on alkali halides promoted by crown ethers, which shows excellent reusability, and a yield of DMC of 40% was obtained.[170] Liu *et al*. reported they synthesised DMC from carbon dioxide, methanol and epoxide catalysed by alkali carbonate under an initial CO_2 pressure of only 0.5 MPa, and a 63.5% yield of DMC was attained.[171]

1.9.2.4 Carbonylation of methyl nitrite

Another way to synthesise DMC is the carbonylation of methyl nitrite.[172] (Pd–$CuCl_2$)/γ-Al_2O_3 was used an efficient catalyst for the synthesis of DMC from carbon monoxide and CH_3ONO with nitric oxide as a by-product.[173] Dong *et al*. used the potassium ion containing Pd/NaY catalyst to promote the synthesis of DMC from carbon monoxide and methyl nitrite.[174] The problem with this process is that CO has been used in the reaction.

1.9.2.5 Direct synthesis from carbon dioxide and methanol

Tomishige *et al*. reported a method for the direct synthesis of DMC from methanol and CO_2 catalysed by zirconia.[175] DMC was also produced from carbon dioxide and methanol over Mg-Al hydrotalcite-silica hyogels.[176] Additionally, DMC was synthesised from CO_2 and MeOH catalysed

by CeO_2, and a yield of 96% was achieved.[177]

1.9.2.6 Alcoholysis of urea

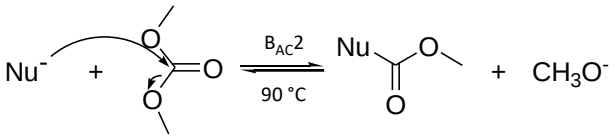
DMC can be synthesised *via* the alcoholysis of urea in methanol using various catalysts.[178-183] This reaction pathway consists of two steps with methyl carbamate as the reaction intermediate. Metal oxides and polyphosphoric acid have been found to be the most active catalysts for this process.[178,179,181,182] An evident merit of this procedure is that the by-product NH_3 can be utilised to reform the reactant urea.[184] Hou *et al*. reported that they synthesised DMC by direct alcoholysis of urea under supercritical methanol successfully, and a yield of DMC of 98% was obtained,[185] which implies that the supercritical technique could be an efficient way to improve the yield of DMC synthesised from direct alcoholysis of urea in methanol.

1.9.3 The reactivity of DMC

1.9.3.1 The basic mechanism of DMC chemistry

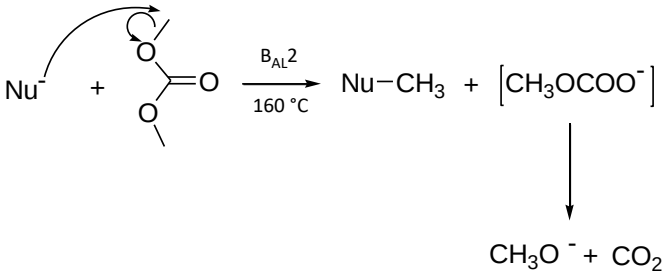
At different temperatures, DMC shows different possible reaction mechanisms:[164]

(a) When the reaction temperature is around 90 °C, the carboxymethylation reaction (Scheme 1.5) predominates *via* a $B_{Ac}2$ mechanism (*i.e*., bimolecular, base-catalysed, acyl cleavage and nucleophilic substitution).



Scheme 1.5 The carboxymethylation mechanism of the DMC and nucleophile at 90 °C

(b) When the reaction temperature is higher than 120 °C (usually T = 160-200 °C), the methylation reaction (Scheme 1.6) predominates *via* a $B_{AL}2$ mechanism (*i.e*., bimolecular, base-catalysed, alkyl cleavage and nucleophilic substitution):

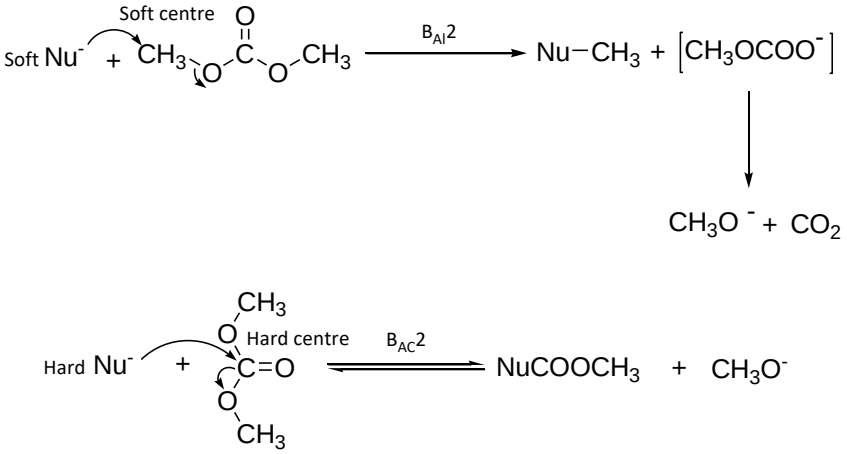


Scheme 1.6 The methylation mechanism of the DMC and nucleophile at 160 °C

Although both Scheme 1.5 and Scheme 1.6 can be used as rational theories to predict and explain many reactions of DMC, some DMC methylation or carboxymethylation reactions occur regardless of the temperature.[165] Hard-Soft Acid-Base (HSAB) theory has also been used as another way to explain the possible mechanism of basic DMC chemistry.

1.9.3.2 HSAB theory and its explanation for the basic mechanism of DMC chemistry

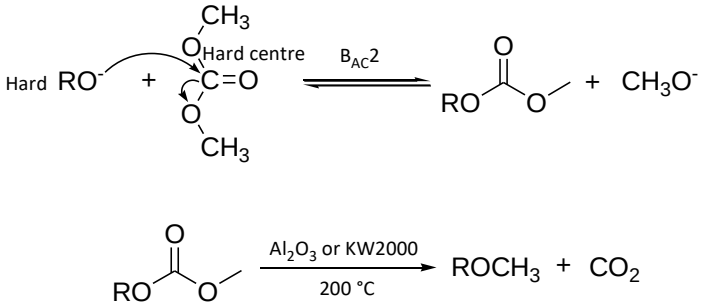
HSAB theory was proposed by Pearson in 1963 and improved by Mendez.[186-188] According to HSAB, hard species have higher effective nuclear charge, smaller atomic radius and lower polarisability, while soft species have lower effective nuclear charge, larger atomic radius and higher polarisability.[189] HSAB theory suggests that softer nucleophiles react with softer centres, while harder nucleophiles tend to react with harder electrophiles.



Scheme 1.7 The basic DMC reaction mechanism based on the HSAB theory

DMC has three reaction centres and is an ambident electrophile. The saturated carbon atoms in the two methyl centres of DMC have sp^3 hybridised orbits, while the central carbon adopts sp^2 hybridisation and has a polarised positive charge thanks to the electronegativity of the three adjacent oxygen atoms (the carbonyl dominating).[190] On the basis of HSAB theory, the carbonyl group is the harder electrophile while the methyl groups are the softer electrophiles.

Scheme 1.7 shows the basic DMC reaction mechanism based on the HSAB theory.[190] According to the HSAB theory, the soft nucleophile reacts with the soft methyl group on the DMC *via* a $B_{AL}2$ mechanism, while hard nucleophile reacts with the hard carbonyl group on the DMC by a $B_{AC}2$ mechanism. Tundo *et al*. suggested that aliphatic hydroxyl is a hard nucleophile.[190] Based on the HSAB theory, aliphatic hydroxyl group prefers to react with the hard carbonyl group electrophile in DMC to form methyl carbonate rather than methyl ether, no matter what temperature is applied in the reaction (Scheme 1.8). If alumina or hydrotalcite KW2000 (a synthetic hydrotalcite with formula $Mg_{0.7}Al_{0.3}O_{1.15}$) is used in the process with high temperature, some of the methyl carbonates may undergo decarboxylation to produce methyl ethers.[191,192]

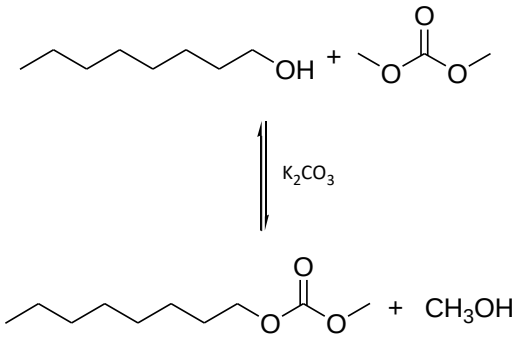


Scheme 1.8 The possible mechanism for the methylation of aliphatic alcohol based on HSAB theory

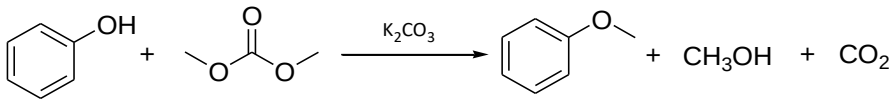
However, the base-catalysed mechanism of DMC currently has not been confirmed completely. As a result, both of the mechanisms can be used to explain the phenomenon of the reactions observed.

1.9.4 Application of DMC as carboxymethylation and methylation agents for alcohols

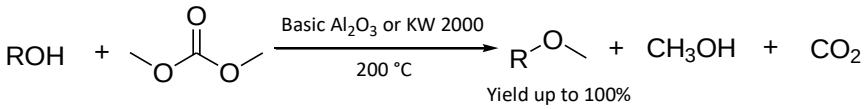
At present, most DMC mediated carboxymethylation and methylation reactions are catalysed by bases. Potassium carbonate is one of the most common base catalysts used in DMC carboxymethylation and methylation reactions with alcohol and phenols (see Scheme 1.9 and Scheme 1.10 for examples).[163,165,190,193] Potassium *tert*-butoxide (KO*t*-Bu) is another widely applied base and was also found to give excellent conversion and selectivity towards the synthesis of unsymmetrical carbonates from primary and secondary alcohols and DMC at room temperature.[194] Reactions of highly hindered secondary alcohols of isosorbide and DMC have resulted in carboxymethylation with weak bases and methylation with a strong base such as sodium methoxide at reflux.[195]



Scheme 1.9 The carboxymethylation reaction between 1-octanol and DMC catalysed by potassium carbonate



Scheme 1.10 The methylation reaction between phenol and DMC catalysed by potassium carbonate



Scheme 1.11 The methylation reaction of alcohol with DMC catalysed by basic alumina or hydrotalcite KW 2000 at elevated temperature

Basic alumina and hydrotalcite KW 2000 both have good DMC methylation ability for alcohols at high temperature (Scheme 1.11).[191] Moreover, 1,5,7-triazabicyclo [4.4.0] dec-5-ene (TBD) was also applied as a basic catalyst for the carboxymethylation of primary through to tertiary alcohols and for the production of polycarbonates from diols and DMC.[196] The f-block base lanthanum(III) isopropoxide has been reported as an excellent catalyst for the carboxymethylation of primary, secondary and tertiary alcohols in high yield.[197]

In addition to basic catalysts, some other processes of DMC reactions were also developed. Ionic liquid 1-(3-trimethoxysilylpropyl)-3-methylimidazolium chloride was found to be an activated reaction medium for the synthesis of non-symmetrical dialkyl carbonates.[198] Novozym 435, a lipase B from *Candida antarctica*, was also employed to conduct the carboxymethylation of DMC with alcohols.[199] Microwaves were also found to assist the methylation of DMC with dihydroxybenzene in the presence of a base catalyst, and high yield (98%) was achieved for the bis-methylated product at elevated temperatures (170 °C).[200]

Overall, as a green methylation and carboxymethylation agent, DMC is now a valuable compound in synthetic organic chemistry. Many efforts are still needed to expand its application. Specifically, DMC can be used to upgrade platform molecules to bio-based solvents.

1.10 Project aims

This project will focus on the development of bio-based alternative solvents from platform molecules acetoin and solketal by DMC methylation or carboxymethylation reactions for the replacement of the traditional solvents according to the prediction of HSPiP modelling software. Meanwhile, the acid-catalysed DMC chemistry will also be investigated to introduce acid catalysts.

Chapter 2 discusses the synthesis and purification of a novel bio-based solvent 3-methoxybutan-2-one from acetoin and DMC, as replacement solvent for DCM. Its HSPs was calculated by HSPiP software, and its KT parameters were tested. The properties and solvent performance of 3-methoxybutan-2-one were also assessed and compared to various traditional solvents.

Chapter 3 discusses the synthesis and purification of a new bio-based solvent methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate from solketal and DMC for the substitution of a wide range of different common solvents. Its HSPs was calculated by HSPiP, and its KT parameters were determined. The properties and solvent performance of this new bio-based solvent were also be tested and compared to different conventional solvents.

Chapter 4 covers the study of acid-catalysed DMC reactions. Various alcohols and phenols were selected as substrates to conduct DMC mediated carboxymethylation, methylation and dehydration reactions with different acids at 90 °C or 160 °C.

Chapter 2 3-Methoxybutan-2-one as a new bio-based solvent

2.1 Introduction

2.1.1 HSPiP software

Nowadays, searching for new bio-based solvents is an important task for the green chemistry. However, it is very time-consuming and costly for laboratory-based experiments to generate all the possible solvents to find the proper alternatives for traditional solvents. Therefore, it is vital to predict the properties for a new bio-based solvent in order to screen for promising candidates to synthesise.

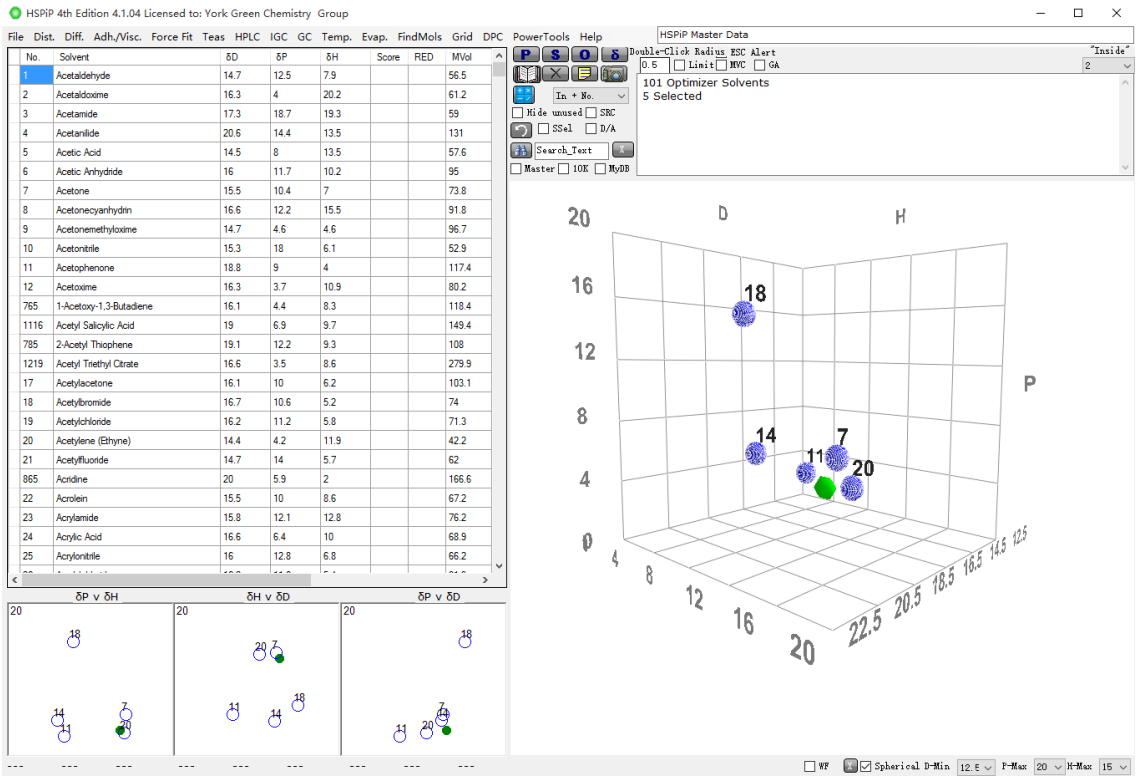


Fig. 2.1 The interface of HSPiP

Hansen Solubility Parameters in Practice (HSPiP, 4th Edition 4.1.04, software interface as shown in Fig. 2.1), developed by Abbott, Hansen and Yamamoto, is a software which can be used as a powerful tool to predict the Hansen solubility parameters (HSPs) and the other various properties of a given chemical. HSPiP has HSPs and other data for 10,000 chemicals in the newest edition.[201] HSPiP can calculate and visualise HSPs in three dimension (3D) Hansen space *via* input the simplified molecular-input line-entry system (SMILES) or IUPAC International Chemical

Identifier (InChI) format of molecular structure. It can also predict other physical properties such as melting point (m.p.), boiling point (b.p.), flash point, refractive index and density for a given compound. HSPiP calculates the HSPs and other physical properties by using Y-MB method (Dr. Hiroshi Yamamoto's neural network molecular breaking technique). The Y-MB method breaks the molecules into functional groups and estimates different properties.[201]

HSPiP now has been widely employed in the world in various research fields.[202-207,148] In this project, it was used as an instructional tool to search for bio-based solvents for the replacement of conventional solvents.

2.1.2 Introduction of acetoin

Acetoin (3-hydroxybutan-2-one or acetylmethylcarbinol), as shown in Fig. 2.2, is a natural compound found in foods such as wines,[208] tea,[209] coffee,[210] milk,[211] apples,[212] honey,[213] strawberry jam,[214] butter,[215] sweet corn products,[216] *etc*. It can be used to synthesise some significant organic intermediates such as 2,4,5-trisubstituted-1*H*-imidazoles,[217] 2-thiocyanoimidazolium salts[218] and benzo[*N*,*N*]-heterocycles.[219] In particular, acetoin was identified by the National Renewable Energy Laboratory (NREL) as one of top 30 platform molecules which can be produced from biomass.[152] Acetoin can be generated by either chemical synthesis or through biological processes.

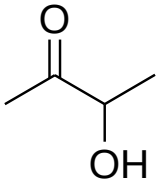
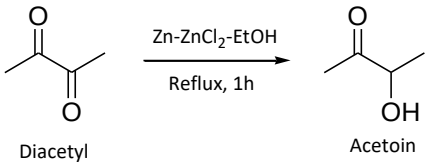


Fig. 2.2 The structure of acetoin

2.1.2.1 Chemical synthesis of acetoin

In 1989, Toda *et al*. from Ehime University in Japan, reported the synthesis of acetoin from diacetyl under the catalytic system of Zn-$ZnCl_2$-EtOH with a yield of 71% (Scheme 2.1).[220] Hilmi

et al. reported that they synthesised acetoin with high yield *via* electro-oxidation of 2,3-butanediol.[221] At present, acetoin is mainly produced from diacetyl in the industry.



Scheme 2.1 The synthesis of acetoin from diacetyl by chemistry method

2.1.2.2 Biological production methods of acetoin

Although many chemical routes to acetoin exist, much research is being perused to give biological production methods for acetoin, by either enzymatic[222-224] or fermentation[225,226] technologies.

1. Enzymatic production of acetoin

Hummel *et al*. patented the production of (+)-acetoin from 2,3-butadione using diacetyl reductase derived from yeast/*Lactobacillus* strain.[227] Silverman and Werkman also found that acetoin could be yielded from the pyruvic acid by carboxylase and carboligase.[223]

2. Acetoin *via* fermentation

Acetoin is a metabolite from some microorganisms such as *Saccharomyces carlsbergensis*,[225] *Leuconostoc citrovorum,*[228] *Lactococcus lactis*[229,230] and *Hanseniaspora guilliermondii*.[231.232] Liu *et al*. patented an invention where they used a mutant strain of *Bacillus subtilis* SFA-H31 to transform glucose to acetoin with high yield and high purity achieved *via* an optimised method.[233] The advantage of this invention is that this method of production of acetoin does not result in contamination from 2,3-butanediol and diacetyl when compared to other strains which normally synthesise these two impurities with acetoin together. This fermentation method of the mutant strain is ideal for the green production of acetoin on a commercial-scale.

Recently, Zhang *et al*. reported that they produced acetoin from a low-cost lignocellulosic resource of pre-treated corn stover by metabolically engineered *Enterobacter cloacae*,[234]

which also promoted the bio-based production of acetoin. Additionally, acetoin was also produced *via* simultaneous utilisation of glucose, xylose and arabinose by engineered *Bacillus subtilis*.[235] However, the drawback of the three cases above is that purification processes are required to separate acetoin from the broth.

Overall, bio-derived acetoin has many potential applications in the future, with its functionality allowing routes to many new compounds, including solvents.

2.1.3 Aims of this chapter

As discussed in Chapter 1, currently there is no bio-based solvent with medium to high polarity and low basicity suitable for replacement of halogenated hydrocarbons such as dichloromethane (DCM). As DCM and other halohydrocarbons present serious problems such as sustainability, carcinogenicity and ozone depletion, it is vital that new greener bio-based solvents be identified as candidates to replace them.

In this chapter, the aim is to synthesise a new bio-based solvent as the substitution of halogenated hydrocarbon solvent *via* reacting a bio-derived platform molecule with green agent dimethyl carbonate (DMC) based on the analysis of HSPiP software. Full solvent characterisation will be carried out, ascertaining various physical properties and Kamlet-Taft (KT) parameters of the new bio-based solvent. Simultaneously solvent performance in comparison with DCM and other traditional organic solvents will be evaluated in Friedel–Crafts and Diels-Alder reactions.

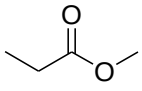
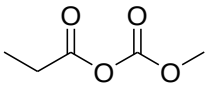
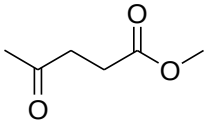
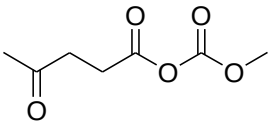
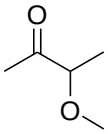
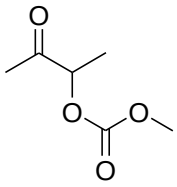
2.2 Results and discussion

2.2.1 In silico analysis for assessing potential bio-based solvents

The initial screening of potential greener solvents by computational chemistry is an efficient methodology. HSPiP software was selected as a silico analytical tool in this Chapter to guide the searching for new bio-based solvents generated from platform molecules with green methylation[236] and carboxymethylation agent DMC.

To replace halogenated solvents, it is important to find a proper volatile solvent, but not too volatile as DCM, that has a lower b.p. (70 °C-139 °C)[161] to make it easy to be removed and recycled after reaction or extraction. HSPs of the new solvents are also needed to be similar to these halogenated solvents such as DCM in order to have the similar solvency power. Therefore,

Table 2.1 The HSPiP predicted properties of the candidate bio-based solvents

Potential bio-based solvents	B.p./°C	Hansen δ_D/MPa$^{0.5}$	Hansen δ_P/MPa$^{0.5}$	Hansen δ_H/MPa$^{0.5}$	Hansen distance to DCM[a]
 Methyl propionate	83	15.7	5.7	7.1	5.13
 Methyl propionyl carbonate	162	16.0	12.1	8.8	7.76
 Methyl 4-oxopentanoate	178	16.7	8.5	7.5	3.97
 Carbonate of levulinic acid	238	16.6	13.8	9.2	8.72
 3-Methoxybutan-2-one	113	16.1	8.0	5.5	4.57
 Methyl 3-oxobutan-2-yl carbonate	179	16.4	9.7	6.5	4.97

[a] The HSPs of DCM (δ_D = 18.2 MPa$^{0.5}$ δ_P = 6.3 MPa$^{0.5}$ δ_H =6.1 MPa$^{0.5}$) can be found in Ref. 139.

Hansen solubility parameters (HSPs) and b.p. were opted as the key parameters to evaluate the

potential green solvents in this section before synthesis.

Among the top 30 platform molecules, illustrated in chapter 1, the molecules with only one nucleophilic group were selected. This is because (a) nucleophilic group is needed when reacting with DMC; (b) more than two nucleophilic groups, such as hydroxyl group, potentially decrease the reaction selectivity for the desired solvent and increase the difficulty during purification. As such, propionic acid, levulinic acid and acetoin were selected as the candidate platform molecules. Their possible methylation and carboxymethylation products with properties predicted by HSPiP are listed in Table 2.1.

Upon Table 2.1, the methylation product of propionic acid and carboxymethylation products of propionic acid and levulinic acid all have far Hansen distances (Ra) (Ra > 5.00) to DCM, which demonstrates they have an entirely different solvency ability to halogenated solvents. Moreover, methyl propionate has a very similar b.p. to DMC (90 °C),[237] which increases the difficulty during separation. In addition, carboxymethylation products of propionic acid and levulinic acid have undesired high b.p. (>139 °C). Hence, they will not be considered further as candidate solvents. For methyl 4-oxopentanoate, 3-methoxybutan-2-one and methyl 3-oxobutan-2-yl carbonate, only 3-methoxybutan-2-one has the accepted b.p. (113 °C) which can be easily recovered or distilled off after its usage. Finally, 3-methoxybutan-2-one (MO) was selected as a potential bio-based solvent for the replacement of halogenated solvents in potential applications such as extraction, solvation and cleaning applications. Additionally, MO does not contain highly polar -OH or -NH functionality, as such it would be classed as a polar aprotic solvent.

2.2.2 Theoretical stability and reactivity of MO

2.2.2.1 The possible reaction of the ketone group of MO

Solvents need to be relatively inert, as such they can have a good performance for solvating reactants without participating. Before the synthesis of MO, its reactivity was initially analysed.

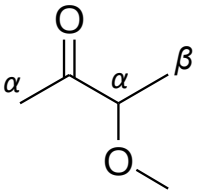
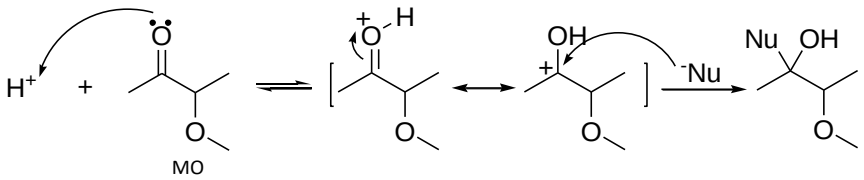
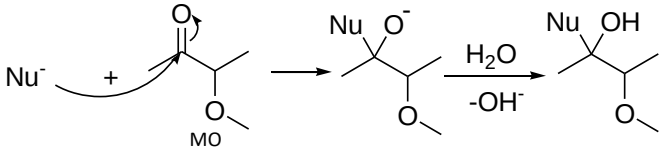


Fig. 2.3 The structure of MO

MO is a molecule which contains both ketone (C=O) and ether (-O-CH_3) functionality (Fig. 2.4). Of these functional groups, the ketone should be the most reactive due to the higher electronegativity of the oxygen atom in comparison with the carbon atom, resulting in a partial negative charge on the former and a partial positive charge on the latter.[238] Therefore under certain conditions, the carbon atom on the ketone could undergo nucleophilic attack.



Scheme 2.2 Possible acid-catalysed mechanism of nucleophilic addition of MO

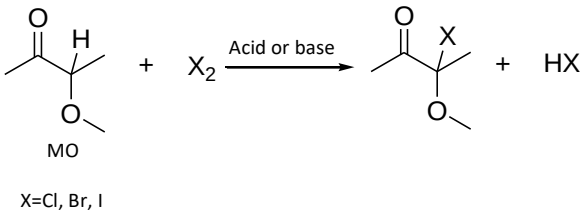


Scheme 2.3 Possible base-catalysed mechanism of nucleophilic addition of MO

Nucleophilic addition of MO *via* attack of the carbonyl can be either acid or base catalysed, and the mechanisms are illustrated in Scheme 2.2 and Scheme 2.3, respectively. Under acidic conditions, the lone pair electrons on the ketone of MO pick up a proton from the solution, before undergoing nucleophilic attack to yield the product. In the other hand, with the catalysis of the base, the nucleophilic anion attacks the MO carbonyl, before capturing a proton to yield the product.

2.2.2.2 Possible reactions of the most labile proton of MO

Both the carbonyl and ether functionalities of MO contain electron withdrawing oxygen atoms, with one proton that is *α* to both. As a result, the pKa for this proton will be markedly lower than any other, making it potentially susceptible to a number of reactions. For instance, under acidic or basic conditions, halogen substitution of the *α*-H could occur.[239]

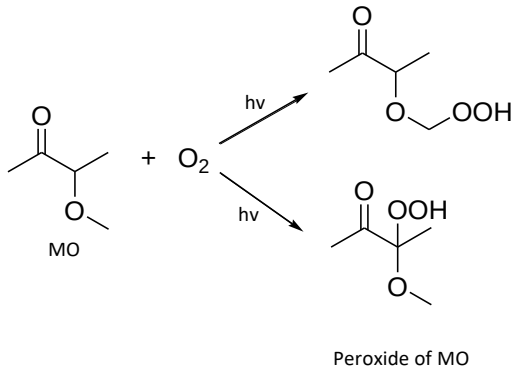


Scheme 2.4 Halogenation of MO

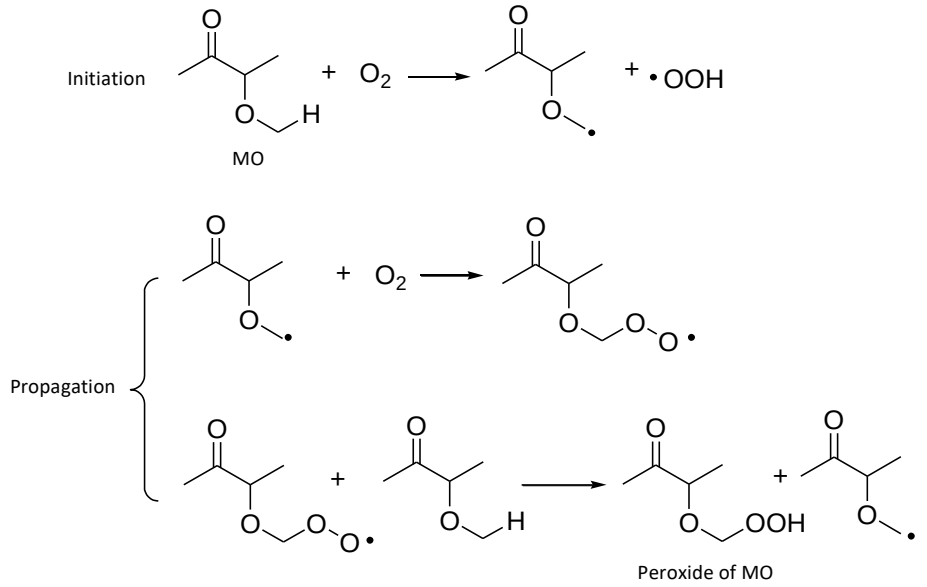
In summary, MO may not be a proper solvent for reaction conducted in strongly acidic or basic environment.

2.2.2.3 Possible peroxide formation in MO

Since MO contains an ether group (CH-O-CH_3), it can potentially form peroxides on exposure to oxygen and light (as shown in Scheme 2.5). This is a common problem for solvents with ether functionality such as diethyl ether.[240] Two potential radical initiated auto-oxidation products of MO are illustrated in Scheme 2.6.[241] Due to safety issue surrounding organic peroxides, an antioxidant may be required to scavenge radical species in the new solvent MO in order to avoid the formation of such explosive species. Therefore, the ability of MO to form peroxides needs to be monitored and evaluated once synthesised.



Scheme 2.5 The formation of peroxide of MO



Scheme 2.6 An example of auto-oxidation of MO

Overall, based on all the preliminary evaluation, although MO may not be stable in strongly acidic or basic conditions, and has a risk of formation of peroxide, its lower b.p. and similar HSPs to DCM still provide evidence to synthesise for further investigation of its properties.

2.2.3 MO synthesis *via* DMC chemistry

2.2.3.1 Catalyst screening and selection

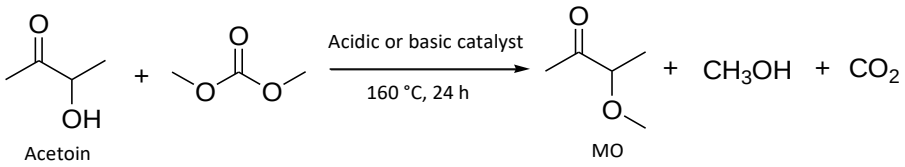
Scheme 2.7 shows the general reaction for the synthesis of MO from acetoin and DMC. In order to find a proper route for the synthesis, different classes of catalysts were screened. These

catalysts included:

(a) Basic catalysts of sodium bicarbonate, sodium carbonate, potassium carbonate, basic aluminium oxide, hydrotalcite ($Mg_6Al_2(CO_3)(OH)_{16}{\cdot}4(H_2O)$), sodium acetate, sodium hydroxide, potassium hydroxide;

(b)Acidic catalysts of acidic aluminium oxide, Starbon®400, Starbon®600 and *p*-toluenesulfonic acid (PTSA).

Additionally, a control reaction in the absence of catalyst was also carried out.



Scheme 2.7 The synthesis of MO from acetoin and DMC assisted by different catalysts

Table 2.2 shows the results of reactions between acetoin and DMC in the presence of various catalysts as determined by gas chromatography (GC), where the GC distribution intends GC area% among the corresponding compounds. At this early stage, results were analysed by peak area alone without calibrating for response factors. This was to aid in rapid screening of a wide range of catalysts or reagents.

After analysis for components of the mixtures, according to Table 2.2, for the reactions catalysed by acidic Al_2O_3, basic Al_2O_3 and no catalyst control experiment, methyl 3-oxobutan-2-yl carbonate (MC) was synthesised which indicates that the carboxymethylation reaction between acetoin and DMC has occurred (Scheme 2.8) under these conditions. This possible reason is that at elevated temperature, the proton on the hydroxyl group of acetoin is removed readily and the nucleophilic group attacks the centre of DMC to produce MC. The acidic and basic Al_2O_3 did not methylate the acetoin properly, the possible reasons for this were that: (a) MC did not continue to undergo decarboxylation to yield MO, or (b) acetoin did not attack the methyl group of DMC effectively to produce MO under this condition.

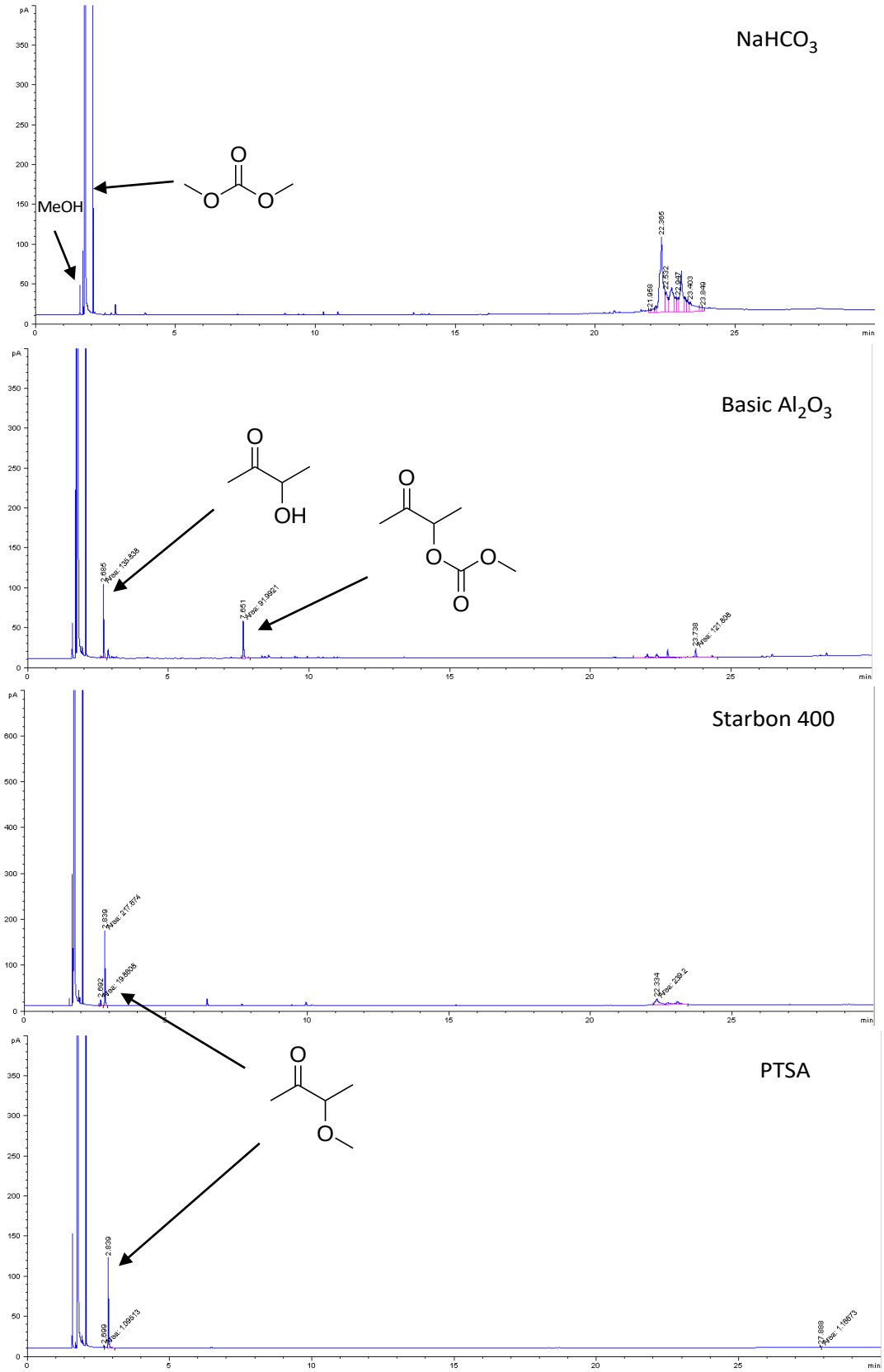


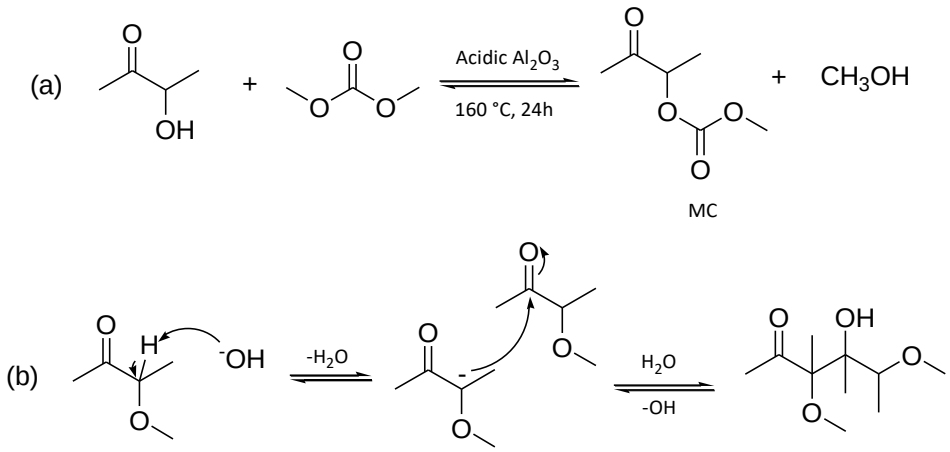
Fig. 2.4 GC results of the reactions between DMC and acetoin catalysed by different catalysts

Table 2.2 The experimental results of the reactions between DMC and acetoin catalysed by different catalysts[a]

		GC distribution (%)			
Entry	Catalysts	Acetoin	MO	MC	Other by-products[b]
1	$NaHCO_3$	0	0	0	100
2	Na_2CO_3	0	0	0	100
3	K_2CO_3	0	0	0	100
4	Basic Al_2O_3	39	0	26	35
5	Acidic Al_2O_3	39	0	27	34
6	Hydrotalcite[c]	0	0	0	100
7	$NaCOOCH_3$	0	0	0	100
8	NaOH	0	0	0	100
9	KOH	0	0	0	100
10	S-Starbon 400®	4	46	0	50
11	S-Starbon 600®	3	40	0	57
12	PTSA	1	98	0	1
13	No catalyst	68	0	15	17

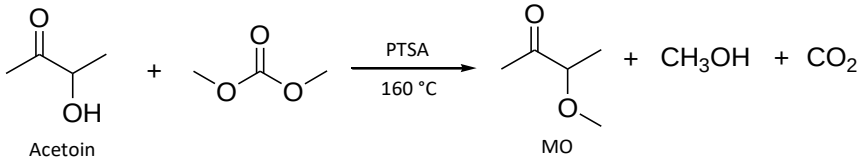
[a] Reaction conditions: acetoin/DMC/catalysts = 5 mmol : 60 mmol : 0.25 mmol; *T* = 160 °C; reaction time 24 h. [b] The GC retention time of the by-products is mainly around 23 min. [c] w/w of hydrotalcite to acetoin is 0.3 : 1.

Meanwhile, all the basic catalysts, including sodium bicarbonate, potassium carbonate, sodium carbonate, sodium acetate, hydrotalcite, sodium hydroxide and potassium hydroxide, did not produce the MO or MC but with high conversion. Instead, high b.p. by-products were formed (Table 2.2). The possible reason is that due to the strong basicity, once the MO forms firstly in the reaction, it then reacts with another MO molecule *via* aldol condensation reaction to convert to those high boiling product by-products (see Scheme 2.8 (b) for an example). This demonstrates that MO may not be a proper solvent under basic conditions.



Scheme 2.8 The carboxymethylation and possible aldol condensation reactions during the synthesis of MO from acetoin and DMC

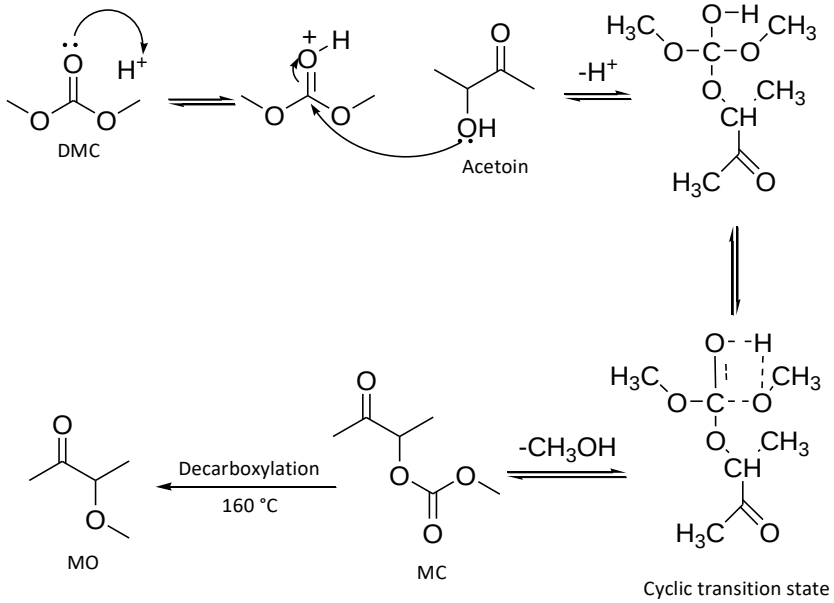
Interestingly, S-Starbon®400 and S-Starbon®600 have the ability to methylate acetoin with DMC successfully. Starbon® is mesoporous carbon which is produced after low-temperature carbonisation of expanded starch.[242] S-Starbon®400 and S-Starbon®600 were obtained respectively after 400 °C and 600 °C carbonisation of expanded starch with Brønsted acid sites – SO_3H fixed on them. Since the Brønsted acid sites on the S-Starbon®400 and S-Starbon®600 were both grafted from sulphuric acid, hence, the organic acid PTSA with Brønsted acid sites $–SO_3H$ should have the similar or even better ability for the methylation of acetoin *via* DMC chemistry than S-Starbon®400 and S-Starbon®600. As a consequence, the PTSA catalyst experiment was then carried out, and the result is also listed in Table 2.2 (entry 12). After the synthesis, the starting material acetoin converted near quantitative, and MO has obtained a high GC distribution of 98%. The equation for the reaction between acetoin and DMC catalysed by PTSA is then proposed in Scheme 2.9. Hence, PTSA was selected as an ideal DMC methylation catalyst for acetoin in this research.



Scheme 2.9 The PTSA catalysed methylation reaction of acetoin with DMC

2.2.3.2 The possible mechanisms of PTSA catalysed DMC reactions for acetoin

Currently, limited research covering acid-catalysed methylation or carboxymethylation reactions *via* dialkyl carbonate chemistry can be found in the literature. As such, the mechanism by which acid-catalysed DMC methylation occurs is still unconfirmed. Based on a previously proposed Brønsted acid catalysed transesterification mechanism,[243] a possible mechanism for the methylation and carboxymethylation of acetoin under acidic condition with DMC is suggested in Scheme 2.10.

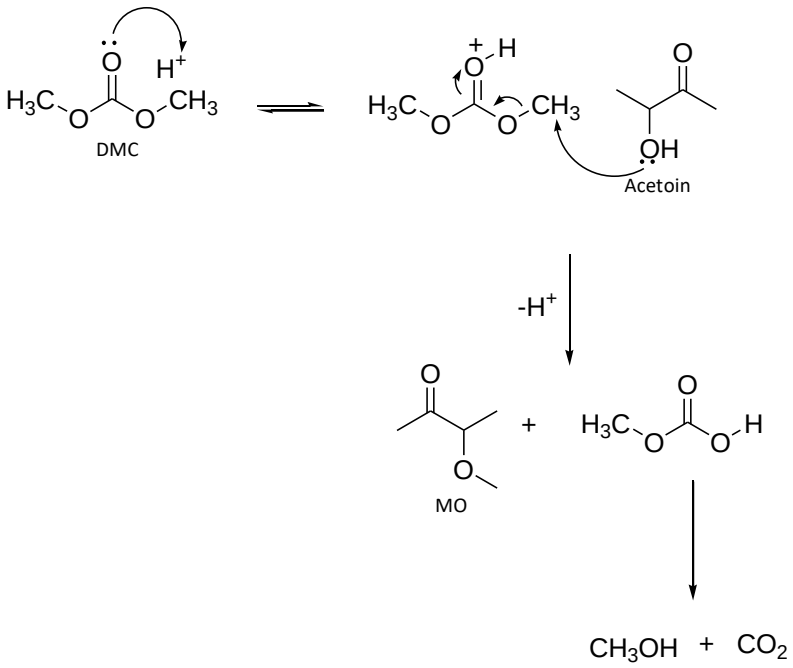


Scheme 2.10 The possible mechanism of the methylation and carboxymethylation of acetoin with DMC under acidic condition

Under acidic environment, the lone pair of DMC ketone is protonated, before conducting the nucleophilic attack to the carbonyl carbon of DMC from the acetoin. After losing a proton, the hemiketal intermediate forms and then eliminates methanol to produce the carboxymethylation product MC. At higher temperature (160 °C), MC undergoes the decarboxylation reaction to yield the MO.

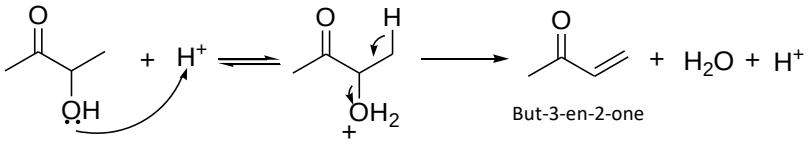
Alternatively, based on the proposed base-catalysed DMC methylation mechanism,[163] Scheme 2.11 gives another possible acid-catalysed mechanism for the methylation of acetoin by DMC without forming MC firstly. At elevated temperature (160 °C), the lone pair of DMC ketone is

protonated, before carrying out the nucleophilic attack to the methyl carbon of DMC from the acetoin. After losing a proton, MO, methanol and carbon dioxide are produced. The confirmation of the mechanism is needed as a future work.



Scheme 2.11 The possible mechanism of the direct methylation of acetoin by DMC under acidic condition

It is worth to be mentioned that under acidic condition at high temperature (usually around 100 °C), acetoin, as a secondary alcohol, may carry out the unimolecular elimination (E1) pathway to be dehydrated, as shown in Scheme 2.12.[244] Initially, the lone pair electrons on the hydroxyl group of the acetoin capture the proton to yield the pronated acetoin, and then it loses water to yield the dehydration product but-3-en-2-one. However, after the reaction catalysed by PTSA between acetoin and DMC, the but-3-en-2-one was not observed by GC.



Scheme 2.12 The possible E1 path of dehydration of acetoin under acidic environment

2.2.4 The optimisation of DMC synthesis of MO

After the purification process of MO, to investigate the highest yield of MO, the effect of catalytic loading, substrates mole ratio and reaction time was explored.

2.2.4.1 The effect of catalytic loading on the synthesis of MO

In order to investigate the effect of equivalence of PTSA on the synthesis of MO from DMC and acetoin, the corresponding experiments were conducted, and the experimental results are exhibited in Table 2.3. Since highly pure MO was synthesised, GC calibration curve was then established and used to determine yield of MO without further isolation. The initial reaction conditions selected were the same as the purification experiment in Section 5.3.4.

Table 2.3 The effect of PTSA catalytic loading on the synthesis of MO[a]

Entry	Equivalence of PTSA (%)	Yield of MO (%)[b]
1	10	31
2	5	30
3	3	26
4	1	5
5	0.5	<1

[a] Reaction conditions: acetoin/DMC = 0.5 mol : 0.5 mol; *T* = 160 °C; reaction time 2 h. [b] Yield was identified by ^{1}H NMR and GC based on tetradecane as internal standard.

The yield of MO is around 30% when 10% and 5% equivalent PTSA is used in the reaction (entry 1 and 2, Table 2.3). When 3% equivalent PTSA is utilised in the reaction, the yield of MO started to decline. This trend is even more apparent when 1% equivalent PTSA is used with only 5% yield obtained. 0.5% equivalence of PTSA performed worst with a yield less than 1%. Hence, 5% was selected as the optimised catalytic loading condition for the synthesis of MO.

2.2.4.2 The effect of mole ratio of DMC to acetoin on the synthesis of MO

In Section 2.2.4.1, 5% equivalent PTSA was selected as the optimised reaction condition for the synthesis of MO. Following that, the effect of mole ratio of DMC to acetoin on the yield of MO was then explored by using 5% equivalent PTSA as the catalytic loading condition, and the experimental data is listed in Table 2.4.

When mole ratio of DMC to acetoin is 12:1 or 8:1, the yield of MO is high (95%). However, when corresponding mole ratios are 4:1 and 3:1, yields of MO then decreases to 75% and 50%, respectively. Furthermore, when 2:1 or 1:1 of mole ratio is applied then the yield of MO drops down to only around 30%. These results demonstrate that a large excess of DMC can provide a higher yield of MO. An overall consideration of these results, 8:1 of mole ratio of DMC to acetoin was finally selected as the optimised reaction condition.

Table 2.4 The effect of mole ratio of DMC to acetoin on the synthesis of MO[a]

Entry	Mole ratio of DMC to acetoin	Yield of MO (%)[b]
1	12:1	95
2	8:1	95
3	4:1	75
4	3:1	50
5	2:1	37
6	1:1	30

[a] Reaction conditions: acetoin/PTSA = 0.5 mol : 0.025 mol; *T* = 160 °C; reaction time 2 h. [b] Yield was identified by ^{1}H NMR and GC based on tetradecane as internal standard.

2.2.4.3 The effect of reaction time on the synthesis of MO

After application of optimised reaction conditions derived in Section 2.2.4.1 and 2.2.4.2, then the effect of reaction time (from 10 min to 120 min) on the synthesis of MO was discovered. Reaction time 0 min is defined at when the reaction temperature just reached 90 °C, and 0.5 cm^3 sample was taken every 10 min by opening the valve of the high-pressure reactor. The

experimental results indicate the highest yield (95%) of MO can be obtained after 100 min (entry 10, Table 2.5).

In summary, 5% of PTSA catalytic loading, 8:1 of mole ratio of DMC to acetoin and reaction time of 100 min have been selected as the optimised reaction conditions.

Table 2.5 The effect of reaction time on the synthesis of MO[a]

Entry	Reaction time (min)[b]	Yield of MO (%)[c]
1	10	0
2	20	13
3	30	58
4	40	86
5	50	90
6	60	93
7	70	93
8	80	94
9	90	94
10	100	95
11	110	95
12	120	95

[a] Reaction conditions: acetoin/DMC/PTSA = 0.5 mol : 4 mol : 0.025 mol; *T* = 160 °C. [b] Reaction time 0 min is defined at when the reaction temperature just reached 90 °C. [c] Yield was identified by ^{1}H NMR; Selectivity > 99% in all reaction time towards MO calculated by ^{1}H NMR.

2.2.5 Defining the solvent parameters of MO

2.2.5.1 Boiling point and melting point of MO

B.p. and m.p. are basic and vital physical properties of a solvent while applying in reaction or extraction process. B.p. of MO was finally confirmed by distillation to be 112 °C under normal pressure as an average value of three different runs.

In this study, differential scanning calorimetry (DSC) was employed to test the m.p. of MO. DSC is a thermal analysis method. Generally, sample adsorbs or releases a quantity of heat (endothermic or exothermic) when a phase change occurs, glass transition or chemical reaction, and the DSC can record how much heat flow needed to be changed in order to retain the same temperature between the sample and the reference.[245] Therefore, DSC can be used to determine the m.p. of a given compound based on the variation of heat flow in phase change. The lowest temperature the DSC employed can achieve is -90 °C and as such phase changes between room temperature and this point were investigated. Upon running the analysis, no change of state was observed, indicating that the m.p. of MO must be below -90 °C.

In summary, at atmospheric pressure, MO could be a suitable solvent for reactions proceeding at a temperature between -80 °C to 112 °C. In addition, unlike DCM or other halohydrocarbon solvents, MO contains no halogen atoms and therefore does not form highly toxic compounds such as phosgene or significantly deplete the ozone layer.[246]

2.2.5.2 The measurement of density of MO

The density of MO was experimentally measured at 25 °C (298 K) and ambient pressure. Three different batches of MO products were used for the density testing in order to obtain the average value. The measurement of the density of MO was carried out by determining the mass of 1 cm^3 MO in a 1 cm^3 volumetric flask. Finally, the result shows the density of MO is 0.90 $g \cdot cm^{-3}$.

2.2.5.3 The measurement of viscosity of MO

The dynamic viscosity of MO was determined by an Ostwald viscometers at 20 °C (293 K) and normal pressure. Three different batches of MO products were employed for the viscosity testing in order to attain the average value. Finally, the result shows its dynamic viscosity is 0.48 cP, which is a low viscosity around room temperature.

2.2.5.4 The measurement of formation of peroxide of MO

Since MO contains an ether functional group, it is possible that MO may form potentially explosive peroxide compounds by reacting with oxygen as discussed in Section 2.2.2.3. A preliminary measurement to monitor the formation of peroxides in MO was conducted by using peroxide test strip (Macherey-Nagel, QUANTOFIX® Peroxide-100) with detection limit (DL) of 1-100 $mg \cdot dm^{-3}$. Monitoring of 7.5 cm^3 MO was sealed in a transparent small bottle with air and irradiated by light over a period of 224 days, in the absence of antioxidants or stabilisers. Results of peroxide formation are listed in Table 2.6.

Table 2.6 The monitoring of formation of peroxide of MO[a]

Entry	Time	Concentration of peroxide ($mg \cdot dm^{-3}$)[b]
1	0 day[c]	Less than DL
2	7 days	Less than DL
3	14 days	Less than DL
4	21 days	Less than DL
5	28 days	Less than DL
6	56 days	Less than DL
7	84 days	Less than DL
8	112 days	Less than DL
9	168 days	Less than DL
10	224 days	Less than DL

[a] no antioxidant or stabiliser added. [b] The concentration of peroxide of MO was measured by peroxide test strip. [c] 0 day represents isolated MO was just obtained by distillation.

After 224 days of testing, the total peroxide concentration in MO was less than DL (< 1 $mg \cdot dm^{-3}$). This result demonstrates that although possessing ether functionality, MO has a low risk of forming hazardous peroxides. In spite of this, stabilisers, such as butylated hydroxytoluene (BHT),[247] are still recommended to limit the occurrence of auto-oxidation of MO.

2.2.5.5 Ames test for MO

In this research, the mutagenicity of newly developed bio-based solvents was investigated by Ames mutagenic test (referred to hereafter simply as Ames test).

Ames test is a commonly used method to screen for the mutagenicity of chemicals in a short time.[248] Mutational *Salmonella typhimurium* (His^-) employed in Ames test can only grow in a medium containing histidine as it cannot synthesise the required amino acid by itself.[249] After exposing His^- to a chemical, if the chemical compound is mutagenic, it can return these His^- strains back to its prototrophic state (His^+) in which it can synthesise the amino acid and so grow in the histidine-free medium.[248,250]

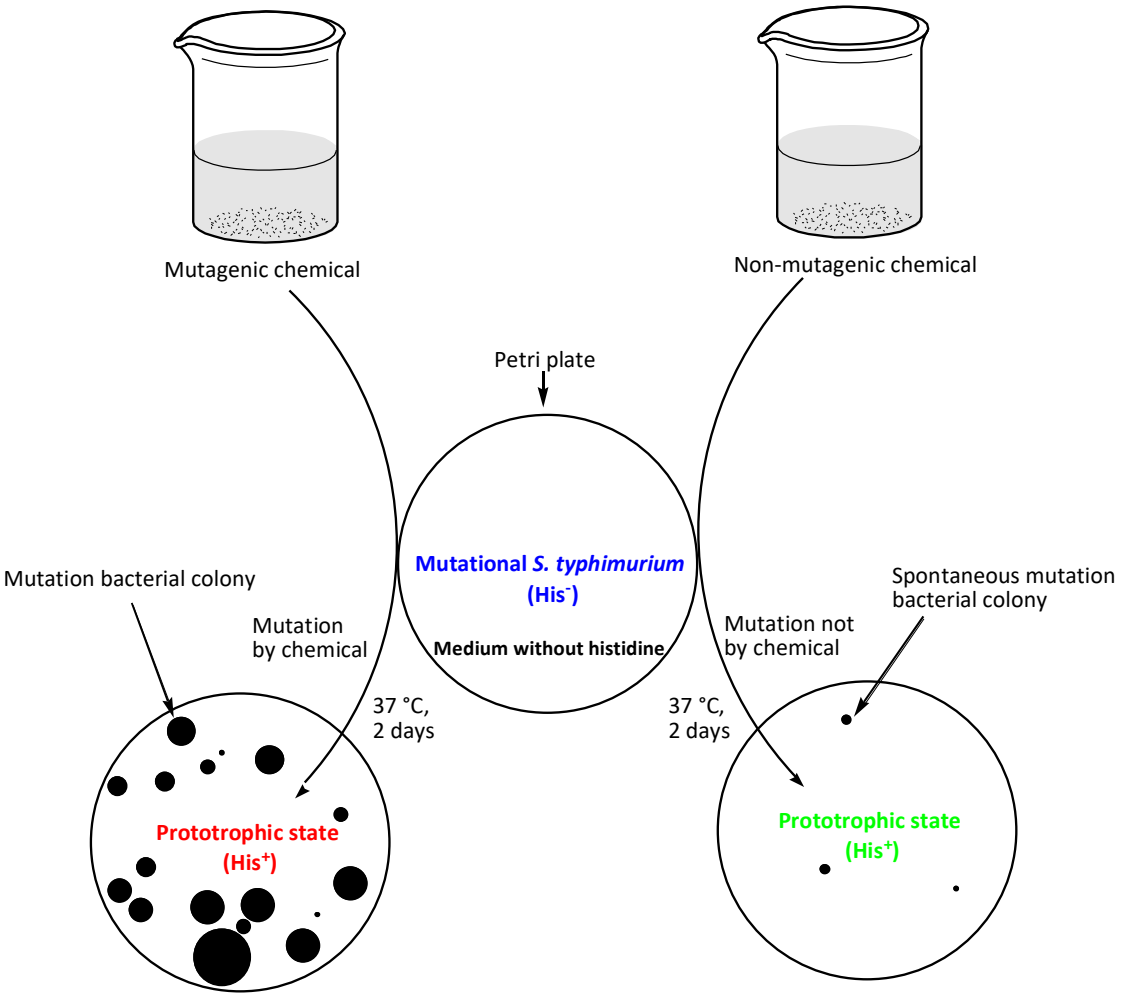


Fig. 2.5 The process of Ames test for the mutagenicity of chemicals

Fig. 2.5 briefly introduces a general method of Ames test:[251] Firstly, the candidate chemical is added into a petri plate containing His^- and culture media without histidine. The sample is then incubated at 37 °C for two days, after which if; (a) that chemical is mutagenic, then large-scale mutation of His^- to His^+ occurs and large number of bacterial colonies grows; (b) the chemical is non-mutagenic, then no bacteria colony or few macroscopic spontaneous mutation His^+ bacterial colonies forms.

As health is a key determiner of a green solvent,[252] any new molecule wanted to be termed as such it is necessary to be non-mutagenic. Therefore, Ames testing is a key technique to be applied to neoteric solvents.

In this study, mutational *Salmonella typhimurium* TA98 (*hisD3052*) and TA100 (*hisG46*) were used to verify the mutagenicity of MO. TA98 and TA100 were utilised for the detection of frameshift mutations and base substitution mutations, respectively. Dimethyl sulfoxide (DMSO) was used as a solvent (negative) control. A mixture of 2-nitrofluorene (2-NF) and 4-nitroquinoline-*N*-oxide (4-NQO) was used as the positive control. This Ames test did not use S9 microsomal activation, which means this experimental results cannot predict the mutagenicity of MO in the human body through the liver metabolism.

After the testing, no mutagenicity for MO was observed for both TA98 and TA100 strains since no dose effect occurred. Although this result is highly promising, a full set of toxicity tests will be needed prior to scale commercial exploitation of this solvent.

2.2.5.6 UV-vis. test of KT parameters of MO

The KT parameters of MO were determined based on the ultraviolet-visible (UV-vis.) of different dyes of Nile red (NR), 4-nitroaniline (NA) and *N,N*-diethyl-4-nitroaniline (NN), respectively. Table 2.7 lists the λ_{max} of UV-vis. of NR, NA and NN in MO.

Table 2.7 The λ_{max} of UV-vis. of different dyes in MO

	NR	NA	NN
λ_{max}	531 nm	350 nm	394 nm

KT parameters α,[117] β,[253] and π^*[253] of MO can be then obtained based on Equation 2.1, 2.2 and 2.3 below.

$$\alpha = \frac{20.47 - (\nu_{max\ in\ NR} / 1000\ cm^{-1}) - 1.95\pi^*}{1.01} \quad (2.1)$$

$$\beta = \frac{(1.035\nu_{max\ in\ NN} / 1000\ cm^{-1}) - (\nu_{max\ in\ NA} / 1000\ cm^{-1}) + 2.64}{2.8} \quad (2.2)$$

$$\pi^* = \frac{27.52 - (\nu_{max\ in\ NN} / 1000\ cm^{-1})}{3.182} \quad (2.3)$$

Where $\nu_{max\ in\ NR}$, $\nu_{max\ in\ NA}$ and $\nu_{max\ in\ NN}$ stand for the wavenumbers at maximum absorbance on the UV-vis. spectra for NR, NA and NN, respectively. The KT parameters of MO were calculated by the equation 2.1-2.3 to be: α = 0.33, β = 0.12 and π^* = 0.67.

2.2.5.7 The solvent properties of MO in comparison with other conventional aprotic solvents

Table 2.8 summaries and lists the properties of MO, compared to a range of different types of traditional aprotic solvents such as DCM, chloroform, ethyl acetate, diethyl ether, acetonitrile, acetone, cyclohexane, DMC and propylene carbonate.

The m.p. of MO is as yet unknown but is below -90 °C as determined by DSC in Section 2.2.5.1. This property is similar to DCM, chloroform, ethyl acetate, diethyl ether and acetone, indictaing MO is potentially a good solvent for low temperature applications. The b.p. of MO is 112 °C, which is a VOC and easy to be removed after distillation. Compared to DCM, MO is less volatile.

MO has a viscosity of 0.48 cP at 20 °C (293 K) and is comparable to DCM (0.44 cP) or ethyl acetate (0.45 cP) at the same temperature, demonstrating MO has a good solvent

performance in terms of viscosity. At 25 °C (298 K), the density of MO (0.90 g·cm^{-3}) is significantly lower that these chlorinated solvents such as DCM (1.32 g·cm^{-3}) and chloroform (1.48 g·cm^{-3}). However, as MO has been observed to be water miscible, therefore it cannot be applied in two-phase liquid-liquid separations.

Table 2.8 The properties of MO and other traditional aprotic solvents

	MO	DCM	Chloroform	Ethyl acetate	Diethyl ether	Acetonitrile	Acetone	Cyclohexane	DMC	Propylene carbonate
Mwt	102.1[a]	84.9[d]	119.4[d]	88.1[d]	74.1[d]	41.1[d]	58.1[d]	84.2[d]	90.1[a]	102.1[d]
KT α	0.33	0.13[e]	0.20[e]	0.00[i]	0.00[i]	0.35[j]	0.20[j]	0.00[l]	0.00[l]	0.00[p]
KT β	0.12	0.10[e]	0.10[e]	0.48[i]	0.51[i]	0.37[j]	0.54[j]	0.00[l]	0.32[l]	0.38[p]
KT π^*	0.67	0.82[e]	0.58[e]	0.54[i]	0.28[i]	0.80[j]	0.70[j]	0.00[l]	0.55[l]	0.90[p]
δ_D/MPa$^{0.5}$	16.1[a]	18.2[f]	17.8[f]	15.8[f]	14.5[f]	15.3[f]	15.5[f]	16.8[f]	15.5[f]	20.0[f]
δ_P/MPa$^{0.5}$	8.0[a]	6.3[f]	3.1[f]	5.3[f]	2.9[f]	18.0[f]	10.4[f]	0.0[f]	3.9[f]	18.0[f]
δ_H/MPa$^{0.5}$	5.5[a]	6.1[f]	5.7[f]	7.2[f]	5.1[f]	6.1[f]	7.0[f]	0.2[f]	9.7[f]	4.1[f]
Hansen distance[b]	0.00	4.57	5.97	3.25	6.03	10.14	3.07	9.70	5.99	12.76
B.p./°C	112	40[d]	61[d]	77[d]	34[d]	82[d]	56[d]	81[d]	90[m]	242[d]
M.p./°C	<-90[c]	-95[d]	-64[d]	-84[d]	-116[d]	-44[d]	-95[d]	7[d]	5[n]	-55[d]
ρ/g·cm^{-3} at 298 K	0.90	1.32[d]	1.48[d]	0.89[d]	0.71[d]	0.78[d]	0.78[d]	0.77[d]	1.06[m]	1.20[d]
Viscosity /cP at 293 K	0.48	0.44[g]	0.576[h]	0.45[d]	0.24[d]	0.36[g]	0.33[k]	0.98[d]	0.62[o]	2.76[d]

[a] Calculated by HSPiP. [b] Hansen distance to MO. [c] Measured by DSC. [d] Ref. 22. [e] Ref. 137. [f] Ref. 139. [g] Ref. 254. [h] Ref. 255. [i] Ref. 119 and Ref. 134. [j] Ref. 135. [k] Ref. 256 [l] Ref. 133. [m] Ref. 237. [n] Ref. 257. [o] Ref. 258. [p] Ref. 136.

The KT solvatochromic parameters α, β, $\pi^*$of MO and other traditional solvents were listed in Table 2.8. Jessop recently suggested that α value of aprotic solvent is <0.5, while for protic solvent the value is >0.5.[132] All the solvents in this investigation, including MO,

were aprotic solvents with the values of α lower than 0.40 (Table 2.8). A two dimension (2D) aprotic solvent map was then established with β and π^* as the vertical and horizontal coordinate respectively.[132] The solvent map for this research is illustrated in Fig. 2.6.

On the basis of Fig. 2.6, the β and π^* of MO are both similar to that of DCM and chloroform. This suggests that MO may have similar solvent behaviour to DCM or chloroform, and it has the potential to substitute the halogenated medium since few bio-based or non-halogenated solvents simultaneously have a medium polarity and low basicity similar to the chlorinated hydrocarbon solvents.

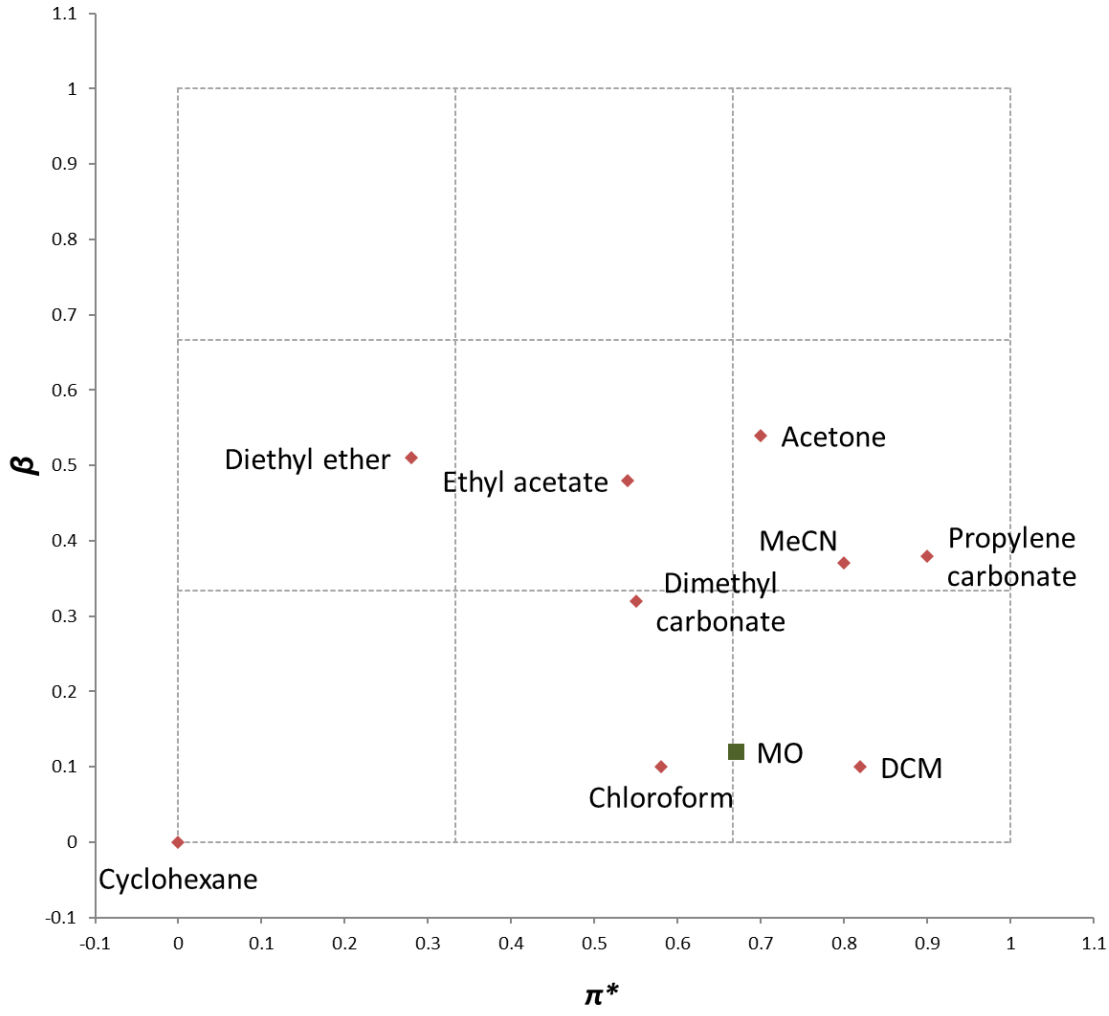


Fig. 2.6 The KT solvent map of MO and other nearby traditional aprotic solvents investigated in this research

HSPs δ_D, δ_P and δ_H of MO were calculated by HSPiP (Table 2.8), while data of other traditional solvents was acquired from the literature. Fig. 2.7 is the 3D Hansen space for MO and other conventional solvents established by HSPiP software. In the Hansen space, the small Hansen distance between two different solvents, the closer their solubility will be. According to this, MO has solubility properties between DCM, ethyl acetate and acetone (Ra < 5.00) (Fig. 2.7). On the contrary, Hansen distances of cyclohexane, propylene carbonate and acetonitrile are quite far from MO (Ra > 9.00), indicating MO has a rather different solvency power to these solvents.

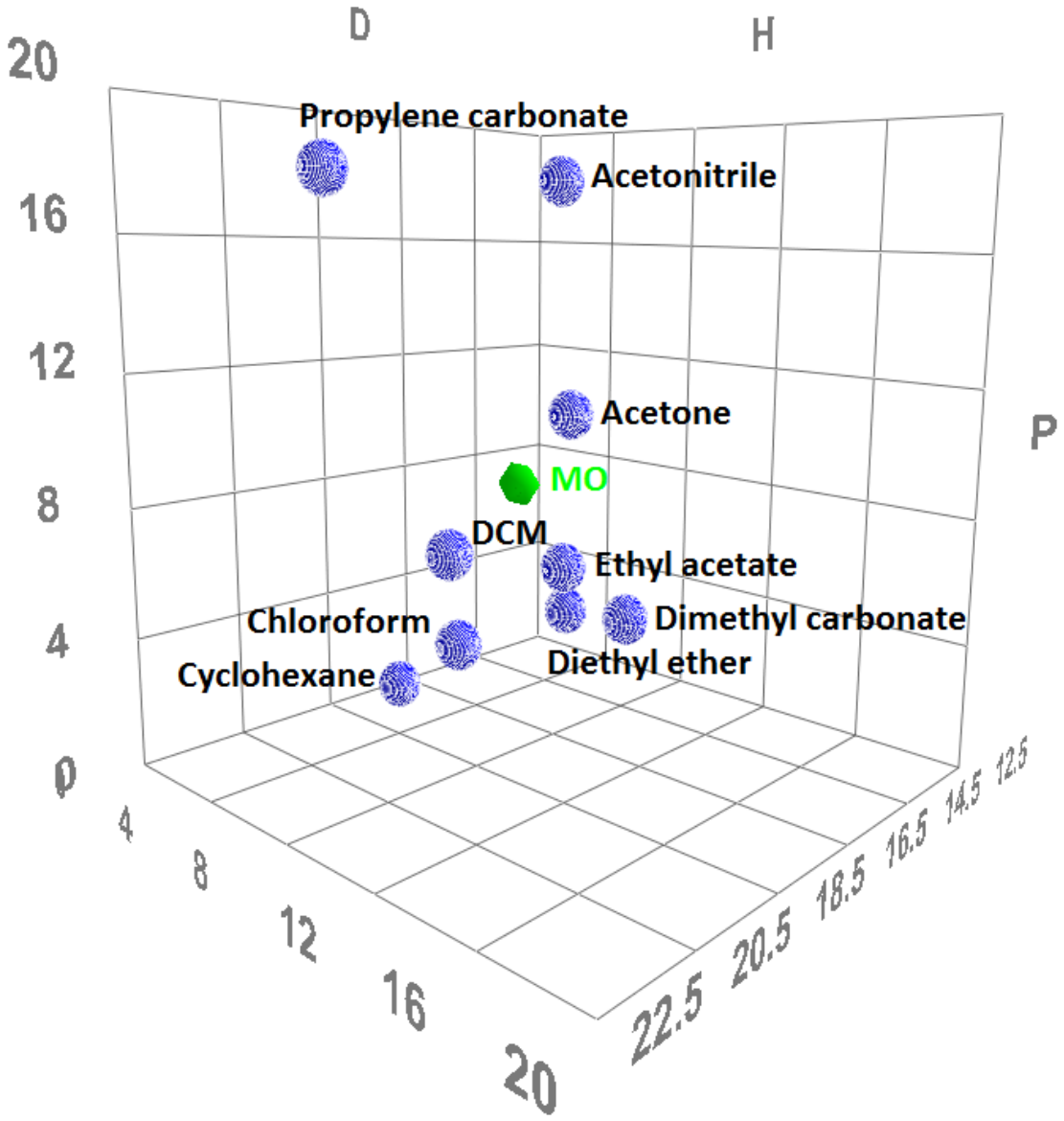
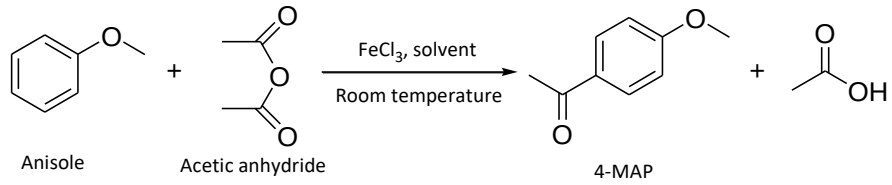


Fig. 2.7 The site of MO and the other traditional solvents in Hansen space constructed by HSPiP software, where D, P and H represent δ_D/MPa$^{0.5}$, δ_P/MPa$^{0.5}$ and δ_H/MPa$^{0.5}$, respectively

2.2.6 The solvent test in Friedel-Crafts and Diels-Alder reactions

Since MO has similar KT parameters and HSPs to DCM as discussed in Section 2.2.5.7, therefore it is worth to test MO compared to DCM as well as other conventional solvents in actual reactions in order to evaluate their solvent performances.

Friedel-Crafts and Diels-Alder reactions were both selected to assess MO in comparison with other traditional solvents in this section. Friedel-Crafts reaction is a category of electrophilic aromatic substitution reaction commonly proceeded in unsustainable chlorinated solvents such as DCM.[259-261] Diels-Alder reaction is a [4+2]-π-electron cycloaddition process between a



Scheme 2.13 The Friedel-Crafts synthesis of 4-MAP from anisole and acetic anhydride promoted by iron (III) chloride in different solvents

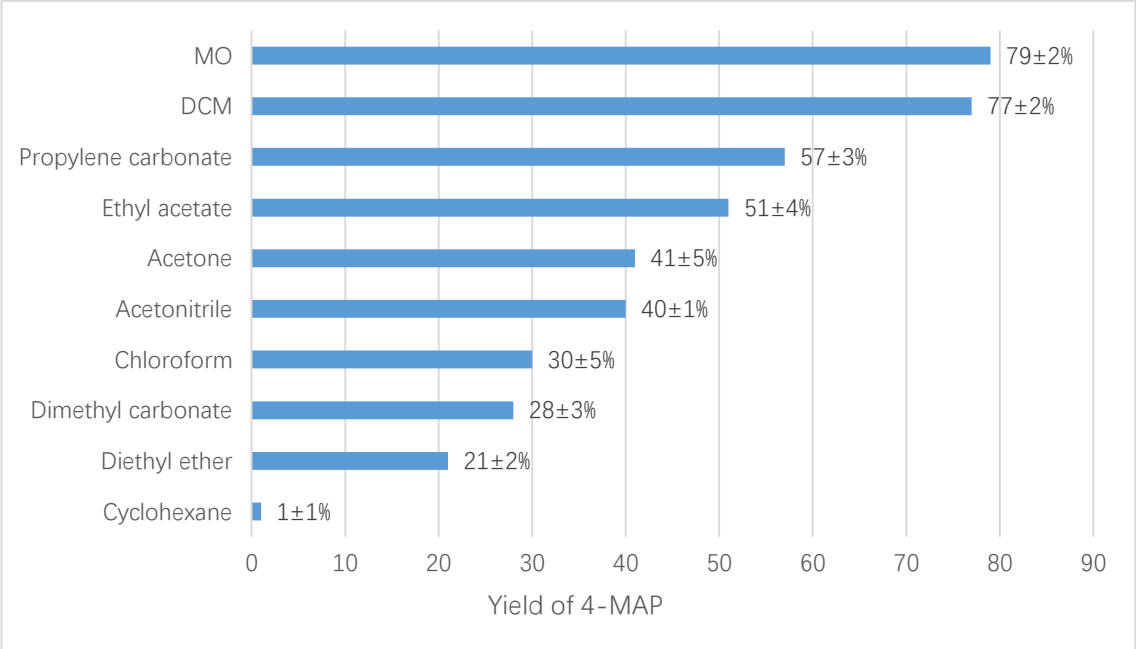
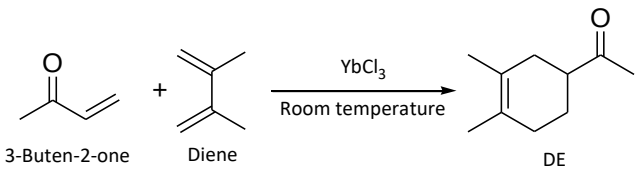


Fig. 2.8 The GC yield of 4-MAP synthesised from anisole and acetic anhydride in various solvents promoted by iron (III) chloride *via* Friedel-Crafts reaction; selectivity >99% towards 4-MAP during all the solvents investigated in the research

dienophile and a diene to yield a cyclohexene product, which normally catalysed by Lewis acid.[262] Many Diels-Alder reactions carry out in halogenated solvent.[263-265] By analysis of experimental results, the solvent performance of DCM and MO can be compared, and MO can also be contrasted to other common solvents.

In this preliminary study, the commercial Lewis acid ($FeCl_3$) promoted the synthesis of 4-methoxyacetophenone (4-MAP) from anisole and acetic anhydride was used to compare the suitability of MO for the substitution of conventional organic solvents in Friedel-Crafts reaction (Scheme 2.13). It is observed that MO provides higher yield (79%) than the chlorinated solvents DCM (77%) and chloroform (30%) (Fig. 2.8). In fact, MO exhibits the highest yield in this experiment, while propylene carbonate, ethyl acetate, acetone, acetonitrile, DMC and diethyl ether only perform medium to low yields. The reaction in cyclohexane almost did not conduct due to its low polarity to activate Lewis acid. This result demonstrates the significant potential for using MO as a bio-based solvent for the replacement of chlorinated solvents in organic synthesis.

In this study, the performances of MO and other traditional solvents in Diels-Alder reaction were evaluated by the synthesis of 1-(3,4-dimethylcyclohex-3-enyl) ethanone (DE) from 2,3-dimethylbuta-1,3-diene (diene) and 3-buten-2-one catalysed by anhydrous ytterbium(III) chloride (Scheme 2.14).[263] It can be clearly seen in Fig. 2.9 that MO was not an effective solvent for the reaction proceeded in Diels-Alder reaction. The possible reason for this is that MO may form complexation with Lewis acid ytterbium(III) chloride, which interferes the promotion of $YbCl_3$ for the energy level of lowest unoccupied molecular orbital (LUMO) of substrates, as such the yield was low.



Scheme 2.14 The Diels-Alder synthesis of DE from 3-buten-2-one and diene catalysed by ytterbium(III) chloride in different solvents

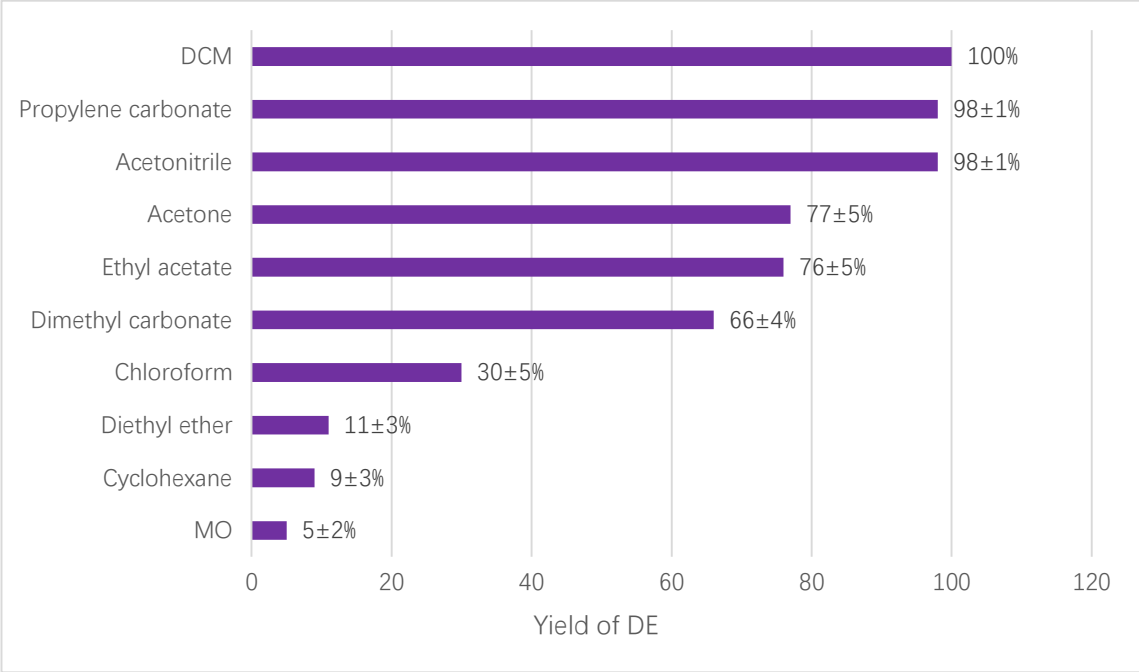


Fig. 2.9 The GC yield of DE synthesised from 3-buten-2-one and diene in various solvents catalysed by ytterbium(III) chloride *via* Diels-Alder reaction; selectivity >99% towards DE during all the solvents investigated in the research

2.3 Conclusion

This chapter successfully explored a synthesis and optimisation method for the production of MO from bio-based platform molecule acetoin and green methylation agent DMC catalysed by PTSA based on the prediction of HSPiP modelling software. And a yield of 95% was obtained. Its solvent properties were tested and compared to other traditional solvents, which proved MO is the only bio-based solvent at the time of writing for the replacement of DCM.

Specifically, firstly, MO, synthesised from platform molecule acetoin and DMC, was selected as a potential bio-based solvent after screening as the substitution of halogenated solvents based on the HSPiP software. After analysis of stability of MO, then PTSA was selected as a proper catalyst for the production of MO after catalyst screening. Optimisation experiments of synthesis of MO were conducted, and 5% of PTSA catalytic loading, 8:1 of mole ratio of DMC to acetoin and reaction time of 100 min were selected as the optimised reaction conditions. Then b.p., m.p., density and viscosity of MO were defined, proving it is a proper solvent under room temperature

or lower temperature. Importantly, MO did not exhibit any mutagenicity in a preliminary Ames mutagenicity test, while a peroxide test highlighted the limited formation of peroxide after 224 days (less than 1 $mg \cdot dm^{-3}$). The KT parameters of MO were tested to be similar to DCM and chloroform with low basicity and medium polarity. MO was demonstrated to be comparable to DCM in the Friedel-Crafts reaction but not suitable for the Diels-Alder reaction.

Chapter 3 Methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate as a new bio-based solvent

3.1 Introduction

3.1.1 Glycerol derivatives as bio-based solvents

As mentioned in Chapter 1, considering the surplus production of glycerol around the world, it is sensible to utilise it as a green solvent or convert it to valuable new products. Glycerol's reactive -OH groups restrict its application as a solvent but this problem can be readily overcome by upgrading glycerol to a new solvent family called "glycerol derived solvents", in which a wide range of solvent properties is available. Currently, the main research fields of glycerol derived solvents are alkyl glycerol ethers, glycerol carbonate/esters of glycerol carbonate, glycerol-based ILs, glycerol formal and solketal (Fig. 3.1).[266]

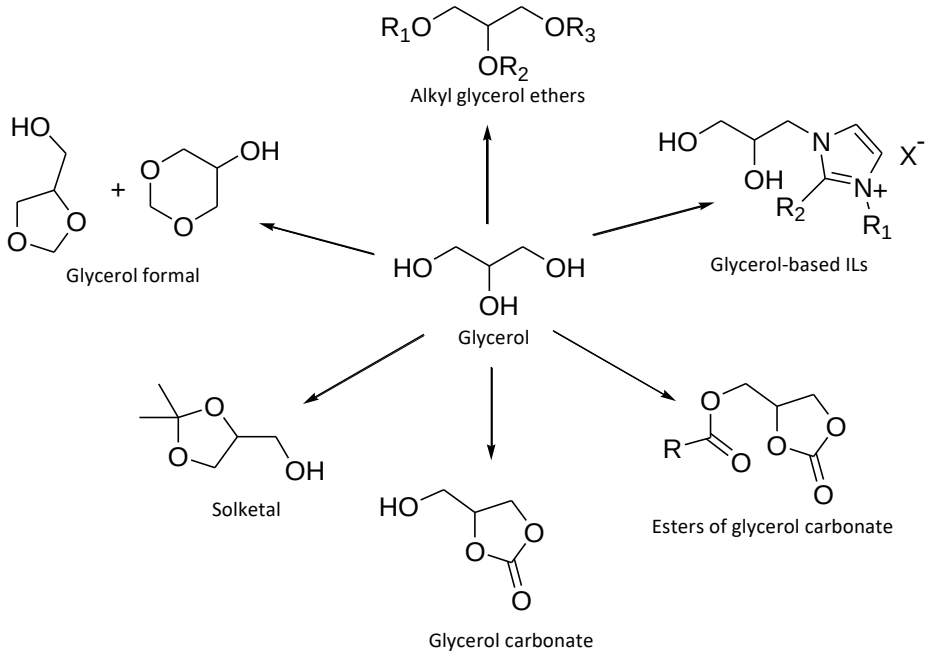


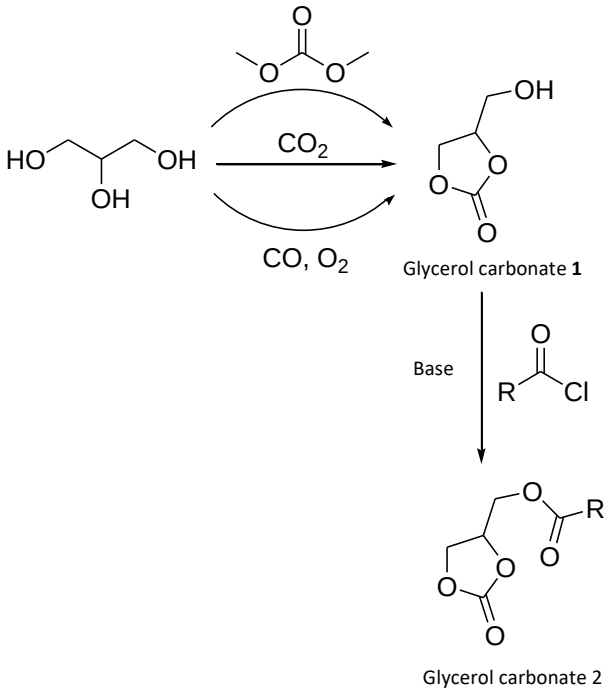
Fig. 3.1 Glycerol derivatives solvents

3.1.1.1 Glycerol carbonate

At present, organic carbonates have been commonly accepted as a family of green solvents for organic synthesis thanks to their biodegradability as well as low toxicity.[267] Glycerol carbonates are essential components of organic carbonates and are of great interests in the application as bio-based solvents.

Glycerol carbonate **1**, for example, can be readily prepared by transesterification with dimethyl carbonate (DMC) from glycerol,[268] or by direct carbonation of glycerol with carbon dioxide,[269] or *via* oxidative carbonylation of glycerol (Scheme 3.1).[270] Furthermore, glycerol carbonate **1** can be transformed to glycerol carbonate **2** which has a higher boiling point (b.p.) by reacting with an acyl chloride, and glycerol carbonate **2** was proved to be suitable solvents for the reactions carried out at high temperature.[271]

Glycerol carbonate and its derivatives have already been utilised as solvents in cosmetic, washing, cleaning agents and adhesives, and they are also used as medium for the production of paints and dyes.[272]

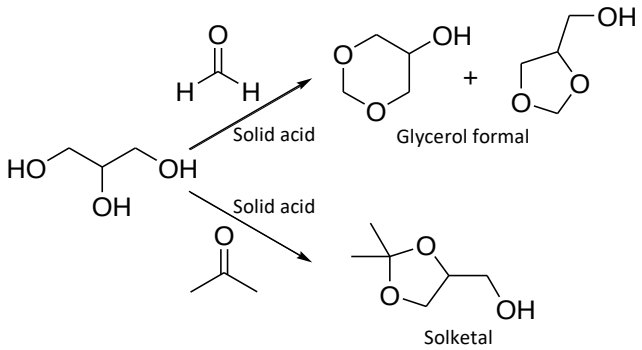


Scheme 3.1 Synthetic routes to glycerol carbonates

3.1.1.2 Glycerol formal and solketal

Glycerol can be converted to high-value cyclic acetals, such as glycerol formal and solketal by the condensation reaction with formaldehyde or acetone (Scheme 3.2). Glycerol formal and solketal are high b.p. solvents, and they have been employed as low toxicity solvents in many areas such as injectable preparations, paints, plasticiser and insecticide delivery systems.[266] In particular.

solketal is a bio-based compound attracting much interest. It is a non-toxic potential green solvent,[273] and it is used as a fuel additive.[274] It is worth mentioning that since acetone can be generated from biomass,[107] this synthesis becomes even more sustainable.



Scheme 3.2 The synthesis of glycerol formal and solketal from glycerol catalysed by solid acid catalysts

However, these glycerol derivative solvents such as glycerol carbonate, glycerol formal and solketal still retain a reactive hydroxyl group. Thus they can be further upgraded to less reactive bio-based solvents.

3.1.2 Aims of this chapter

Since a low b.p. bio-based solvent, 3-methoxybutan-2-one (MO), has been synthesised and discussed in Chapter 2, the target of this work is to develop a new high b.p. (>160 °C) aprotic bio-based medium for the substitution of conventional halogenated solvents. In order to do this efficiently, Hansen Solubility Parameters in Practice (HSPiP) modelling software will be used to predict suitable candidates, and DMC chemistry will be exploited to upgrade these glycerol derivatives. Characterisation of the novel bio-based solvent will be conducted, defining various physical properties and Kamlet-Taft (KT) parameters. Its performance in comparison to dichloromethane (DCM) and other traditional organic solvents will then be assessed in Friedel–Crafts and Diels-Alder reactions.

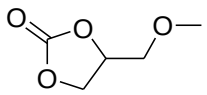
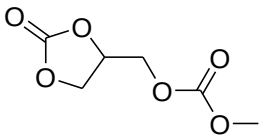
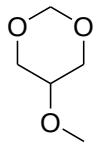
3.2 Results and discussion

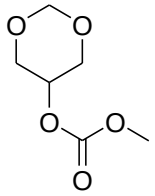
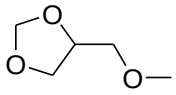
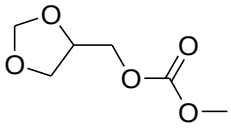
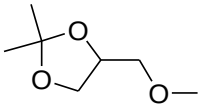
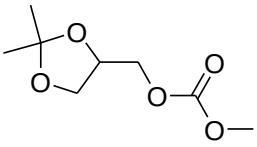
3.2.1 In silico analysis for assessing potential bio-based solvents

As discussed in Chapter 2, HSPiP is a powerful software to calculate the properties of solvents. As such, in this chapter, HSPiP was still used as a guide to explore the new compounds.

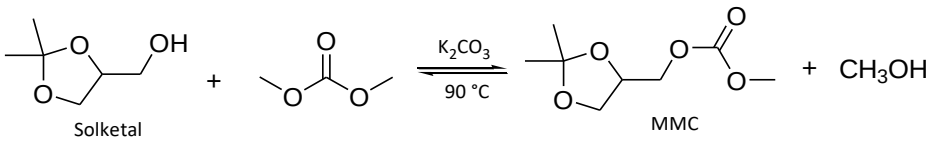
Potential new green solvents, which can be produced from glycerol derivatives and DMC, are listed in Table 3.1. Their b.p. and Hansen solubility parameters (HSPs) have been calculated by HSPiP. After the screening, methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC) was finally selected as the desired compound due to its high b.p. (>160 °C), lower Hansen distance (Ra) to DCM (Ra < 5.00) and less ether functionality (lower risk of generating peroxides).

Table 3.1 The HSPiP predicted properties of the candidate bio-based solvents synthesised from glycerol derivatives *via* DMC chemistry

Potential bio-based solvents	B.p./°C	Hansen δ_D/MPa$^{0.5}$	Hansen δ_P/MPa$^{0.5}$	Hansen δ_H/MPa$^{0.5}$	Hansen distance to DCM[a]
 4-(Methoxymethyl)-1,3-dioxolan-2-one	282	17.1	18.0	7.0	11.94
 Methyl (2-oxo-1,3-dioxolan-4-yl)methyl carbonate	342	17.0	19.3	7.8	13.33
 5-Methoxy-1,3-dioxane	140	17.0	8.3	7.2	3.31

 1,3-Dioxan-5-yl methyl carbonate	206	17.0	10.3	8.1	5.08
 4-(Methoxymethyl)-1,3-dioxolane	147	17.0	8.0	7.2	3.14
 (1,3-dioxolan-4-yl)Methyl methyl carbonate	211	17.0	10.1	8.1	4.92
 4-(Methoxymethyl)-2,2-di methyl-1,3-dioxolane	163	16.1	5.9	5.0	4.36
 Methyl (2,2-dimethyl-1,3-diox olan-4-yl)methyl carbonate	222	16.2	7.9	6.0	4.31

[a] The HSPs of DCM (δ_D = 18.2 MPa$^{0.5}$ δ_P = 6.3 MPa$^{0.5}$ δ_H =6.1 MPa$^{0.5}$) can be found in Ref. 139.



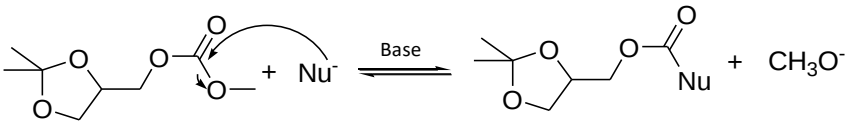
Scheme 3.3 The synthesis of MMC from solketal and DMC catalysed by potassium carbonate at DMC reflux temperature

Although the synthesis of MMC from solketal and DMC has been previously reported in the literature (Scheme 3.3),[275] the optimisation of reaction conditions and the investigation of its solvent properties have not been conducted. Hence, optimisation of the proposed synthetic route to MMC and the determination of the solvent properties are the focus of this lab-based

work.

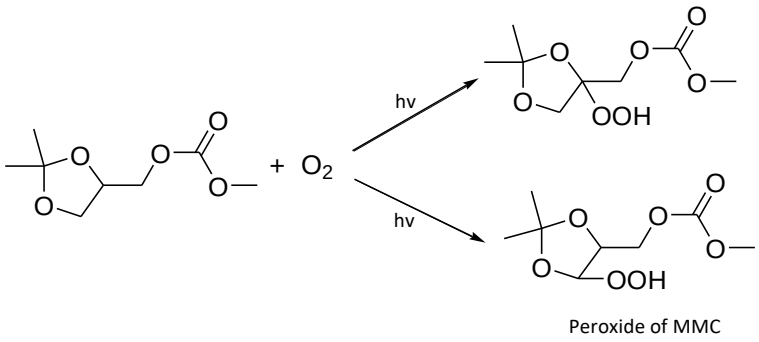
3.2.2 Theoretical stability and reactivity of MMC

Similar to Chapter 2, before synthesis, it is important to predict the reactivity of MMC to understand its suitability for different applications. The carbonate group in MMC limits its use in strongly acidic or basic conditions as it would be susceptible to nucleophilic attack (Scheme 3.4).



Scheme 3.4 The reaction of MMC with nucleophile catalysed by base

MMC also possesses ether functionality, which has the potential to produce peroxides that may be explosive (Scheme 3.5). Consequently, antioxidants may be required in commercialised MMC.



Scheme 3.5 The possible formation of peroxide of MMC

3.2.3 The optimisation of DMC synthesis of MMC

3.2.3.1 The effect of the reaction time on the synthesis of MMC

To investigate the effect of the reaction time on the synthesis of MMC, reaction time between 1 h to 50 h was selected. Table 3.2 shows that the gas chromatography (GC) yield of MMC increases gradually from 42% to a maximum of 97% after 20 hours. As such, 20 hours was selected as an

optimal reaction condition. The high selectivity towards MMC (99%) is maintained at all reaction times in this study.

Table 3.2 The effect of the reaction time on the synthesis of MMC[a]

Entry	Time (h)	Selectivity (%)[b]	GC yield (%)
1	1	>99	42
2	2	>99	61
3	5	>99	84
4	10	>99	92
5	15	>99	96
6	20	>99	97
7	25	>99	97
8	50	>99	97

[a] Reaction conditions: solketal/DMC/K_2CO_3 = 6 mmol : 240 mmol : 7.2 mmol; *T* = 90 °C. [b] Selectivity towards MMC.

3.2.3.2 The effect of the catalytic loading on the synthesis of MMC

To optimise the catalytic loading, the amount of potassium carbonate used during synthesis was varied from 0% to 200% (Table 3.3). It can be seen that potassium carbonate is a very efficient catalyst for this reaction. Surprisingly, only 0.1% catalytic loading is required to produce MMC in high yield (96%) (entry 10, Table 3.3). When 0.05% equivalent potassium carbonate is used in the reaction, the yield of MMC drops down to 40% (entry 11, Table 3.3). Furthermore, when 0.01% equivalent is employed in the reaction, the yield of MMC falls to only 3% (entry 12, Table 3.3). Specifically, the control experiment (entry 13, Table 3.3) demonstrated that the carboxymethylation reaction between solketal and DMC did not take place in the absence of a catalyst. During this investigation, the selectivity towards MMC is preserved (99%). As a result, 0.1% potassium carbonate equivalent is selected as an optimised reaction condition.

Table 3.3 The effect of catalytic loading on the synthesis of MMC[a]

Entry	K_2CO_3 equivalents (%)	Selectivity (%)[b]	GC yield (%)
1	200.00	>99	97
2	120.00	>99	97
3	80.00	>99	97
4	40.00	>99	96
5	10.00	>99	97
6	5.00	>99	97
7	3.00	>99	98
8	1.00	>99	98
9	0.50	>99	97
10	0.10	>99	96
11	0.05	>99	40
12	0.01	>99	3
13	0.00	>99	0

[a] Reaction conditions: solketal/DMC = 6 mmol : 240 mmol; *T* = 90 °C; reaction time 20 h. [b] Selectivity towards MMC.

3.2.3.3 The effect of the mole ratio of DMC to solketal on the synthesis of MMC

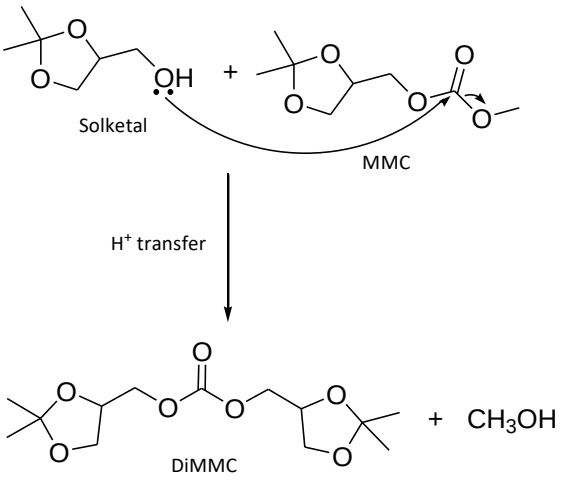
Using the optimised conditions as mentioned above, the effect of the mole ratio of DMC to solketal was tested in the range of 5:1 to 40:1, and the results are listed in Table 3.4. When the mole ratio of DMC to solketal increases, the selectivity and GC yield towards MMC improve from 90% to 99% and 90% to 96%, respectively (entry 1-5, Table 3.4). As such, the 20:1 mole ratio of DMC to solketal is found to be optimal. During these experiments, the main by-product is observed to be (4,4-dimethyl-1,3-dioxolan-2-yl) methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (diMMC).

Table 3.4 The effect of mole ratio of substrates on the synthesis of MMC[a]

Entry	Mole ratio of DMC/solketal	Selectivity (%)[b]	GC yield (%)
1	5:1	90	90
2	10:1	96	94
3	15:1	97	94
4	20:1	>99	96
5	40:1	>99	96

[a] Reaction conditions: solketal/K_2CO_3 = 6 mmol : 0.006 mmol; *T* = 90 °C; reaction time 20 h. [b] Selectivity towards MMC.

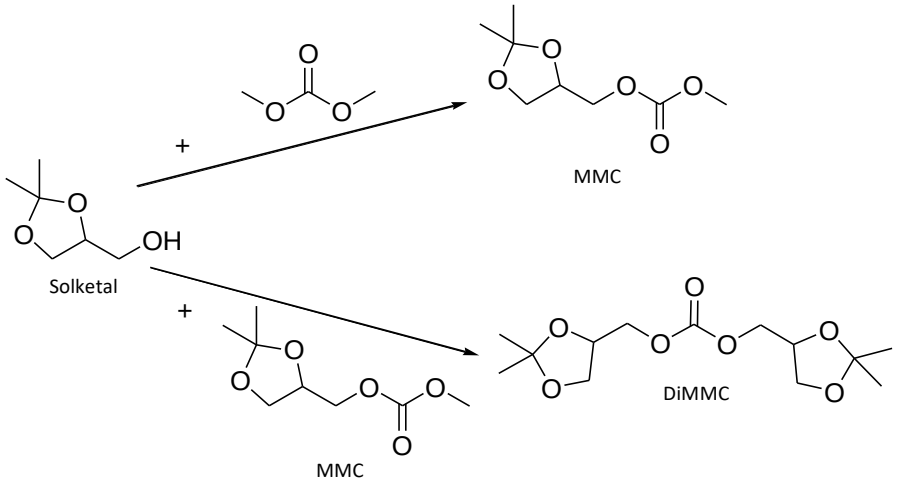
Scheme 3.6 demonstrates the formation mechanism of diMMC: the lone pair electrons on the oxygen of the hydroxyl group of the solketal molecule attacks the centre carbon of the carbonate (-OCOO-) of MMC, following which the proton transfer occurs to yield diMMC and methanol.



Scheme 3.6 The synthesis of diMMC from solketal and MMC catalysed by potassium carbonate

Scheme 3.7 illustrates the competing reaction among solketal, DMC and MMC. During the reaction, MMC is produced firstly from the reaction between DMC and solketal. After that, excessive solketal reacts with MMC to produce diMMC. In other words, DMC and MMC have the competitive relationship to react with solketal to yield different products. It is possible that MMC is more sterically hindered than DMC. This means solketal has a higher probability of reaction with DMC rather than MMC. As a consequence, if the DMC is in a significant excess, the solketal should preferentially react with DMC rather than MMC. Therefore, when the mole ratio of DMC

to solketal increases, the selectivity towards MMC improves.



Scheme 3.7 The competing reaction among solketal, DMC and MMC

In summary, reaction time 20 h, 0.1% catalytic loading and 20:1 of mole ratio of DMC to solketal are the optimal reaction conditions for the synthesis of MMC. The remaining DMC and methanol after synthesis can be easily recovered by distillation.

3.2.4 Defining the solvent parameters of MMC

3.2.4.1 Boiling point and melting point of MMC

In this research, thermogravimetric analysis (TGA) is used to estimate the b.p. of MMC. TGA is a technique of thermal analysis in which variations in physical and chemical properties of samples are tested as a function of temperature or time.[276] The rate of mass loss can be obtained by TGA as such the b.p. of a compound can be estimated. Since the differential thermogravimetric (DTG) curve represents the mass loss rate, the lowest point of that curve has the maximum mass loss rate, and thus the b.p. of MMC can be observed.

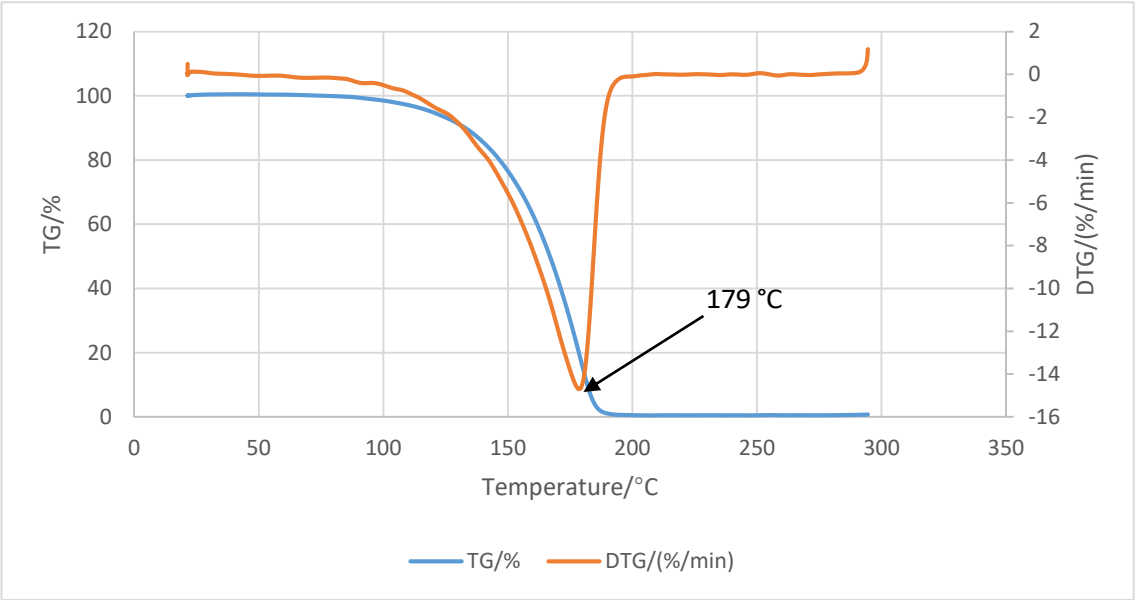


Fig. 3.2 The TGA of MMC

The actual b.p. of MMC was measured by TGA to be approximately 179 °C (Fig. 3.2). Since MMC was previously experimentally shown not to decompose at 179 °C,[277] this was confirmed to be its b.p. The high b.p. of MMC implies that MMC possibly has less environmental and safety risks than many traditional volatile organic compound (VOC) solvents.

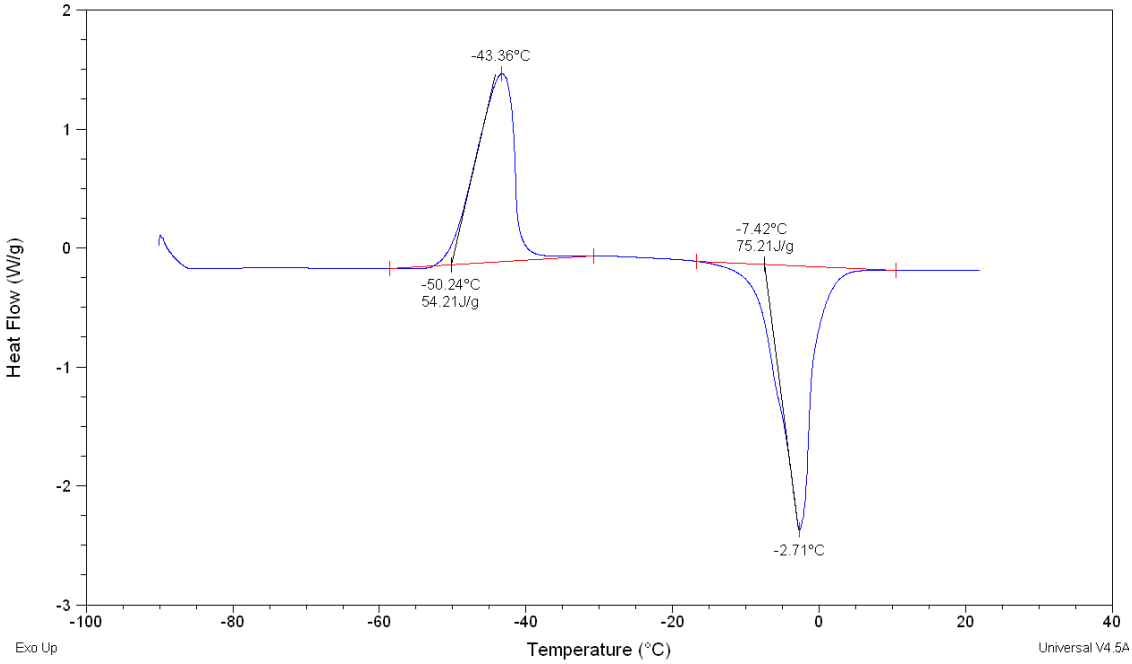


Fig. 3.3 The DSC of MMC

The melting point (m.p.) of MMC was measured by differential scanning calorimetry (DSC) (Fig. 3.3). The methods of identification of m.p. and crystallisation point (c.p.) in the DSC were referenced from the literature recommended by the Nomenclature Committee of the International Confederation for Thermal Analysis (ICTA).[278] Based on these methods, the m.p. and c.p. of MMC were identified to be -7°C and -50 °C as shown in Fig. 3.3, respectively. It is worth to be mentioned that the "Exo Up" in Fig. 3.3 means the exothermic peak upturns in the diagram, while the endothermic peak is opposite.

In summary, at ambient pressure, MMC may be a suitable solvent for reactions conducted between a temperature range of 5 °C to 179 °C. In contrast to the chlorinated solvents, MMC also does not include any halogen atoms and hence it does not form highly toxic compounds such as phosgene (on oxidation) or deplete the ozone layer through incineration.[11]

3.2.4.2 The measurement of density of MMC

The density of MMC was experimentally determined at 25 °C (298 K) and atmosphere pressure. Three different batches of MMC products were utilised for the density testing to obtain the average value. The measurement of the density of MMC was conducted by determining the mass of 1 cm^3 MMC in a 1 cm^3 volumetric flask. Its density was found to be 1.14 $g \cdot cm^{-3}$.

3.2.4.3 The measurement of viscosity of MMC

The dynamic viscosity of MMC was measured by Ostwald viscometer at 20 °C (293 K) and atmosphere pressure. Three different batches of MMC products were used for the viscosity testing to obtain the average value. Finally, the result shows its dynamic viscosity is 3.50 cP, which is a high viscosity around room temperature. Therefore, the solvent performance of MMC may be limited.

3.2.4.4 The measurement of formation of peroxide of MMC

MMC includes ether groups, and therefore could potentially form explosive peroxide. A preliminary test in this study to investigate the production of peroxides from MMC was implemented *via* employing peroxide test strip (Macherey-Nagel, QUANTOFIX® Peroxide-100), which has a detection limit (DL) between 1 to 100 mg·dm^{-3}, following the instruction of the manufacturer. Monitoring of 7.5 cm^3 MMC was sealed in a transparent small bottle with air and irradiated by light over a period of 224 days, in the absence of antioxidants or stabilisers.

Table 3.5 The monitoring of formation of peroxide of MMC[a]

Entry	Time	Concentration of peroxide (mg·dm^{-3})[b]
1	0 day[c]	Less than DL
2	7 days	Less than DL
3	14 days	Less than DL
4	21 days	Less than DL
5	28 days	Less than DL
6	56 days	Less than DL
7	84 days	Less than DL
8	112 days	Less than DL
9	168 days	Less than DL
10	224 days	Less than DL

[a] no antioxidant or stabiliser added. [b] The concentration of peroxide of MMC was tested by peroxide test strip. [c] 0 day represents isolated MMC was just obtained by distillation.

This investigation was conducted during an extended period of 224 days. Table 3.5 lists the testing results. After 224 days, the total peroxide concentration in MMC solvent was Less than DL (<1 mg·dm^{-3}). This result signified that although MMC has little risk of production of hazardous peroxides under these test conditions, further work would be needed to determine the extent of peroxide formation at elevated temperatures and also under ultraviolet (UV) light sources.

3.2.4.5 UV-vis. test of KT parameters of MMC

The KT parameters of MMC were identified based on the ultraviolet-visible (UV-vis.) spectrum of different dyes of Nile red (NR), 4-nitroaniline (NA) and *N,N*-diethyl-4-nitroaniline (NN), respectively.

Table 3.6 The λ_{max} of UV-vis. of different dyes in MMC

	NR	NA	NN
λ_{max}	522 nm	356 nm	394 nm

Table 3.6 lists the λ_{max} of UV-vis. of NR, NA and NN in MMC. KT parameters α, β, and π^* of MMC were then calculated based on Equation 2.1, 2.2 and 2.3 in Chapter 2 to be: α = 0.00, β = 0.29 and π^* = 0.67.

3.2.4.6 The solvent properties of MMC in comparison with other conventional aprotic solvents

Table 3.7 lists the properties of MMC, compared to a range of different categories of traditional aprotic solvents such as DCM, $CHCl_3$, ethyl acetate, diethyl ether, acetonitrile, acetone, cyclohexane, DMC and propylene carbonate.

Fig. 3.4 illustrates the sites of MMC and other investigated solvents in three dimension (3D) Hansen space. As discussed in Chapter 2, if a lower Ra value exists between two different solvents, they are more to likely possess similar solvency power. Table 3.7 and Fig. 3.4 show that MMC has similar HSPs to DCM, which indicates that MMC is a potential substitute for DCM. Additionally, MMC has similar solvency power to ethyl acetate and acetone with Ra values between them less than 5.00. MMC also has similar medium solvency to chloroform, diethyl ether and DMC with Ra values in the range of 5.00 to 7.00. Acetonitrile, propylene carbonate and cyclohexane have a much longer distance to MMC than the other traditional solvents with Ra values higher than 9.50.

Table 3.7 The properties of MMC and other traditional aprotic solvents

	MMC	DCM	Chloroform	Ethyl acetate	Diethyl ether	Acetonitrile	Acetone	Cyclohexane	DMC	Propylene carbonate
Mwt	190.2[a]	84.9[d]	119.4[d]	88.1[d]	74.1[d]	41.1[d]	58.1[d]	84.2[d]	90.1[a]	102.1[d]
KT α	0.00	0.13[e]	0.20[e]	0.00[i]	0.00[i]	0.35[j]	0.20[j]	0.00[l]	0.00[l]	0.00[p]
KT β	0.29	0.10[e]	0.10[e]	0.48[i]	0.51[i]	0.37[j]	0.54[j]	0.00[l]	0.32[l]	0.38[p]
KT π^*	0.67	0.82[e]	0.58[e]	0.54[i]	0.28[i]	0.80[j]	0.70[j]	0.00[l]	0.55[l]	0.90[p]
δ_D/MPa$^{0.5}$	16.2[a]	18.2[f]	17.8[f]	15.8[f]	14.5[f]	15.3[f]	15.5[f]	16.8[f]	15.5[f]	20.0[f]
δ_P/MPa$^{0.5}$	7.9[a]	6.3[f]	3.1[f]	5.3[f]	2.9[f]	18.0[f]	10.4[f]	0.0[f]	3.9[f]	18.0[f]
δ_H/MPa$^{0.5}$	6.0[a]	6.1[f]	5.7[f]	7.2[f]	5.1[f]	6.1[f]	7.0[f]	0.2[f]	9.7[f]	4.1[f]
Hansen distance[b]	0.00	4.31	5.78	2.97	6.11	10.26	3.03	9.87	5.63	12.78
B.p./°C	179[c]	40[d]	61[d]	77[d]	34[d]	82[d]	56[d]	81[d]	90[m]	242[d]
M.p./°C	-7[q]	-95[d]	-64[d]	-84[d]	-116[d]	-44[d]	-95[d]	7[d]	5[n]	-55[d]
ρ/g·cm^{-3} at 298 K	1.14	1.32[d]	1.48[d]	0.89[d]	0.71[d]	0.78[d]	0.78[d]	0.77[d]	1.06[m]	1.20[d]
Viscosity /cP at 293 K	3.50	0.44[g]	0.576[h]	0.45[d]	0.24[d]	0.36[g]	0.33[k]	0.98[d]	0.62[o]	2.76[d]

[a] Calculated by HSPiP. [b] Hansen distance to MMC. [c] Measured by TGA. [d] Ref. 22. [e] Ref. 137. [f] Ref. 139. [g] Ref. 254. [h] Ref. 255. [i] Ref. 119 and Ref. 134. [j] Ref. 135. [k] Ref. 256 [l] Ref. 133. [m] Ref. 237. [n] Ref. 257. [o] Ref. 258. [p] Ref. 136.[q] Measured by DSC.

MMC is considered to be an aprotic solvent due to its low α. KT solvent plots can be used to establish how the β and π^* properties of MMC compared to other conventional aprotic solvents (Fig. 3.5). Based on Table 3.7 and Fig. 3.5, MMC is placed closer to DCM and other highly dipolar/polarisable solvents with low hydrogen bonding potential. These results provide evidence that MMC may have properties (basicity and polarity) between these solvents and can be employed as a more sustainable replacement solvent for a broad range of different types of conventional solvents. Meanwhile, MMC shows entirely different solvent properties to cyclohexane in both KT parameters and HSPs. This

demonstrates that MMC may not be its suitable replacement solvent.

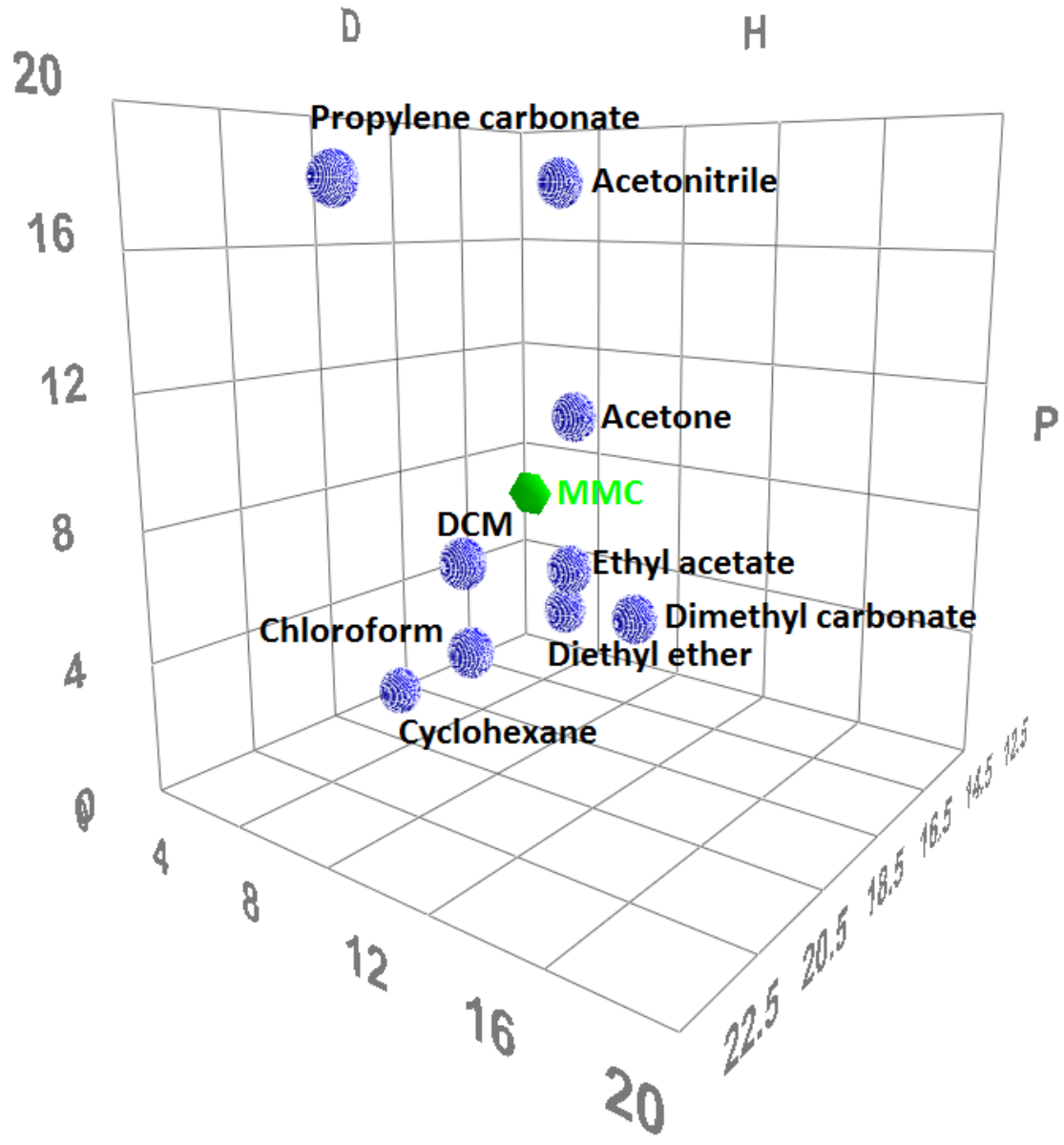


Fig. 3.4 The site of MMC and the other traditional solvents in Hansen space constructed by HSPiP software, where D, P and H represent δ_D/MPa$^{0.5}$, δ_P/MPa$^{0.5}$ and δ_H/MPa$^{0.5}$, respectively

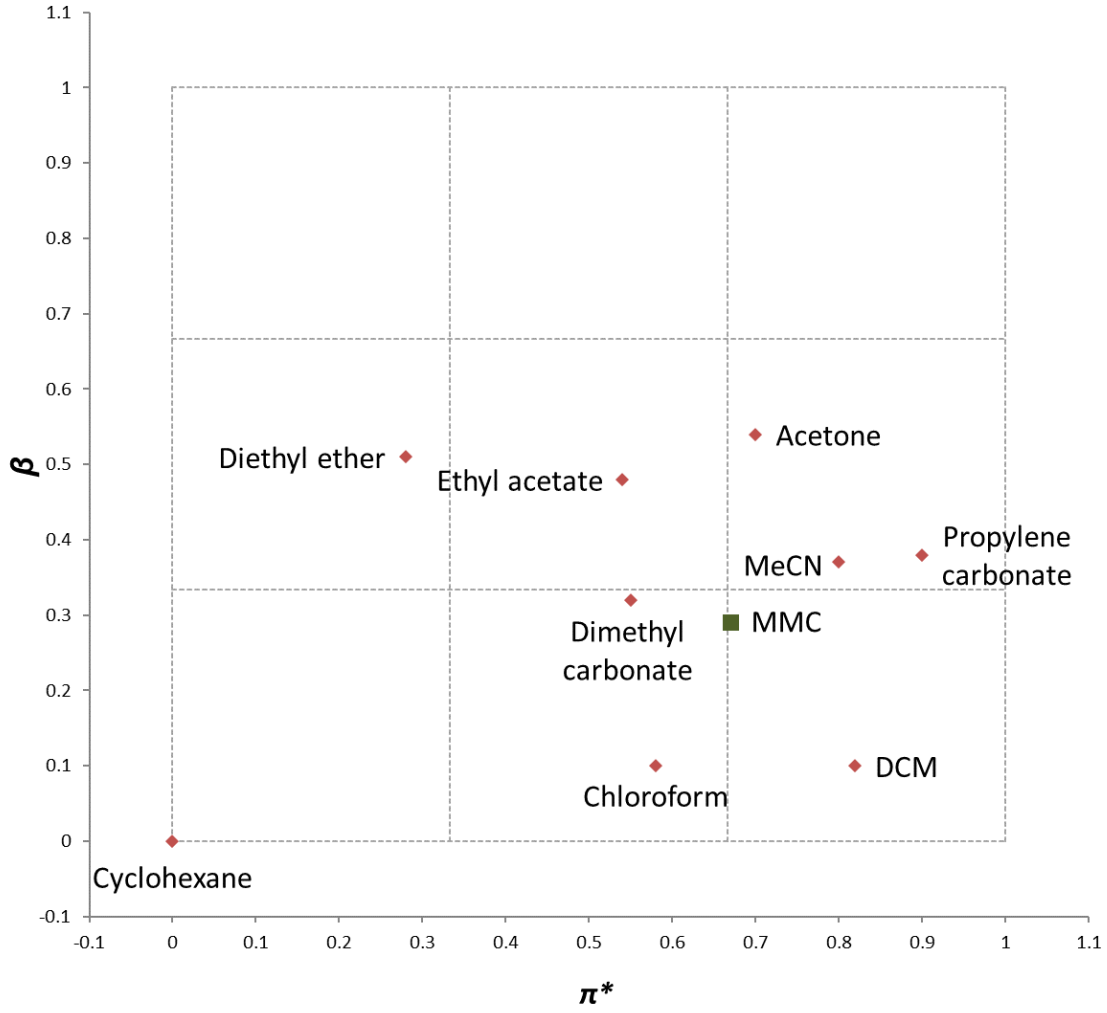
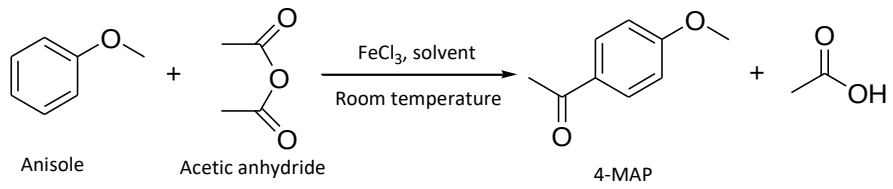


Fig. 3.5 The KT solvent plot of MMC and other traditional aprotic solvents investigated in this research

3.2.5 The solvent test in Friedel-Crafts and Diels-Alder reactions

As MMC has both similar KT parameters and HSPs to DCM as well as a group of other organic solvents, its performance as the reaction medium in two chemical reactions was tested against a range of traditional solvents. Friedel-Crafts and Diels-Alder reactions were both selected to assess MMC compared to other conventional solvents. MMC's ether and carbonate functional groups were expected to remain inert in both of these reactions.

The synthesis of 4-methoxyacetophenone (4-MAP) from anisole and acetic anhydride promoted by iron (III) chloride, as shown in Scheme 3.8, was selected to evaluate the performance of MMC in the Friedel-Crafts reaction. The experimental results are listed in Fig. 3.6.



Scheme 3.8 The Friedel-Crafts synthesis of 4-MAP from anisole and acetic anhydride promoted by iron (III) chloride in different solvents

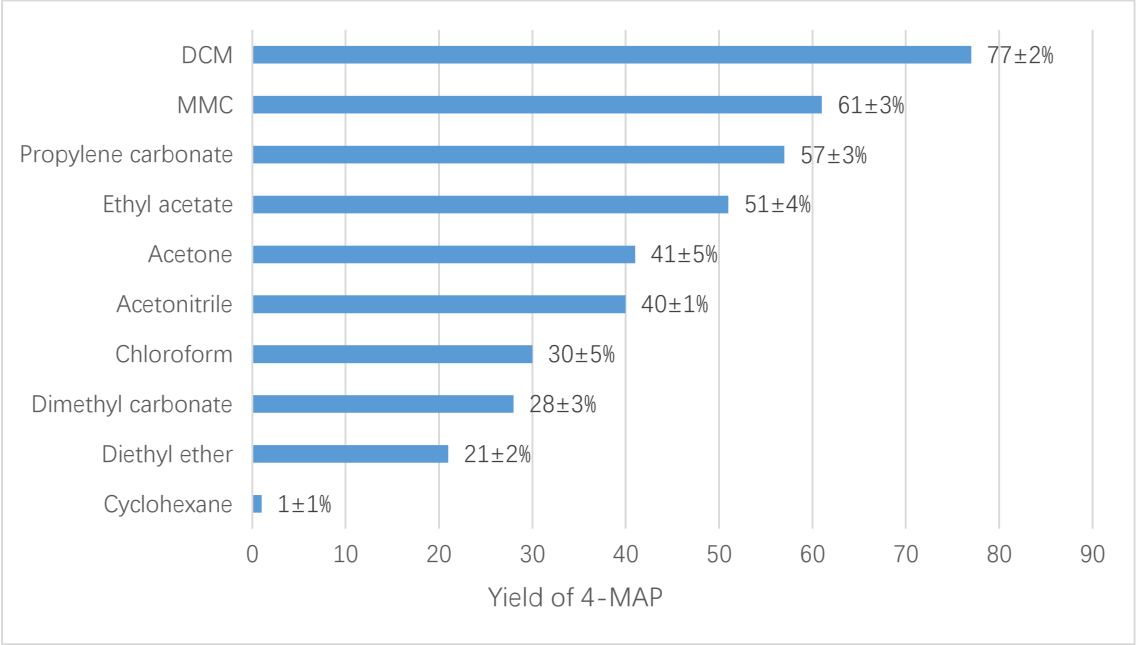
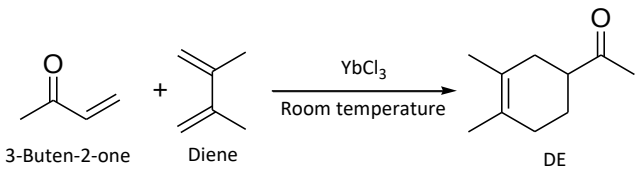


Fig. 3.6 The GC yield of 4-MAP synthesised from anisole and acetic anhydride promoted by $FeCl_3$ in MMC and other common solvents with selectivity >99% towards 4-MAP in all the experiments

The reaction conducted in MMC results in a yield of 61% 4-MAP, while the yields of 4-MAP for DCM, ethyl acetate and propylene carbonate are found to be 77%, 51% and 57%, respectively. These results support the evidence put forward by the KT solvatochromic parameters that indicate that MMC demonstrated solvent properties between DCM,

ethyl acetate and propylene carbonate.



Scheme 3.9 The Diels-Alder synthesis of DE from 3-buten-2-one and diene catalysed by ytterbium(III) chloride in different solvents

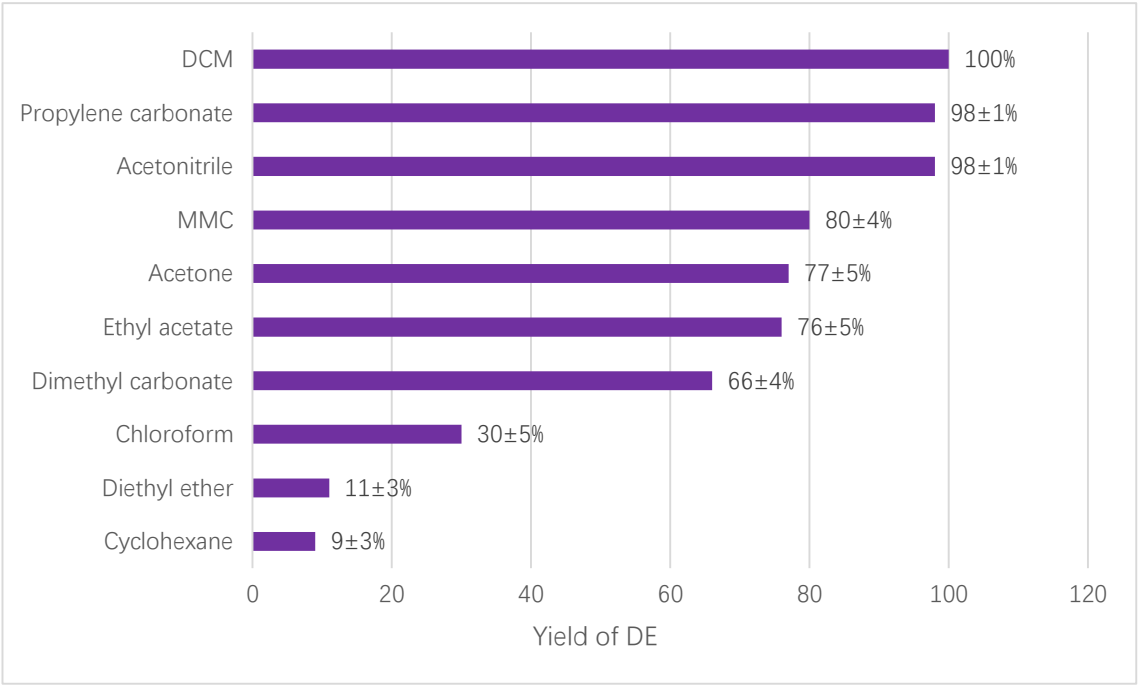


Fig. 3.7 The GC yields of DE synthesised from 3-buten-2-one and diene catalysed by $YbCl_3$ in different solvents with selectivity >99% towards DE in all the experiments

The performance of MMC in the Diels-Alder reaction was also evaluated for the synthesis of 1-(3,4-dimethylcyclohex-3-enyl) ethanone (DE) from 2,3-dimethyl-1,3-butadiene (diene) and 3-buten-2-one catalysed by anhydrous ytterbium(III) chloride (Scheme 3.9). DCM, propylene carbonate and acetonitrile all exhibit high yields (>95%) in this reaction, while ethyl acetate, acetone and MMC generate moderate yields of 75%-80% (Fig. 3.7). DMC, chloroform, diethyl ether and cyclohexane only have medium to low yield. These results indicate that MMC has similar solvent properties to the ketone and ester solvents which were tested in the Diels-Alder reaction.

The possible reason for the lower yield of MMC than that of DCM in Friedel-Crafts and Diels-Alder reactions is that the Lewis acid $FeCl_3$ and $YbCl_3$ form complexation with the highly electronegative ketonic oxygen of MMC solvent, which decreases the availability of active catalyst for the substrates (Fig. 3.8).[279] Meanwhile, the high viscosity of MMC reduces the reaction rate which also results in the lower yield of MMC than that of DCM and some other solvents.

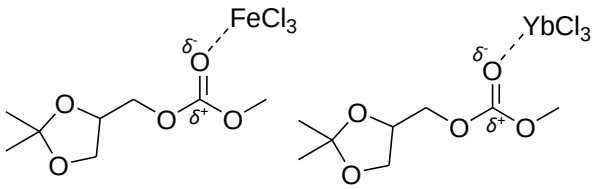


Fig. 3.8 The complexation of MMC with Lewis acid catalysts

The results of the two experimental case studies also show both reactions are highly dependent on the polarity of the medium. Specifically, a high π^* is favoured, a trend that is especially true in the case of the Diels-Alder reaction.[280] MMC is competitive based upon the yields provided. Although DCM is the more proficient solvent due to its superior polarity, it is a possible carcinogen.

3.2.6 Ames test for MMC

For a molecule to be a suitable substitute to traditional solvents, it must be safer than the solvents it is replacing. As such, the toxicology investigation of MMC was implemented by the Ames test.

Mutational *Salmonella typhimurium* TA98 (*hisD3052*) and TA100 (*hisG46*) were employed to verify the mutagenicity of MMC. Dimethyl sulfoxide (DMSO) was employed as a solvent (negative) control. A mixture of 2-nitrofluorene (2-NF) and 4-nitroquinoline-*N*-oxide (4-NQO) was utilised as the positive control. This Ames test was conducted without S9 microsomal activation, which is typically derived from mammalian liver.

Table 3.8 Ames test for MMC with TA98[a]

Concentration of MMC ($mg \cdot cm^{-3}$)	Replicate 1[b]	Replicate 2[b]	Replicate 3[b]	Average value of replicates 1-3
0[c]	7	6	4	6
0.16	7	4	11	7
0.31	6	7	8	7
0.63	10	8	12	10
1.25	20	16	11	16
2.5	15	20	18	18
5	26	21	28	25
2-NF + 4-NQO[d]	48	47	48	48

[a] Without S9 microsomal activation. [b] Number of mutagenic wells of 48 wells. [c] Negative control. [d] Positive control.

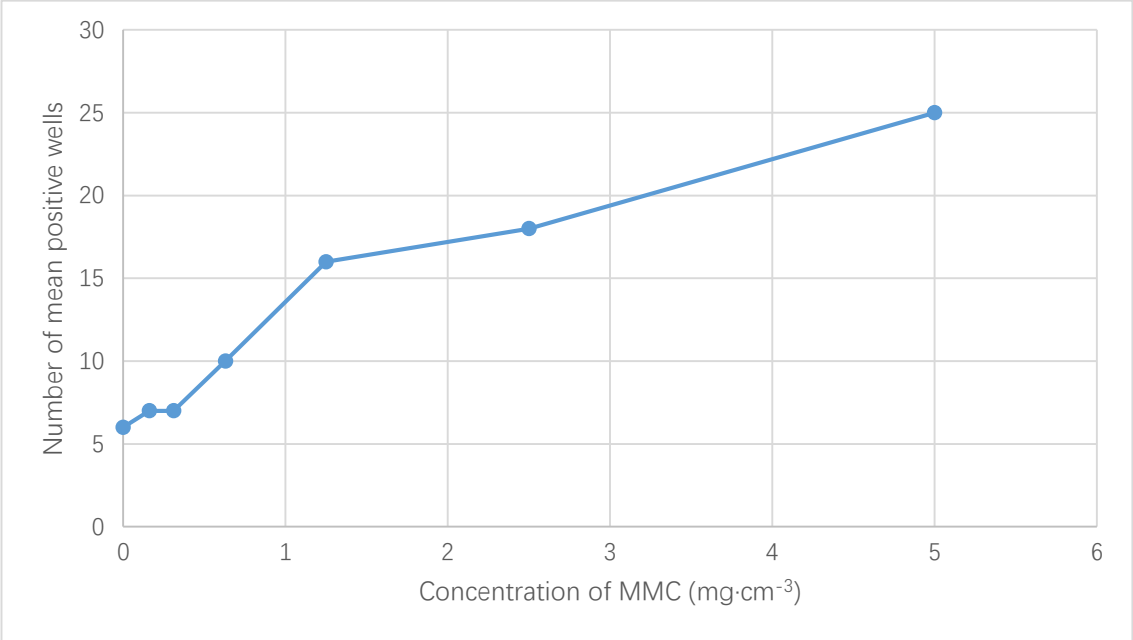


Fig. 3.9 The dose effect of MMC for TA98 in Ames test

Table 3.9 Ames test for MMC with TA100[a]

Concentration of MMC ($mg \cdot cm^{-3}$)	Replicate 1[b]	Replicate 2[b]	Replicate 3[b]	Average value of replicates 1-3
0[c]	2	0	2	1
0.16	0	0	1	0
0.31	0	0	2	1
0.63	1	1	2	1
1.25	3	1	0	1
2.5	2	0	3	2
5	1	3	0	1
2-NF + 4-NQO[d]	48	48	48	48

[a] Without S9 microsomal activation. [b] Number of mutagenic wells of 48 wells. [c] Negative control. [d] Positive control.

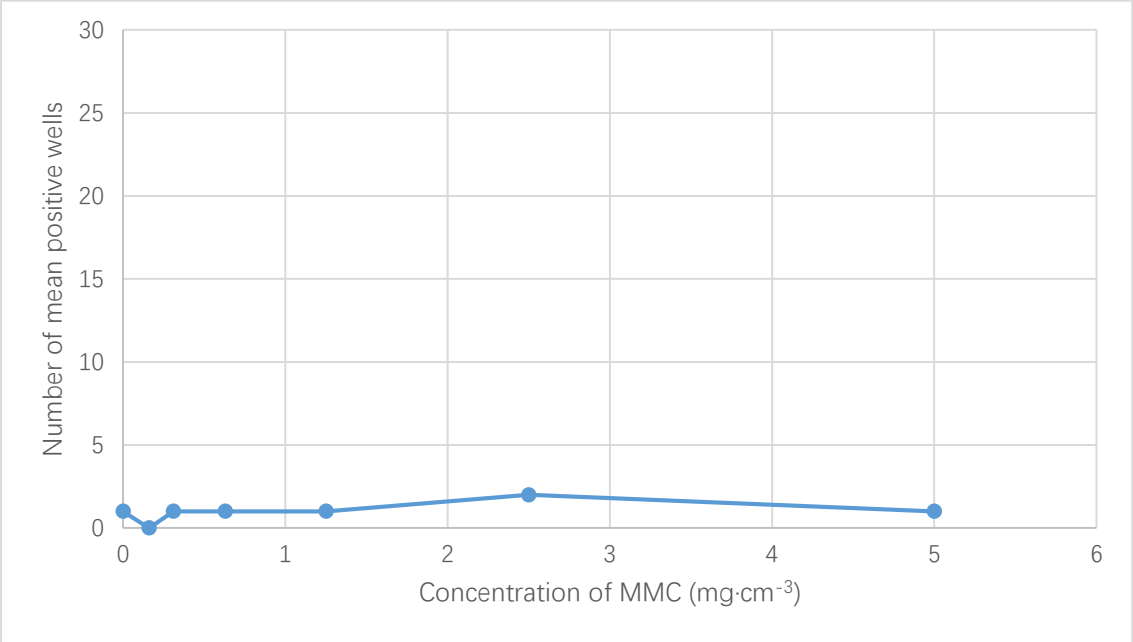


Fig. 3.10 The dose effect of MMC for TA100 in Ames test

After the testing, no mutagenicity of MMC was observed for TA100 (Table 3.9, Fig. 3.10), since no dose effect existed. However, mutagenicity was observed for MMC with the TA98 strain because dose effect exhibited (Table 3.8, Fig. 3.9). This indicates that MMC is a mutagenic solvent. In summary, although MMC is a bio-based solvent, its mutagenicity results in it not being

classified as a green solvent. This test also demonstrates that any new bio-based solvent needs Ames test before application to confirm whether it is a green solvent. These results highlight the importance of toxicity testing in the early stages of solvent development.

3.3 Conclusion

This chapter describes the solvent selection process as well as the optimisation of a synthetic route to a new bio-based solvent, MMC, from glycerol based solketal and DMC.

Specifically, MMC was selected as a new bio-based medium after screening based on HSPiP software. Screening of different reaction conditions for the synthesis of MMC from solketal and DMC catalysed by potassium carbonate was then implemented, and it was found that a reaction time of 20 h, 0.1% catalytic loading and 20:1 of mole ratio of DMC to solketal were the optimal conditions. B.p., m.p., density and viscosity of MMC were also determined. The results demonstrate potential limitations in its performance due to the high viscosity. Peroxide testing was also conducted, and the results provided evidence that MMC does not generate hazardous peroxide compounds. HSPs, KT parameters, Friedel-Crafts and Diels-Alder reactions of MMC testified that MMC could be a potential sustainable replacement for a wide range of traditional solvents in organic synthesis. Importantly, MMC was proved to be mutagenic by Ames test, showing although it is a bio-based solvent but not a green solvent and thus should be eliminated as a potential candidate for solvent replacement.

Chapter 4 The new developments in acidic DMC chemistry

Part of the work presented in this chapter has appeared in:

S. Jin, A. J. Hunt, J. H. Clark and C. R. McElroy, Acid-catalysed carboxymethylation, methylation and dehydration of alcohols and phenols with dimethyl carbonate under mild conditions, *Green Chem*., 2016, **18**, 5839-5844.

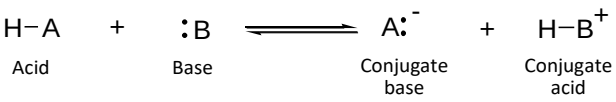
Poster given at The 4th Annual G2C2 Workshop and Symposium: Green Chemistry for China, Sichuan University, Chengdu, P. R. China, July 2016

4.1 Introduction

4.1.1 The definition of acid and base

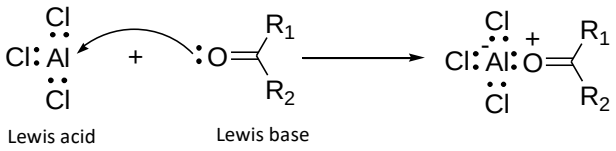
There are two main definitions of acid and base; they are Brønsted-Lowry definition and Lewis definition.[281]

Brønsted-Lowry defines an acid as a substance which donates a proton (H^+) and a base as a substance which accepts a proton.[281] The species generated when an acid donates a proton is defined as the conjugate base while the species produced when a base accepts a proton is defined as the conjugate acid (Scheme 4.1). Some of most commonly used Brønsted acids are sulphuric acid, hydrochloric acid, nitric acid, *p*-toluenesulfonic acid (PTSA), acetic acid, *etc*.



Scheme 4.1 The general equation for Brønsted acid

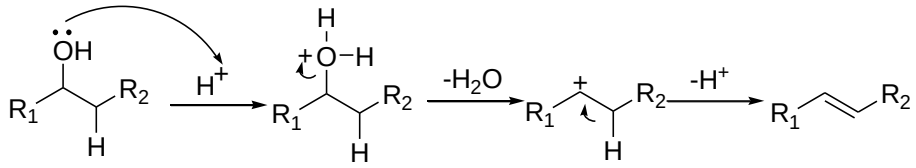
A classification which is much broader than Brønsted-Lowry concept is the Lewis definition of acid and bases: A Lewis acid is a substance which accepts an electron pair; a Lewis base is a substance which donates an electron pair.[281] For example, many transition-metal compounds, such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, $TiCl_4$ and $SnCl_4$ are good Lewis acids due to their vacant valence orbitals which can accept an electron pair from Lewis base (Scheme 4.2). According to the concept of Lewis base, most oxygen- or nitrogen-containing organic compounds, such as ethanol, acetone and trimethylamine, are excellent Lewis bases due to their lone pairs.[281]



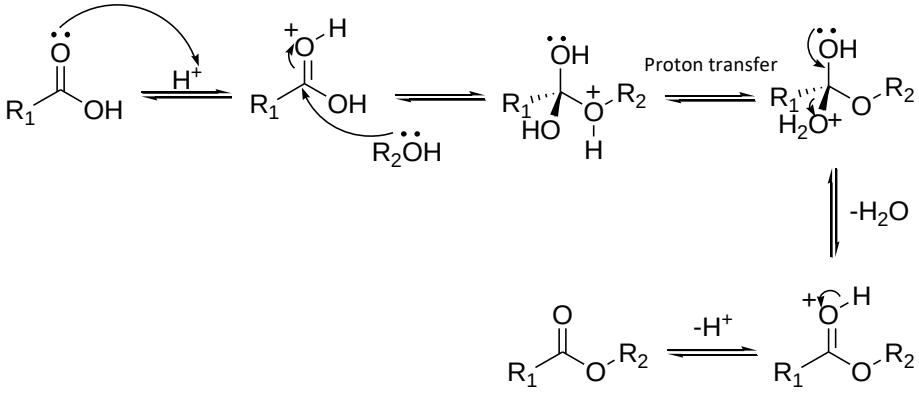
Scheme 4.2 The Lewis acid-base reaction

4.1.2 Acids as catalysts

Numerous chemical reactions are carried out in the presence of acid catalysts. Brønsted acids are commonly used as acid catalysts in organic synthesis since they can protonate reactants, resulting in the formation of carbonium ion intermediate or improve electrophilicity of substrates.[127,282] For example, the dehydration of alcohol can be catalysed by a Brønsted acid such as sulphuric acid: The sulphuric acid donates a proton to protonate the alcohol hydroxyl group, before dehydration occurs *via* a unimolecular elimination (E1) mechanism (Scheme 4.3) to yield a carbonium ion.[127] Finally, the relevant dehydration product is obtained after eliminating a proton.



Scheme 4.3 The dehydration of alcohol catalysed by sulphuric acid

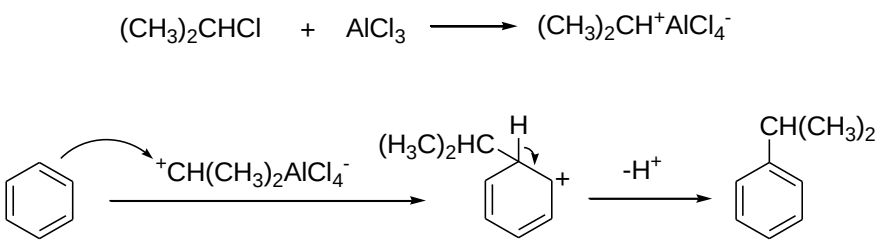


Scheme 4.4 The Brønsted acid catalysed Fischer esterification reaction

Another example of Brønsted acid catalysed reaction is the Fischer esterification reaction (Scheme. 4.4), where the acid catalyst improves the electrophilicity of the carbonyl carbon.[282]

Lewis acids, such as $AlCl_3$, are also popularly employed as acid catalysts due to their ability to increase the electrophilicity of relevant reactants. For instance, Lewis acid can be used as a catalyst to promote the electrophilic aromatic substitution, such as Friedel-Crafts reaction

(Scheme 4.5).[283]



Scheme 4.5 $AlCl_3$ catalysed Friedel-Crafts reaction

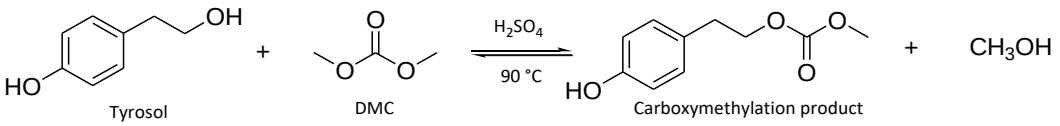
Currently, more sustainable and reusable heterogeneous catalysts have been extensively developed, such as Starbon®,[284] amorphous carbon with SO_3H group,[285] biomass derived sulfonated carbons as solid acid[286] and macroporous resin solid acid.[287]

Overall, acid catalysts have been used ubiquitously in various organic synthesis, and their application in green syntheses, such as dimethyl carbonate (DMC) reaction, is of interest in this project.

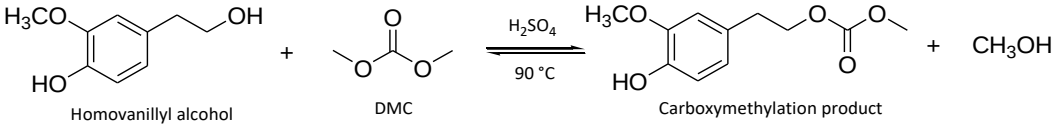
4.1.3 Acid-catalysed DMC chemistry for alcohols

As discussed in Chapter 1, DMC is a green methylation and carboxymethylation agent. However, currently most reactions between DMC and alcohols are base-catalysed. Due to the possible interaction between acid catalysts and the carbonyl group, DMC reactions may be promoted by Brønsted acid or Lewis acid. Significantly, in Chapter 2, Brønsted acid PTSA was identified as the best catalyst to promote methylation of acetoin with DMC at 160 °C. It was this result which directed the investigation into acid-catalysed reactions of DMC in this chapter.

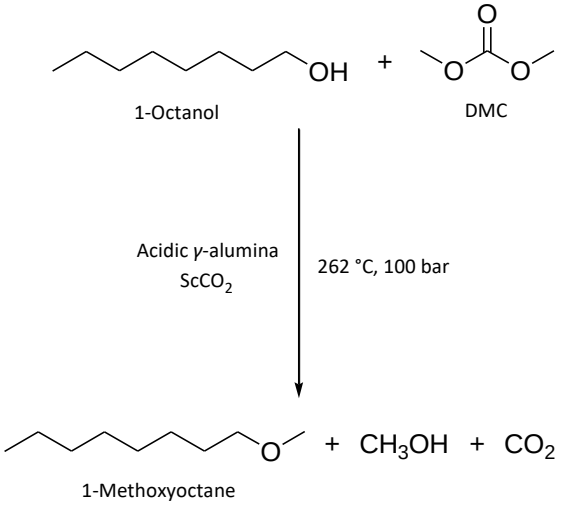
To date, limited literature has been reported on acid-catalysed (Brønsted or Lewis acid) carboxymethylation or methylation reactions between aliphatic alcohols/phenols and DMC. Bernini *et al*. used sulphuric acid as a catalyst to promote the carboxymethylation reaction between tyrosol or homovanillyl alcohol and DMC at 90 °C (Scheme 4.6 and Scheme 4.7).[288]



Scheme 4.6 The sulphuric acid catalysed DMC carboxymethylation reaction for tyrosol



Scheme 4.7 The sulphuric acid catalysed DMC carboxymethylation reaction for homovanillyl alcohol



Scheme 4.8 The methylation reaction between 1-octanol and DMC catalysed by acidic *γ*-alumina in $ScCO_2$

Gooden *et al*. reported that acidic *γ*-alumina was used to promote the DMC methylation reaction for 1-octanol in supercritical CO_2 ($ScCO_2$), and a yield of 86% was obtained at 262 °C under 100 bar (Scheme 4.8).[289]

However, these sporadic articles did not investigate the acid-catalysed DMC chemistry systematically. Therefore, it is necessary to study the acid-catalysed DMC reaction comprehensively with various alcohols and acid catalysts at a different temperature.

Significantly, if acid-catalysed DMC chemistry is possible, such a system will offer several major

advantages over existing procedures (Fig. 4.1). These benefits are three-fold and may include:

1. The substrates, which cannot conduct the reaction under basic condition, can be included in DMC chemistry after introducing acid catalysts, thus expanding the range of applications of DMC.

2. The number of available catalysts in DMC chemistry can be dramatically increased after adding acid catalysts.

3. Acid catalysts have potentially lower market prices as compared to common base catalysts used in existing DMC chemistry (such as potassium carbonate, sodium methoxide and potassium *tert*-butoxide).[290] Therefore, acidic DMC chemistry is worth exploring.

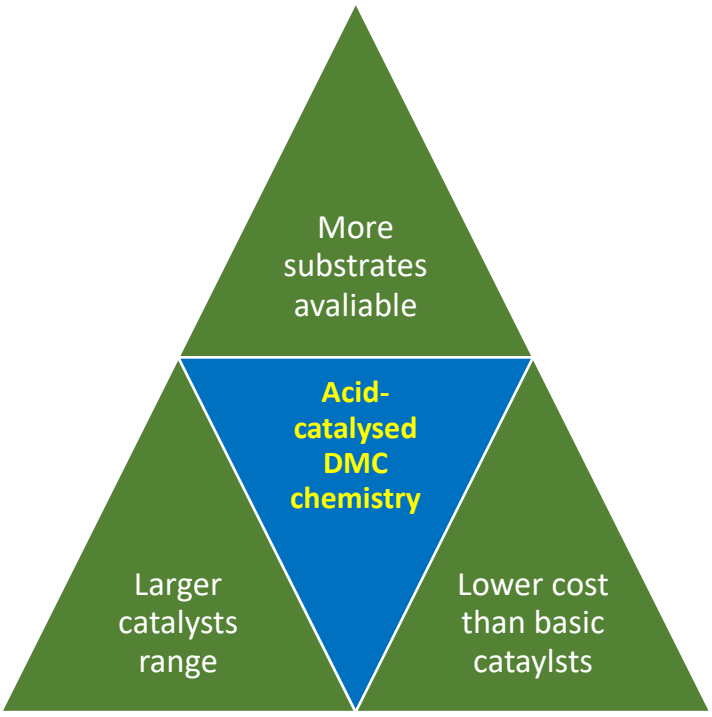
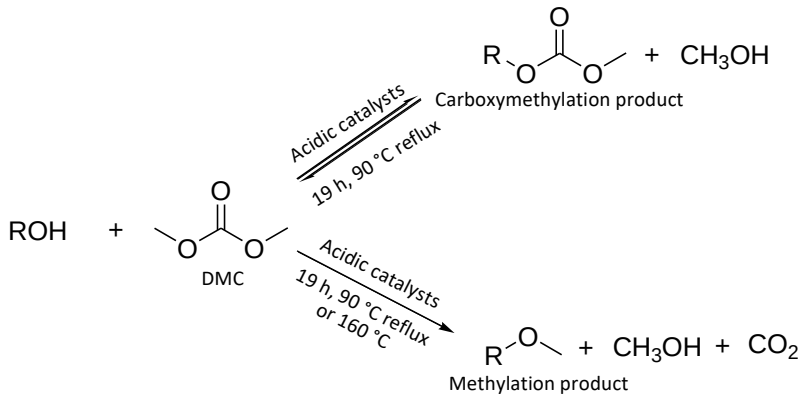


Fig. 4.1 The main advantages of introducing acid catalysts in DMC chemistry

Herein, widely available Brønsted and Lewis acids including PTSA, sulphuric acid, aluminium trichloride and iron (III) chloride have been selected to promote carboxymethylation and/or methylation reactions for various alcohols and phenols at 90 °C and 160 °C (Scheme 4.9).



Scheme 4.9 Acid-catalysed DMC carboxymethylation/methylation reaction for different alcohols and phenols at 90 °C or 160 °C

4.2 Results and discussion

4.2.1 Acid-catalysed DMC chemistry at 90 °C

Typically, base-catalysed reactions are carried out at reflux with DMC as both solvent and reactant result in carboxymethylation.[163] Acid-catalysed reactions should proceed in a similar manner and as such these were the initial conditions studied.

4.2.1.1 Carboxymethylation products obtained by the catalysis of Brønsted acid

PTSA and sulphuric acid were selected as typical Brønsted acids for the investigation of acid-catalysed DMC carboxymethylation chemistry at reflux temperature (90 °C). Table 4.1 and Table 4.2 show the conversion and selectivity towards carboxymethylation products synthesised from different alcohols and phenols in the presence of DMC and catalytic (0.05 equivalent) or stoichiometric (1.00 equivalent) amounts of PTSA or sulphuric acid, respectively.

Catalytic loading of PTSA resulted in carboxymethylation of primary alcohols 1-butanol and 1-octanol (entry 1 and 4, Table 4.1) with near quantitative selectivity and conversion (>99%). Under similar conditions, PTSA also promotes carboxymethylation of secondary alcohols 2-butanol and 2-octanol with quantitative selectivity (>99%) but reduced conversion of 65% and 28%, respectively (entry 2 and 5, Table 4.1). When stoichiometric PTSA is employed, the conversion

and selectivity towards carboxymethylation for all primary and secondary alcohols are quantitative. However, PTSA was ineffective at promoting the reaction of *tert*-butanol, highlighting that this catalyst did not promote the DMC methylation and carboxymethylation of tertiary alcohols.

Table 4.1 Conversion and selectivity of the PTSA promoted carboxymethylation reaction between various alcohols and DMC[a]

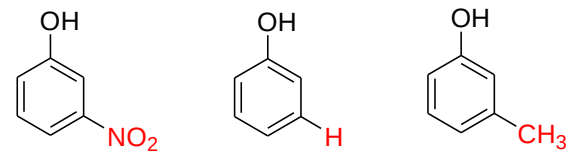
Entry	ROH	Catalytic PTSA		Stoichiometric PTSA	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	1-Butanol	>99	>99	>99	>99
2	2-Butanol	65±3	>99	>99	>99
3	*tert*-Butanol	0	0	0	0
4	1-Octanol	>99	>99	>99	>99
5	2-Octanol	28±2	>99	>99	>99
6	3-Nitrophenol	0	0	0	0
7	Phenol	0	0	0	0
8	*m*-Cresol	0	0	0	0

[a] Reaction conditions: ROH/DMC/PTSA = 6.00 mmol : 240.00 mmol : 0.30/6.00 mmol; *T* = 90 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methyl carbonates.

Phenols were also studied in order to expand the application of acidic DMC chemistry in aromatic compounds and investigate if hard-soft acid-base (HSAB) theory also applies under such conditions. Moreover, since phenolic compounds extensively exist in organisms, and thus if acid-catalysed DMC reaction for phenols is feasible, then this syntheses may be used to modify or upgrade these natural phenols in the future.

Fig. 4.2 illustrates the phenols studied in this research, including (a) phenol with deactivation group (3-nitrophenol), (b) phenol with no directing group (phenol) and (c) phenol with activation group (*m*-cresol). Methyl group has the electron-donating hyperconjugation effect, which increases the electron cloud density on the hydroxyl group and benzene ring of phenol. Nitro group has the electron-withdrawing inductive effect and electron-withdrawing conjugation

effect, which reduces the electron cloud density on the OH group and benzene ring of phenol. As such, these three substrates were selected to observe the effect of electron density upon the reactivity of phenol in these methylation reactions, and the availability of HSAB theory in acidic DMC chemistry thus can be verified.



3-Nitrophenol Phenol *m*-Cresol

Fig. 4.2 The phenols investigated in this study

Table 4.2 Conversion and selectivity of the sulphuric acid promoted carboxymethylation reaction between various alcohols and DMC[a]

Entry	ROH	Catalytic H_2SO_4		Stoichiometric H_2SO_4	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	1-Butanol	94±2	>99	>99	>99
2	2-Butanol	52±4	>99	>99	0[c]
3	*tert*-Butanol	0	0	0	0
4	1-Octanol	>99	>99	>99	>99
5	2-Octanol	41±3	>99	>99	0[c]
6	3-Nitrophenol	0	0	0	0
7	Phenol	0	0	0	0
8	*m*-Cresol	0	0	16±3	10[d]

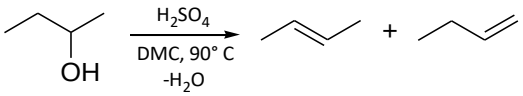
[a] Reaction conditions: ROH/DMC/H_2SO_4 = 6.00 mmol : 240.00 mmol : 0.30/6.00 mmol; *T* = 90 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methyl carbonates. [c] Selectivity >99% towards dehydration products. [d] Selectivity 90% towards the methylation product.

The desired carboxymethylation products of 3-nitrophenol, phenol and *m*-cresol were not produced with either catalytic or stoichiometric amount of PTSA (entry 6-8, Table 4.1). The results highlighted that despite the introduction of electron-donating (-CH_3) or electron-withdrawing (-NO_2) group substitution on the aromatic ring of phenol, the carboxymethylation

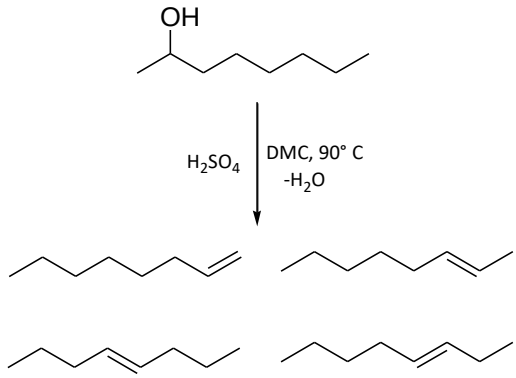
reaction did not occur between DMC and phenolic derivatives in the presence of PTSA.

Sulphuric acid was selected as a representative inorganic acid. Sulphuric acid is a widely available inorganic acid that will provide a cost-effective alternative to base-catalysed DMC chemistry. In this research, when catalytic amount of sulphuric acid is employed, selectivity (towards methyl carbonate) of reactions with primary and secondary alcohols is quantitative (>99%), with good conversions for primary alcohols (entry 1 and 4, Table 4.2), but medium conversion (40%-55%) for secondary alcohols (entry 2 and 5, Table 4.2).

In the presence of stoichiometric sulphuric acid, the conversion of both primary and secondary alcohols becomes quantitative (entry 1, 2, 4 and 5, Table 4.2). With regard to primary alcohols, selectivity is exclusively towards carboxymethylation, whereas, for secondary alcohols 2-butanol and 2-octanol only dehydration to the corresponding alkenes is observed. Scheme 4.10 and Scheme 4.11 demonstrate the dehydration process of 2-butanol and 2-octanol in DMC and stoichiometric sulphuric acid at DMC reflux temperature, respectively. During the dehydration process, the double bond shift also exhibits with various butene and octene isomers produced, consisting of different E/Z configurations.



Scheme 4.10 The dehydration of 2-butanol in DMC promoted by stoichiometric H_2SO_4 at 90 °C



Scheme 4.11 The dehydration of 2-octanol in DMC promoted by stoichiometric H_2SO_4 at 90 °C

The reason why 2-butanol and 2-octanol proceeds *via* dehydration rather than carboxymethylation in the presence of stoichiometric sulphuric acid and DMC is due to the stability of carbonium ion intermediate of secondary alcohols being higher than that of primary alcohols during acid-catalysed dehydration (Fig. 4.3). To be specific, secondary carbonium ions have more electron donating groups than primary carbonium ions resulted in lower activation energy needed for formation. This therefore results in carboxymethylation for primary alcohol, while secondary alcohol carries out a dehydration reaction *via* the E1 mechanism.

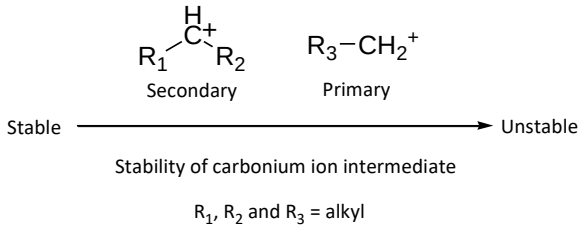
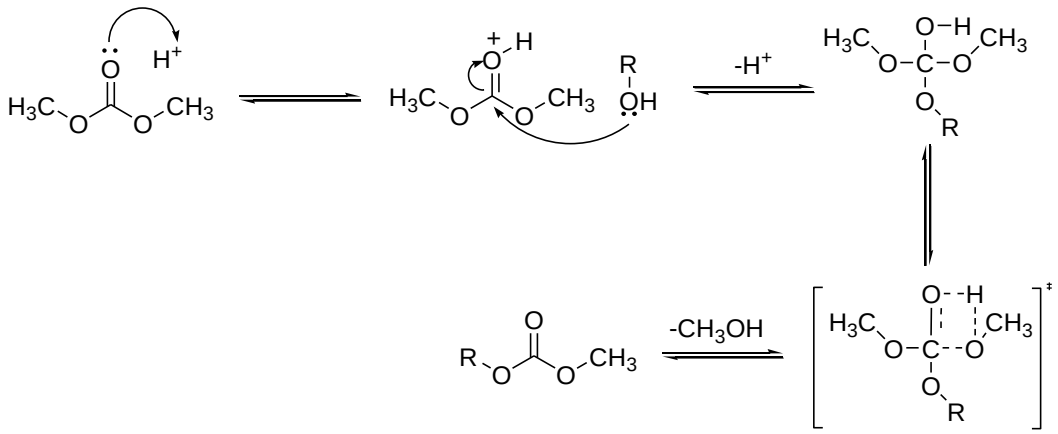


Fig. 4.3 The stability of primary and secondary carbonium ion intermediate

Under such conditions, stoichiometric sulphuric acid has been demonstrated as an excellent reagent for the dehydration of secondary alcohols. This is important since many dehydration reactions for secondary aliphatic alcohols occur at higher temperatures. Specifically, dehydration of 2-octanol has been reported using a molybdenum complex at 150 °C,[291] while heterogeneous Al_2O_3-ZrO_2 needed very high temperatures of 280 °C.[292]



Scheme 4.12 The possible mechanism of Brønsted acid catalysed carboxymethylation between DMC and alcohols

Conventional base-catalysed DMC chemistry with hydroxyl functionality proceeds through deprotonation to produce a strong nucleophile before attack upon the carbonyl (carboxymethylation) or methyl (methylation) carbon of the DMC. A possible mechanism of Brønsted acid catalysed carboxymethylation reaction for alcohols is suggested in Scheme 4.12 and is based on the proposed Brønsted acid catalysed transesterification mechanism.[243] Under acidic conditions, the lone pair of the DMC carbonyl is protonated, before nucleophilic attack from the alcohol occurs. After losing a proton, the hemiketal intermediate forms and then eliminates methanol to obtain the carboxymethylation product.

Similar to PTSA, sulphuric acid did not catalyse any reaction between DMC and *tert*-butanol, 3-nitrophenol or phenol under either catalytic or stoichiometric loading. Stoichiometric H_2SO_4 and DMC results in *m*-cresol giving methylation (selectivity 90%) and carboxymethylation products (selectivity 10%), but at very low conversion (16%) (entry 8, Table 4.2).

4.2.1.2 Carboxymethylation products obtained by the catalysis of Lewis acid

Aluminium chloride and iron (III) chloride were selected as widely available and low-cost Lewis acids to research the effects of such catalysts in DMC chemistry. Table 4.3 gives the conversion and selectivity of different alcohols towards carboxymethylation under different catalytic loading of $AlCl_3$.

Selectivity and conversion of primary alcohols are quantitative regardless of loading of aluminium chloride or reagents (entry 1 and 4, Table 4.3). With regard to secondary alcohols, selectivity remains high at catalytic loadings, but conversion decreases when 1% equivalent aluminium chloride is employed (entry 2 and 5, Table 4.3). At a stoichiometric loading of $AlCl_3$, conversion and selectivity towards carboxymethylation of 2-butanol remain quantitative, however, with 2-octanol, dehydration to the relevant alkenes occurs (entry 5, Table 4.3) with 49% selectivity.

When reacting phenols with DMC in the presence of aluminium chloride at 0.01 and 0.05 molar equivalents, no reaction occurred. However, at 0.20 equivalents or stoichiometric loading, both

carboxymethylation and methylation are observed (entry 6-8, Table 4.3 and entry 1-3, Table 4.4). At 0.2 equivalents of aluminium chloride, the conversion is moderate to low (50%-10%), but selectivity is high towards carboxymethylation rather than methylation, while increasing to stoichiometric loadings dramatically increases conversion but reduces selectivity for carboxymethylation products (entry 6-8, Table 4.3). However, concerning methylation, employing stoichiometric $AlCl_3$ results in good selectivity towards 3-nitroanisole and anisole, with reasonable selectivity to 3-methylanisole (entry 1-3, Table 4.4).

Table 4.3 Conversion and selectivity of the aluminium chloride promoted carboxymethylation reaction between various alcohols and DMC[a]

Entry	ROH	Conv./Sel.[b](%) (0.01 equivalent)	Conv./Sel.[b](%) (0.05 equivalent)	Conv./Sel.[b](%) (0.20 equivalent)	Conv./Sel.[b](%) (1.00 equivalent)
1	1-Butanol	>99/99	>99/>99	>99/>99	>99/>99
2	2-Butanol	77±4/>99	>99/98	>99/>99	>99/99
3	*tert*-Butanol	0/0	0/0	0/0	0/0
4	1-Octanol	99±1/>99	>99/99	>99/>99	>99/>99
5	2-Octanol	8±1/>99	>99/>99	>99/>99	>99/51[c]
6	3-Nitrophenol	0/0	0/0	20±3/76	83±1/29
7	Phenol	0/0	0/0	42±5/94	85±2/33
8	*m*-Cresol	0/0	0/0	14±4/97	90±2/56

[a] Reaction conditions: ROH/DMC = 6.00 mmol : 240.00 mmol; *T* = 90 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methyl carbonates. [c] Selectivity 49% towards dehydration products.

Employing HSAB theory as discussed in Chapter 1 to explain the experimental results, softer nucleophiles prefer to react with the softer methyl carbon (lower positive charge) on the DMC to yield the methylation product, while the harder nucleophilic reagents prefer to react with the harder carbonyl carbon (higher positive charge) of DMC to produce the corresponding carboxymethylation product. Additionally, A base which possesses a more electropositive central atom is softer.[189] Therefore, in this research the order of hardness for the phenols is *m*-cresol >

phenol > 3-nitrophenol based on the electronic effect of the corresponding substituent group on the benzene ring. As such, *m*-cresol should prefer to react with the hard carbon (carbonyl carbon) of DMC to produce the carboxymethylation product, while 3-nitrophenol ought to prefer to react

Table 4.4 Conversion and selectivity of the aluminium chloride promoted methylation reaction between phenols and DMC[a]

Entry	ROH	Catalytic amount (0.20 equivalent) of $AlCl_3$		Stoichiometric amount (1.00 equivalent) of $AlCl_3$	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	3-Nitrophenol	20±3	24	83±1	71
2	Phenol	42±5	6	85±2	67
3	*m*-Cresol	14±4	3	90±2	44

[a] Reaction conditions: ROH/DMC/$AlCl_3$ = 6.00 mmol : 240.00 mmol : 1.20/6.00 mmol; *T* = 90 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methylation products.

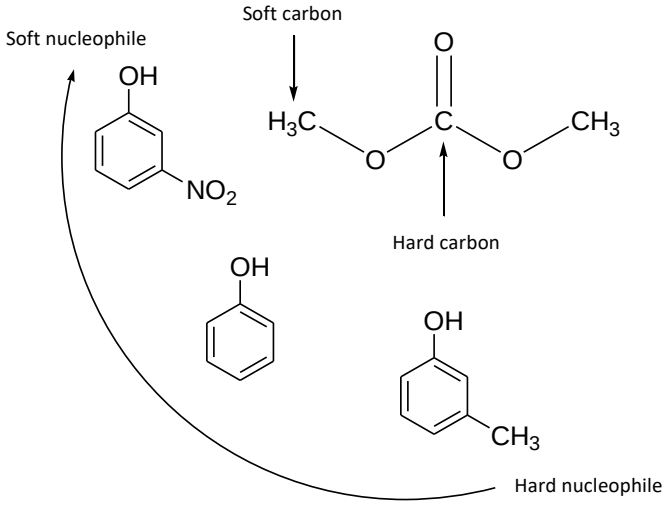


Fig. 4.4 The soft carbon and hard carbon of DMC

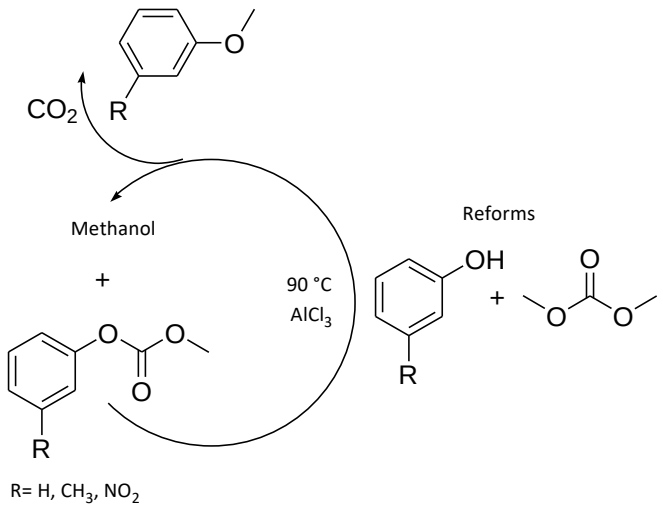
with the soft carbon (methyl carbon) of DMC to yield the methylation product (Fig. 4.4). In Table 4.4, selectivity towards methylation products following this trend. This highlights that reactions between DMC and phenols in the presence of stoichiometric aluminium chloride provides similar methylation results to base-catalysed reactions but with much-improved conversion.[190] However,

when employing 0.2 equivalent of $AlCl_3$, selectivity shifts dramatically towards carboxymethylation for all three reactions regardless of the softness of the nucleophile (entry 6-8, Table 4.3). This is in contrast to base-catalysed reactions.[190]

Table 4.5 Conversion and selectivity of the aluminium chloride promoted carboxymethylation and methylation reactions between phenols and DMC at extended reaction time[a]

Entry	ROH	Conv.[b] (%)	Sel.[b] (%) ROMe	Sel.[b] (%) $ROCO_2Me$
1	3-Nitrophenol	84±3	88	12
2	Phenol	88±1	85	15
3	*m*-Cresol	92±3	62	38

[a] Reaction conditions: ROH/DMC/$AlCl_3$ = 6.00 mmol : 240.00 mmol : 6.00 mmol; *T* = 90 °C; reaction time 60 h. [b] Conversions and selectivity were calculated by ^1H NMR and GC.



R= H, CH_3, NO_2

Fig. 4.5 The reason for the shift of selectivity towards methylation product

To study the impact of extended reaction time at 90 °C, DMC, phenols and stoichiometric aluminium chloride were reacted for 60 h (Table 4.5). In comparison to the 19 h reactions, conversion remains constant (within statistical error) while selectivity towards methylation increases (entry 1-3, Table 4.5). This suggests that initially carboxymethylation of the phenols dominates, but this reaction is reversible (Fig. 4.5). Methylation proceeds much more slowly but is irreversible (Fig. 4.5 and Scheme 4.9) and also leads to the production of methanol, pushing the carboxymethylation equilibrium back to reformation of the phenol. Hence, the longer a

reaction runs, the greater the degree of methylation observed.

Aluminium chloride is not considered to be a green catalyst since it can result in highly acidic and toxic contaminated aqueous wastes,[273,293,294,] and it is also a harmful compound to human respiratory and central nervous systems.[273] For this reason, a second greener Lewis acid, iron (III) chloride was also investigated as a lower toxicity alternative.

Table 4.6 Conversion and selectivity of the iron (III) chloride promoted carboxymethylation reaction between various alcohols and DMC[a]

Entry	ROH	Catalytic $FeCl_3$		Stoichiometric $FeCl_3$	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	1-Butanol	>99	>99	>99	>99
2	2-Butanol	88±2	>99	>99	0[c]
3	*tert*-Butanol	0	0	0	0
4	1-Octanol	>99	>99	>99	>99
5	2-Octanol	74±3	>99	>99	0[c]
6	3-Nitrophenol	9±4	>99	9±3	>99
7	Phenol	0	0	0	0
8	*m*-Cresol	0	0	0	0

[a] Reaction conditions: ROH/DMC/$FeCl_3$ = 6.00 mmol : 240.00 mmol : 0.30/6.00 mmol; *T* = 90 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methyl carbonates. [c] Selectivity >99% towards dehydration products.

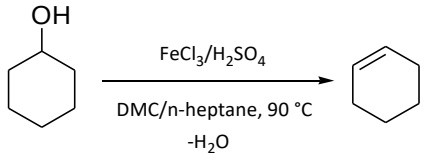
Based on Table 4.6, quantitative conversions and selectivity of primary alcohols are obtained under both catalytic and stoichiometric conditions (entry 1 and 4, Table 4.6). Good conversion and high selectivity of secondary alcohols are also attained under catalytic loading (entry 2 and 5, Table 4.6). Reactions of secondary alcohols and DMC in the presence of stoichiometric iron (III) chloride results in a quantitative conversion, but with selectivity exclusively towards dehydration to the alkenes (entry 2 and 5, Table 4.6), the same as observed with stoichiometric sulphuric acid. Although sulphuric acid is a well-known dehydrating agent,[295] stoichiometric iron (III) chloride is not normally considered in the same way.

When producing alkyl carbonates through Brønsted or Lewis acid catalysed reactions between an aliphatic alcohol and DMC, the ease of attack follows the trend: primary alcohol > short chain secondary alcohol > long chain secondary alcohol > tertiary alcohol. This is consistent with previously published base-catalysed research.[296] Regardless of the system utilised, no acid-catalysed the reaction conducted between a tertiary alcohol (*tert*-butanol) and DMC.

Despite no evidence of a reaction occurring between DMC and phenol/*m*-cresol under either catalytic or stoichiometric $FeCl_3$ (entry 7 and 8, Table 4.6), 3-nitrophenol shows low conversion (9%) to methyl 3-nitrophenyl carbonate with >99% selectivity (entry 6, Table 4.6). At a stoichiometric loading of sulphuric acid, the hardest nucleophile *m*-cresol has high selectivity towards its methylation product while stoichiometric iron (III) chloride and the softest nucleophile 3-nitrophenol results in near quantitative selectivity towards its carboxymethylation product. In both cases, this does not follow HSAB theory.

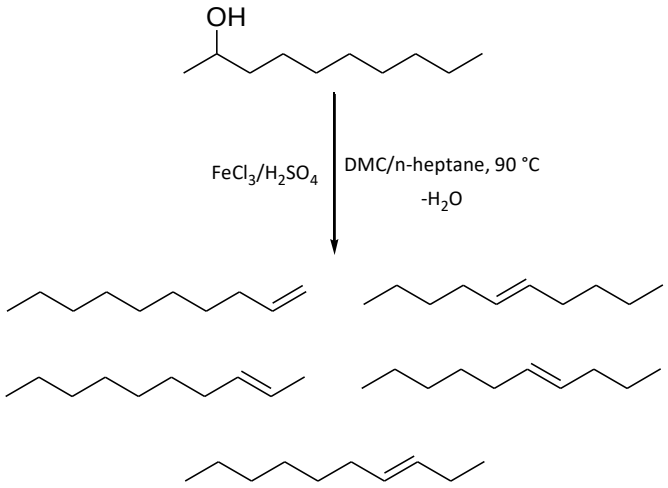
4.2.1.3 Effect of solvents on the acid-catalysed dehydration of alcohols

As mentioned in Section 4.2.1.1 and Section 4.2.1.2, stoichiometric sulphuric acid and iron (III) chloride both exhibit the excellent ability to dehydrate secondary alcohols to their respective alkenes with DMC as the reaction medium. In order to further investigate their capacity to dehydrate other secondary aliphatic alcohols (ring and linear chain) as well as the effect of the solvent, cyclohexanol and 2-decanol were selected as representative substrates for the reaction underwent in either DMC or conventional organic solvent n-heptane (Scheme 4.13 and Scheme 4.14).



Scheme 4.13 The dehydration of cyclohexanol in DMC/n-heptane promoted by stoichiometric $FeCl_3$ or H_2SO_4 at 90 °C

Cyclohexanol was selected because it is one of the widely used alicyclic alcohols in the organic chemistry. 2-Decanol was chosen since it has a longer carbon chain than 2-butanol and 2-octanol, which enables the comprehensive investigation of linear aliphatic secondary alcohols in dehydration reaction in this chapter. n-Heptane was chosen as a comparable solvent as reactions could also occur at 90 °C while still solubilising the substrates.



Scheme 4.14 The dehydration of 2-decanol in DMC/n-heptane promoted by stoichiometric $FeCl_3$ or H_2SO_4 at 90 °C

Table 4.7 indicates the results for the dehydration of cyclohexanol in the presence of stoichiometric $FeCl_3$ or H_2SO_4. When using iron (III) chloride as a catalyst, in DMC, conversion of cyclohexanol is quantitative, although the major product is methoxycyclohexane, with little dehydration to cyclohexene found (entry 1, Table 4.7). The synthesis of methoxycyclohexane is shown in Scheme 4.15. In heptane, cyclohexene is the only product but with low conversion (35%) (entry 2, Table 4.7). It is evident that under such conditions, dehydration of cyclohexanol in either DMC or n-heptane is difficult. Significantly, the methylation of an aliphatic, cyclic alcohol at low temperature with no evidence of carboxymethylation product is observed. These reactions commonly require the utilisation of highly toxic methylating reagents such as iodomethane or dimethyl sulfide,[297,298] or elevated reaction temperature (>170 °C) in the presence of DMC.[299] As such, iron (III) chloride in DMC at 90 °C can be employed as a green system for the methylation of cyclohexanol to substitute these undesired reagents or reaction conditions. Base-catalysed

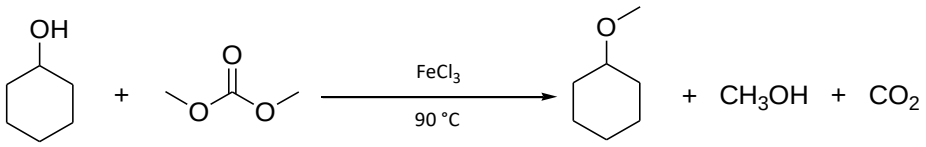
reactions under similar conditions with cyclohexanol as the reactant generally gave poor conversion unless in the presence of an ionic liquid, although selectivity was towards the carboxymethylation product.[300] This highlights that Lewis acid has a very different performance in comparison with base catalysts for alicyclic alcohols in DMC chemistry.

Table 4.7 Conversion and selectivity of the iron (III) chloride or sulphuric acid promoted reaction for cyclohexanol in DMC or n-heptane[a]

Entry	Solvent	Stoichiometric $FeCl_3$[b]	Stoichiometric H_2SO_4[b]
		Conv./Sel.[c]/Sel.[d]	Conv./Sel.[c]/Sel.[d]
1	DMC	>99/12/88	9±3/99/0
2	n-heptane	35±4/99/0	6±2/99/0

[a] Reaction conditions: cyclohexanol/solvent/$FeCl_3$ or H_2SO_4 = 6.00 mmol : 240.00 mmol : 6.00 mmol; *T* = 90 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^1H NMR and GC. [c] Selectivity towards cyclohexene. [d] Selectivity towards methoxycyclohexane.

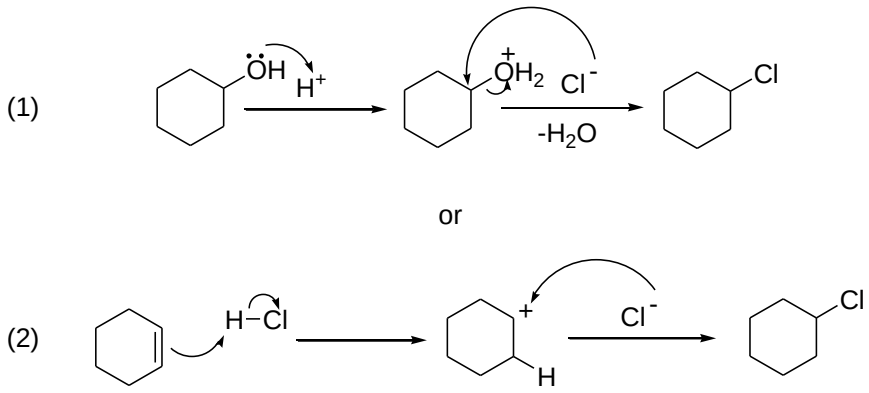
Stoichiometric H_2SO_4 exclusively gives the dehydrated alkenes in both solvents, but with a low conversion (entry 1 and 2, Table 4.7).



Scheme 4.15 The methylation of cyclohexanol with DMC and stoichiometric $FeCl_3$ at 90 °C

Although other experiments in this thesis have not used molecular sieves as the dehydrating agent, interestingly, when molecular sieves are not used during the reaction of cyclohexanol with stoichiometric iron (III) chloride in n-heptane at 90 °C, chlorocyclohexane is produced. In this case, after the reaction, quantitative conversion of cyclohexanol is obtained with selectivity 20% towards cyclohexene and 80% towards chlorocyclohexane. However, none of the chlorocyclohexane is synthesised when molecular sieves are added to the same system (entry 2, Table 4.7). Borukhova *et al*. reported they chlorinated cyclohexanol to yield chlorocyclohexane by hydrochloric acid.[301] As such, chlorocyclohexane may be generated from cyclohexanol and

hydrochloric acid released by the reaction of iron (III) chloride and water (Scheme 4.16).[302] Therefore, molecular sieves are necessary for the dehydration reactions in order to remove water and limit the synthesis to the chlorinated by-products.



Scheme 4.16 The formation process of chlorocyclohexane

In the case of 2-decanol either acid reagent in DMC results in the quantitative conversion with selectivity exclusively towards a mixture of different decene isomers (entry 1, Table 4.8). When n-heptane is used as the solvent, selectivity remains the same but with a lower conversion (entry 2, Table 4.8).

Table 4.8 Conversion and selectivity of iron (III) chloride or sulphuric acid promoted dehydration reaction for 2-decanol in DMC or n-heptane[a]

Entry	Solvent	Stoichiometric $FeCl_3$		Stoichiometric H_2SO_4	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	DMC	>99	99	>99	99
2	n-Heptane	80±4	99	90±3	99

[a] Reaction conditions: 2-decanol/solvent/reagent = 6.00 mmol : 240.00 mmol : 6.00 mmol; *T* = 90 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards decene.

This research highlights several main advantages of acid-catalysed DMC chemistry including, expanding the range of substrates which can be reacted with DMC in the presence of acids. The acid catalysts used in this research have comparable or even lower market prices than the

common base catalysts used in existing DMC chemistry.[290] This is especially true in the case of sulphuric acid which is a widely available, inexpensive inorganic catalyst that provides a cost effective alternative to base-catalysed DMC processes.

Many strong bases traditionally used as catalysts for DMC chemistry, such as sodium methoxide and potassium *tert*-butoxide, are sensitive to water and hazardous to handle. They are also synthesised through energy intensive electrolysis procedure for the production of the corresponding alkali metals.[303] In comparison, all acidic catalysts investigated in this research have low handling and storage hazards, which is one of the fundamental principles of green chemistry. PTSA and sulphuric acid have lower energy requirements for production and are not significantly affected by water.

4.2.2 Acid-catalysed DMC chemistry at 160 °C

4.2.2.1 Brønsted acid promoted DMC chemistry at 160 °C

With base catalysis, carboxymethylation generally occurs at 90 °C while methylation takes place around 160 °C.[163] As such, after investigating acid-catalysed DMC chemistry at 90 °C, it is important to discuss the same substrates and catalysts conducting reactions at an elevated temperature of 160 °C. Since H_2SO_4 is highly corrosive to the high-pressure reactor as well as the rubber o-rings used to seal the vessel, it was not selected as a catalyst in this study. PTSA was chosen as the only Brønsted acid for research of DMC reaction at high temperature.

Table 4.9 shows PTSA catalysed DMC chemistry at 160 °C. Results for primary alcohols under both catalytic and stoichiometric PTSA are identical to those at 90 °C, showing quantitative conversion and selectivity towards carboxymethylation products (entry 1 and 4, Table 4.9). However, for secondary alcohols in the presence of catalytic PTSA, selectivity remains quantitative, while conversion improves to around 80% (entry 2 and 5, Table 4.9) in comparison with the reaction conducted at 90 °C. This result indicates that higher temperature can promote the conversion of secondary alcohols towards carboxymethylation reaction. At 160 °C, stoichiometric PTSA also offers a quantitative conversion and selectivity for secondary alcohols.

Concerning *tert*-butanol and phenols, no reaction occurs under these conditions.

Table 4.9 Conversion and selectivity of the PTSA promoted carboxymethylation reaction between various alcohols and DMC at high temperature[a]

Entry	ROH	Catalytic PTSA		Stoichiometric PTSA	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	1-Butanol	>99	>99	>99	>99
2	2-Butanol	76±4	>99	>99	>99
3	*tert*-Butanol	0	0	0	0
4	1-Octanol	>99	>99	>99	>99
5	2-Octanol	80±3	>99	>99	>99
6	3-Nitrophenol	0	0	0	0
7	Phenol	0	0	0	0
8	*m*-Cresol	0	0	0	0

[a] Reaction conditions: ROH/DMC/PTSA = 6.00 mmol : 240.00 mmol : 0.30/6.00 mmol; *T* = 160 °C; reaction time 19 h.

[b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methyl carbonates.

4.2.2.2 Lewis acid promoted DMC chemistry at 160 °C

In order to be consistent with the previous experiments of DMC chemistry at 90 °C, aluminium chloride and iron (III) chloride were both selected as the Lewis acids in this section.

Based on Table 4.10, in comparison with the same experiments conducted at 90 °C, for primary alcohols, the conversion and selectivity remain quantitative at high temperature under any amount of aluminium chloride (entry 1 and 4, Table 4.10). With respect to the short chain aliphatic alcohols, 2-butanol exhibits the high conversion and selectivity which is consistent with low-temperature experiments (entry 2, Table 4.10). However, 2-octanol obtains >99% of conversion and selectivity in both catalytic or stoichiometric $AlCl_3$ (entry 5, Table 4.10), while the selectivity of 2-octanol is only 51% for the carboxymethylation product and 49% for the dehydration products at 90 °C (entry 5, Table 4.3). This result demonstrates that high

temperature can increase the selectivity towards carboxymethylation products. No reaction was observed for *tert*-Butanol at elevated temperatures (entry 3, Table 4.10).

Table 4.10 Conversion and selectivity of the aluminium chloride promoted carboxymethylation reaction between various alcohols and DMC at high temperature[a]

Entry	ROH	Catalytic $AlCl_3$		Stoichiometric $AlCl_3$	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	1-Butanol	>99	>99	>99	>99
2	2-Butanol	>99	>99	>99	>99
3	*tert*-Butanol	0	0	0	0
4	1-Octanol	>99	>99	>99	>99
5	2-Octanol	>99	>99	>99	>99
6	3-Nitrophenol	0	0	85±1	25[c]
7	Phenol	0	0	88±1	27[d]
8	*m*-Cresol	0	0	92±2	52[e]

[a] Reaction conditions: ROH/DMC/$AlCl_3$ = 6.00 mmol : 240.00 mmol : 0.30/6.00 mmol; *T* = 160 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methyl carbonates. [c] Selectivity (75%) towards methylation product. [d] Selectivity (73%) towards methylation product. [e] Selectivity (48%) towards methylation product.

For phenol and its derivatives, under catalytic aluminium chloride (0.05 equivalent), no reaction was observed at 160 °C (entry 6-8, Table 4.10). When stoichiometric $AlCl_3$ is applied, carboxymethylation and methylation reactions both occur for all of the phenols investigated in this study. Results are extensively the same to those observed 90 °C (entry 6-8, Table 4.10). This result indicates that increasing temperature has little effect on the methylation of phenols.

At high temperature and in the presence of catalytic or stoichiometric $FeCl_3$, for primary alcohol, the results are the same as the experimental data obtained at 90 °C with >99% conversion and selectivity (entry 1 and 4, Table 4.11). Regarding secondary alcohols, when stoichiometric iron (III) chloride is applied, the results are consistent with the experiments at 90 °C with quantitative conversion and selectivity towards dehydration products. Nevertheless, at elevated temperature

under catalytic iron (III) chloride, conversion of secondary alcohols is quantitative, while remains selectivity >99% towards carboxymethylation products (entry 2 and 5, Table 4.11).

Table 4.11 Conversion and selectivity of the iron (III) chloride promoted carboxymethylation reaction between various alcohols and DMC at high temperature[a]

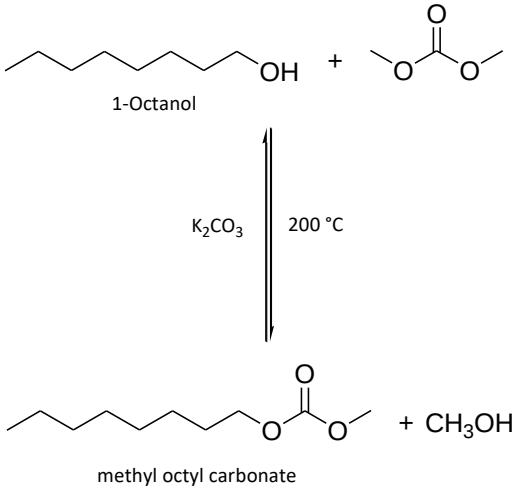
Entry	ROH	Catalytic $FeCl_3$		Stoichiometric $FeCl_3$	
		Conv.[b] (%)	Sel.[b] (%)	Conv.[b] (%)	Sel.[b] (%)
1	1-Butanol	>99	>99	>99	>99
2	2-Butanol	>99	>99	>99	0[c]
3	*tert*-Butanol	0	0	0	0
4	1-Octanol	>99	>99	>99	>99
5	2-Octanol	>99	>99	>99	0[c]
6	3-Nitrophenol	12±1	>99	13±1	>99
7	Phenol	0	0	0	0
8	*m*-Cresol	0	0	0	0

[a] Reaction conditions: ROH/DMC/$FeCl_3$ = 6.00 mmol : 240.00 mmol: 0.30/6.00 mmol; *T* = 160 °C; reaction time 19 h. [b] Conversions and selectivity were calculated by ^{1}H NMR and GC; selectivity towards methyl carbonates. [c] Selectivity >99% towards dehydration products.

Similar to the study of low temperature, 3-nitrophenol obtains high selectivity towards carboxymethylation products with very low conversion at 160 °C, no matter which equivalent of $FeCl_3$ was used (entry 6, Table 4.11). *tert*-Butanol, phenol and *m*-cresol did not react with DMC at 160 °C in the presence of catalytic or stoichiometric iron (III) chloride (entry 3, 7 and 8, Table 4.11).

Significantly, these aliphatic alcohols investigated in this research did not conduct methylation reaction with DMC in the presence of acid catalysts. Tundo *et al*. used potassium carbonate, a typical base catalyst employed in DMC chemistry, to promoted the reaction between DMC and 1-octanol at 200 °C, but methyl octyl carbonate was the exclusive product rather than methyl octyl ether (Scheme 4.17).[191] Only when basic alumina or hydrotalcite KW 2000 were utilised, the methyl octyl ether became the main product.[191] Therefore, these acid catalysts investigated

in this research are comparable to the potassium carbonate for the methylation reaction of aliphatic alcohols. According to the HSAB theory, it is suggested that the aliphatic alcohol is a hard species, which only attacks the carbonyl carbon of DMC to yield the carboxymethylation product regardless of the temperature.[190] The acid-catalysed DMC chemistry may also follow this rule based on these experimental results observed.



Scheme 4.17 The reaction between DMC and 1-octanol promoted by potassium carbonate at 200 °C

Strangely, in Chapter 2 PTSA has a good performance for the methylation reaction between acetoin and DMC at 160 °C. It is speculated that the nature of the nucleophile (soft vs. hard) and the effect of substituent groups (electron-withdrawing or donating) have a dramatic effect on whether the reaction occurs.

4.2.3 Control experiments for all the substrates

For the purpose of the investigation, with regard to every substrate and solvent, control reactions in the absence of any catalyst were also attempted. In each case, negligible conversion of any alcohol or phenol was observed. Therefore, the catalysts play a vital role to reduce the reaction activation energy for the transition state between alcohols/phenols and DMC.

4.3 Conclusion

In summary, this research explored using acids as catalyst or reagents in the presence of alcohols/phenols and DMC as a new field of dialkyl carbonate green chemistry. In comparison with the base, acid catalysts have many advantages such as lower market price, lower hazard, lower production energy needed. Moreover, introducing acid may increase the substrates available and enable larger range of catalysts in DMC chemistry.

At 90 °C, Brønsted and Lewis acids both have promoted carboxymethylation of alcohols with quantitative or near quantitative conversion and selectivity. Methylation or carboxymethylation of phenols is achieved with improved conversion and tunable selectivity in comparison to base-catalysed reactions. Of note is the high activity of aluminium chloride even at low loadings suggesting that greener reusable, heterogeneous Al catalysts may be practical and would be the subject of further work. Stoichiometric iron (III) chloride or sulphuric acid results in dehydration of secondary alcohols, with better results in DMC than in n-heptane. Overall, the system of $FeCl_3$ and DMC has the potential for application to substrates that have previously been difficult to dehydrate. Additionally, $FeCl_3$ and DMC have been found to be a good green methylation system for cyclohexanol at 90 °C. Meanwhile, molecular sieves are indispensable to the reaction and remove water from the system. This inhibits the chlorination of the product.

At 160 °C, the conversion and selectivity (towards carboxymethylation product) of secondary aliphatic alcohol improved effectively, but none of any methylation product of alcohols was observed. *tert*-Butanol did not conduct any reaction in the presence of acid catalysts. The control experiment evidences that catalysts play a vital role on the DMC mediated synthesis.

Chapter 5 Experimental

5.1 Chemicals

Acetoin ≥96%, dimethyl carbonate 99%, *p*-toluenesulfonic acid monohydrate 98.5%, 4-methoxyacetophenone 99%, anhydrous anisole 99.7%, acetic anhydride ≥99%, anhydrous acetonitrile 99.8%, anhydrous cyclohexane 99.5%, anhydrous diethyl ether ≥99%, anhydrous propylene carbonate 99.7%, iron (III) chloride 97%, anhydrous ethyl acetate 99.8%, anhydrous magnesium sulphate 99.5%, methanol 99.9%, dichloromethane 99.8%, acetone 99.9%, chloroform-d ($CDCl_3$, 99.8% D), Nile red ≥98%, 4-nitroaniline ≥99%, chloroform 99.9%, DL-1,2-isopropylideneglycerol (solketal) 98%, anhydrous ytterbium(III) chloride (99.9%), 3-buten-2-one 99%, tetradecane analytical standard, chlorocyclohexane 99%, 2,3-dimethyl-1,3-butadiene 98%, aluminium oxide (activated, acidic, Brockmann I), anhydrous sodium acetate >99%, aluminium oxide (activated, basic, Brockmann I), hydrotalcite (synthetic), 1-butanol 99.8%, 2-butanol 99%, *tert*-butanol 99%, 1-octanol 99%, 2-decanol 98%, phenol 99%, 3-nitrophenol 99%, *m*-cresol 99%, cyclohexanol 99%, aluminium chloride 99%, 3-nitroanisole 99%, cyclohexene 99.0%, silver (I) oxide 99%, iodomethane 99.5%, toluene 99.9% and dimethyl sulfoxide 99.9% were purchased from Sigma-Aldrich.

(±)-2-Octanol 97% was purchased from Acros Organics. 4 Å molecular sieves, 3-methylanisole 99% and methyl phenyl carbonate 97% were purchased from Alfa Aesar. Anhydrous potassium carbonate, anhydrous sodium carbonate (laboratory reagent grade), sodium hydrogen carbonate (analytical reagent grade), sodium hydroxide-pellets (analytical reagent grade), potassium hydroxide (analytical reagent grade), sulphuric acid > 95% and n-heptane (HPLC grade) were purchased from Fisher Scientific. *N,N*-diethyl-4-nitroaniline was purchased from VWR. Ames MPF 98/100 kits, 2-nitrofluorene and 4-nitroquinoline-*N*-oxide were purchased from Xenometrix. TA98 and TA100 were stored at -70 °C. QUANTOFIX® Peroxide 100 was purchased from Macherey-Nagel.

5.2 General analytical and characterisation techniques

5.2.1 GC analysis

Gas chromatography (GC) is a chromatographic technique that is used to separate and analyse the volatile compounds in organic chemistry.[304] It is typically employed to determine the purity of a compound or the relative content of each component in a mixture. GC is also utilised to characterise unknown compounds. The mobile phase used in GC is the carrier gas, which is normally inert gas such as helium, or low reactive gas such as nitrogen. The stationary phase consists of a microscopic layer of liquid or polymer on a surface of an inert solid support, and it is installed in a tubing (chromatographic column) made from glass or metal. During the GC analysis in the chromatographic column, different samples with various physical and chemical properties have different interactions with the stationary phase, varying their pass rates in the carrier gas. When compounds exit from the end of the column, they are detected and then converted into an electrical signal which is transferred to the computer system. Retention time is defined as the interval between the injection of the sample into the GC and the recording of the peak maximum of a compound.[304]

In this research, an Agilent 6890N gas chromatograph with a flame ionisation detector (GC-FID) was used in order to analyse the reaction results. The GC-FID possessed a ZB5HT capillary column (30 m × 250 μm × 0.25 μm nominal, max temperature 400 °C) at 20.2 psi constant pressure. The carrier gas used in the GC-FID was helium with flow rate at 2.0 $cm^3 \cdot min^{-1}$ in constant flow mode. The split ratio used was 5:1.

The GC method employed in Chapter 2 was as follows: the initial oven temperature was held at 30 °C for 3 minutes, before increasing by 4 °C per minute to 110 °C, after which the rate rose rapidly to 30 °C per minute up to 300 °C and was maintained at this temperature for a further 1 minute.

The GC method for Chapter 3 and Chapter 4 was as follows: the initial oven temperature was held at 50 °C for 4 minutes. After which the temperature was increased at a rate of 10 °C per minute to 300 °C and maintained at 300 °C for 10 minutes.

The temperature of the injector was set at 300 °C, and the temperature of the flame ionisation detector was held at 340 °C. Each of these GC samples consisted of 30 mg product mixture and 1.5 cm^3 dichloromethane (DCM) or acetone or toluene as GC solvent.

With respect to analysing the conversion, selectivity and yield of the corresponding starting materials and products, the GC calibration curves for different substrates and products were produced based on the equation below, where R_f is the response factor, and IS stands for the GC internal standard:

$$\text{Mass of sample/Mass of IS} = R_f \times (\text{Peak area of sample/Peak area of IS})$$

Some examples of the calibration graph and the corresponding equation are illustrated in Fig. 5.1-5.4 based on tetradecane as IS. GC calibration curves were used to calculate conversion, selectivity and yield during this research.

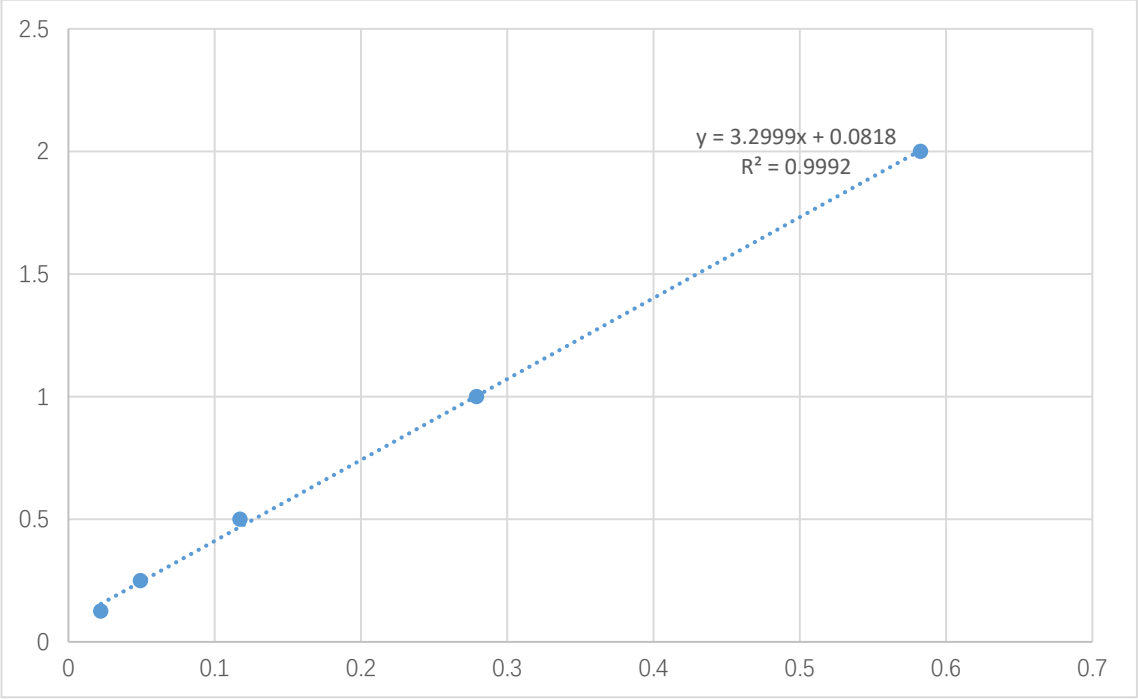


Fig. 5.1 The GC calibration curve of acetoin

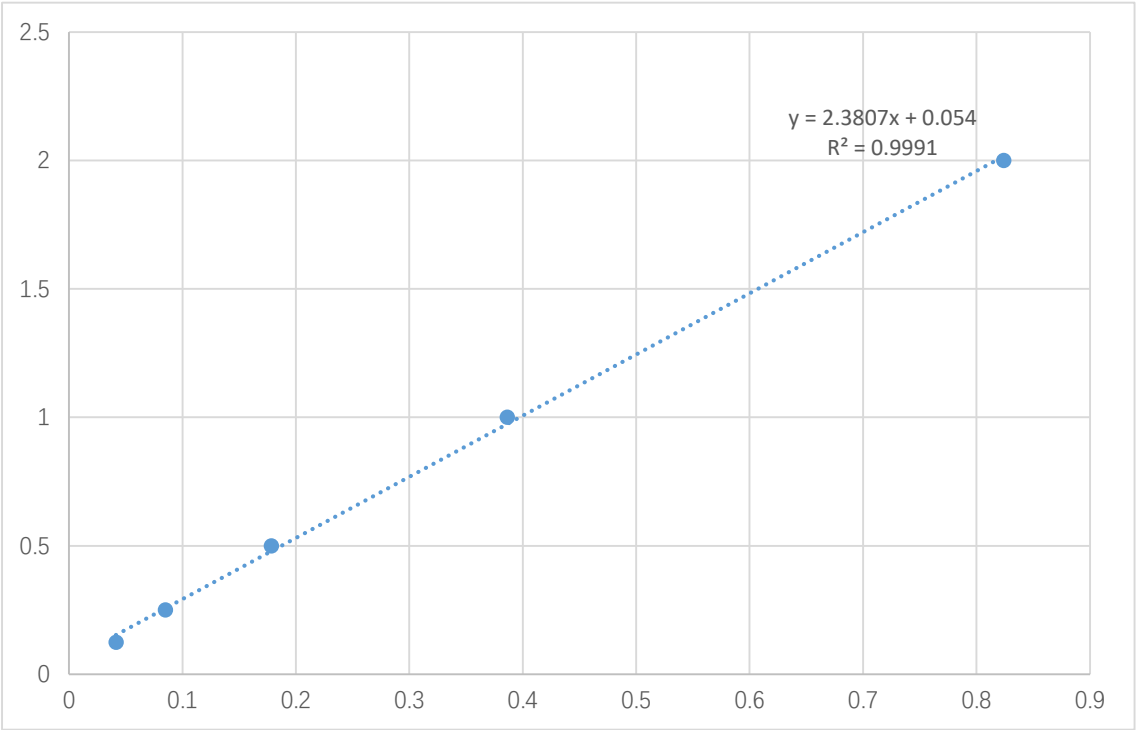


Fig. 5.2 The GC calibration curve of 3-methoxybutan-2-one (MO)

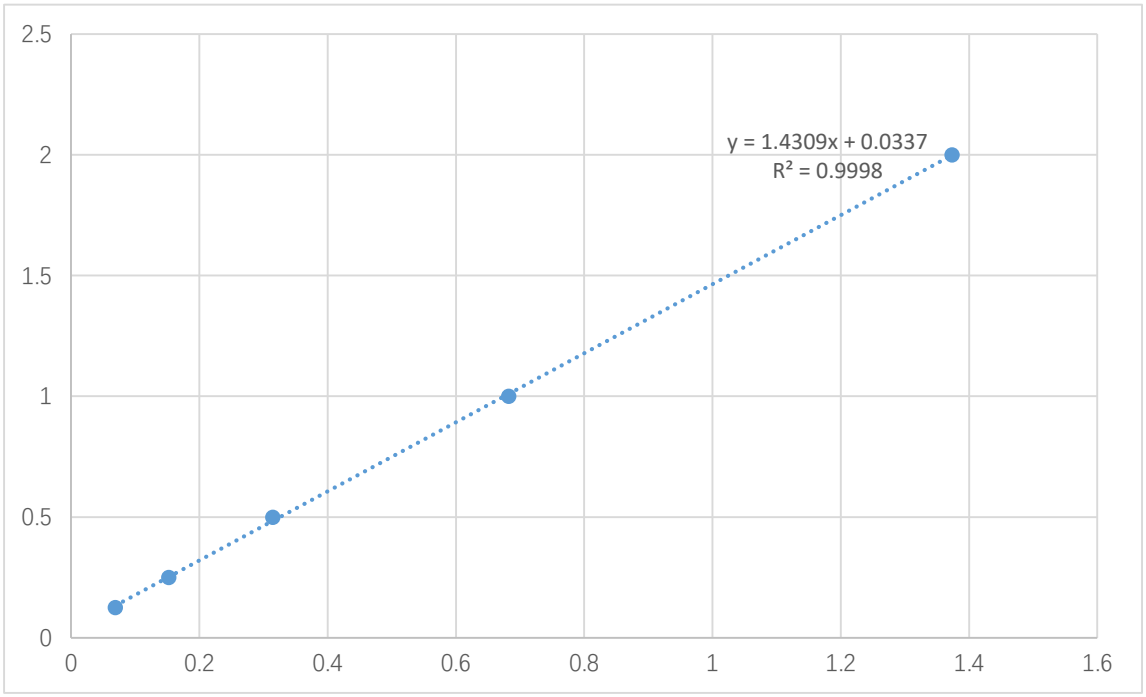


Fig. 5.3 The GC calibration curve of 1-octanol

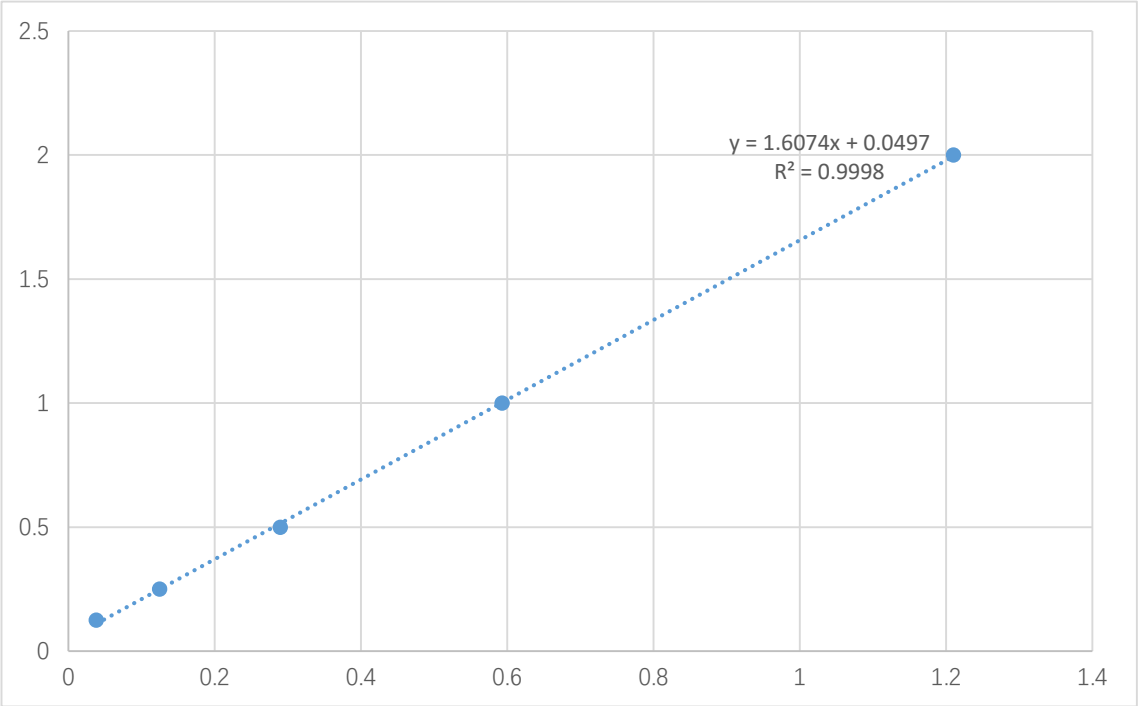


Fig. 5.4 The GC calibration curve of methyl octyl carbonate

5.2.2 GC-MS analysis

Gas chromatography-mass spectrometry (GC-MS) is an analytical technique that combines GC and mass spectrometry (MS) to identify different compounds in a sample. The GC instrument operates as described above. The molecules that flow out of the GC column are captured and analysed by MS. In the MS, all molecules that enter are ionised as they pass through an electron beam. It is commonly known that the ionisation energy of most organic compounds is 7-13 eV. Consequently, due to the high energy of the electron beam in the MS, most molecular ions continue to be rapidly broken down into fragment ions. It is considered that *n* electrons (nonbonding electrons) in organic compounds are more easily lost in the ion source of the MS than π electrons and σ electrons (while π electrons are easier to lose than σ electrons).

During this research, liquid sample analysis was conducted on a Perkin Elmer Clarus 500 GC along with a Clarus 560 S quadrapole mass spectrometer. The instrument was installed with a DB5HT capillary column (30 m × 250 µm × 0.25 µm nominal, max temperature 430 °C). The carrier gas used in the GC-MS was helium with flow rate at 1.0 $cm^3 \cdot min^{-1}$, and the split ratio was 10:1. The injector temperature was held at 330 °C.

For Chapter 2, during the GC analysis, the initial temperature of the oven remained at 30 °C for 3 minutes. Afterwards, the temperature was then ramped with a rate of 4 °C per minute to 110 °C, before the rate rapidly increased to 30 °C per minute up to 300 °C where it was maintained for a further 1 minute.

For Chapter 3 and 4, during the GC analysis, the initial temperature of the oven was maintained at 50 °C for 4 minutes. Afterwards, the temperature was then ramped at a rate of 10 °C per minute to 300 °C and maintained for 10 minutes.

The Clarus 500 quadrupole mass spectrum was conducted in electron ionisation (EI) mode at 70 eV with the source temperature and the quadrupole both at 300 °C. The mass-to-charge ratio (m/z) mass scan was in the range of 40 to 640 m/z. The data was collected by the PerkinElmer enhanced TurboMass (Ver. 5.4.2) chemical software. Some of the compounds were identified by direct comparison of the standard mass spectrum provided in the NIST library (Ver. 2.0). Every GC-MS sample consisted of 30 mg product mixture and 1.5 cm^3 DCM or acetone or toluene as GC-MS solvent.

For gas sample analysis, the MS was a Waters GCT Premier time of flight (TOF) instrument connected to an Agilent 7890 GC system. The column was an Agilent HP-AL/S 30 m, 0.25 mm diameter, 5 um film thickness column. The GC method used was as follows: the start temperature remained at 100 °C for 1 minute. Next, the temperature was ramped at a rate of 5 °C per minute to 135 °C and held for 2 minutes. The data was collected by the Masslynx 4.1 (Ver. 4.1) software. Each of the GC-MS samples consisted of 0.5 cm^3 gas sample from the experiment.

5.2.3 ^{1}H NMR and ^{13}C NMR analysis

The proton nuclear magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectrum results of samples in this work were recorded by a JEOL JNM-ECS 400 MHz spectrometer. During preparation, 100 mg sample from the experiment was dissolved in 1 cm^3 chloroform-d. 16 scans were utilised for ^{1}H NMR analysis, and 256 scans were utilised for ^{13}C NMR analysis. The NMR data was processed and analysed by ACD/NMR Processor Academic Edition software (Ver. 12.01).

5.2.4 FT-IR analysis

A Bruker Vertex 70 Fourier transform infrared spectroscopy (FT-IR) which was fitted with a Specac Golden Gate ATR possessing a diamond top plate analysis window was used for the infrared spectroscopy (IR) analysis in this research. This FT-IR equipment was operated by Opus software (Ver. 5.5). The spectrum was scanned at a range of 4000-600 cm^{-1}. The scan numbers of background and sample were both 64, and the resolution was 2 cm^{-1}.

5.2.5 TGA analysis

Thermogravimetric analysis (TGA) was conducted using a Netsch 409 STA thermal analyser. Samples were mounted in a 3.5 cm^3 ceramic crucible and heated under a flow of nitrogen (50 $cm^3 \cdot min^{-1}$). Before analysis, the oven chamber was evacuated and backfilled twice with nitrogen. Samples were heated from room temperature at 5 °C·min^{-1} to 300 °C.

5.2.6 DSC analysis

The melting point (m.p.) of samples was determined by differential scanning calorimetry (DSC) (TA Instruments, Q2000). During the testing, 8.1 mg sample was hermetically-sealed in Tzero aluminium DSC pan. Thermal runs were conducted under a constant flow of dry nitrogen (50 $cm^3 \cdot min^{-1}$). The dynamic run proceeded at a rate of 5 °C per minute from 25 °C to -90 °C.

5.2.7 UV-vis. spectra analysis

Ultraviolet-visible (UV-vis.) spectra (JENWAY, 6705 UV/Vis. Spectrophotometer) was used to analyse the Kamlet-Taft (KT) parameters of the bio-based solvents. Different dyes, Nile red (NR), 4-nitroaniline (NA) and *N,N*-diethyl-4-nitroaniline (NN), were dissolved in the bio-based solvent in quartz cuvettes at 25 °C to obtain their absorbance maxima wavelengths by UV-vis. spectra with the wavelength range recorded in the range of 400 to 1000 nm.

5.2.8 Ames test

The experiment procedure was based on manufacturer's guidelines as following:[305] TA98 and TA100 were tested at 6 different concentrations (0.16 mg·cm^{-3}, 0.31 mg·cm^{-3}, 0.63 mg·cm^{-3}, 1.25 mg·cm^{-3}, 2.5 mg·cm^{-3}, 5 mg·cm^{-3}) of the bio-based solvent, as well as a positive (concentration of 2 μg·cm^{-3} for 2-nitrofluorene and 0.1 μg·cm^{-3} for 4-nitroquinoline-*N*-oxide) and a negative (dimethyl sulfoxide solvent) control. They grew in a medium including sufficient histidine for 90 minutes to result in approximately twice the cell division. After the exposure, these cultures were diluted in pH indicator medium without histidine and then aliquoted into 48 wells of a 384-well plate. After 48 hours at 37 °C, the wells, including bacteria occurred reversion to His$^+$, changed the colour from purple to yellow since pH of the medium was decreased by the metabolism of the His$^+$ strains. The number of the wells that changed colour were counted manually for each dose. The tests were carried out in triplicate to obtain the average value.

5.3 Chapter 2. 3-Methoxybutan-2-one as a new bio-based solvent

5.3.1 Catalysts screening experiment

5 mmol Acetoin was added to each vessel of a six-point stainless steel pressure reactor followed by 60 mmol dimethyl carbonate (DMC). The relevant catalyst (0.25 mmol) was then added to the pressure reactor which was then tightened and heated to 160 °C with agitation. After 24 h, the reaction was stopped, cooled to room temperature in an ice-bath and then filtered. GC and GC-MS analysis of each reaction mixture was then carried out.

5.3.2 Analysis of the structures of product and by-products after catalysts screening

The structures of products and by-products synthesised from the catalysts screening experiments were analysed. After comparing to the standard samples of methanol, DMC and acetoin, the signals of these compounds in GC were initially identified. 3-Methoxybutan-2-one (MO) (Fig. 5.5) and methyl 3-oxobutan-2-yl carbonate (MC) (Fig. 5.6) are proved to be

synthesised based on the analysis of GC-MS. Scheme 5.1 and Scheme 5.2 respectively show the main cleavage mechanisms, by which these mass fragmentations are formed, of MO and MC in the MS.

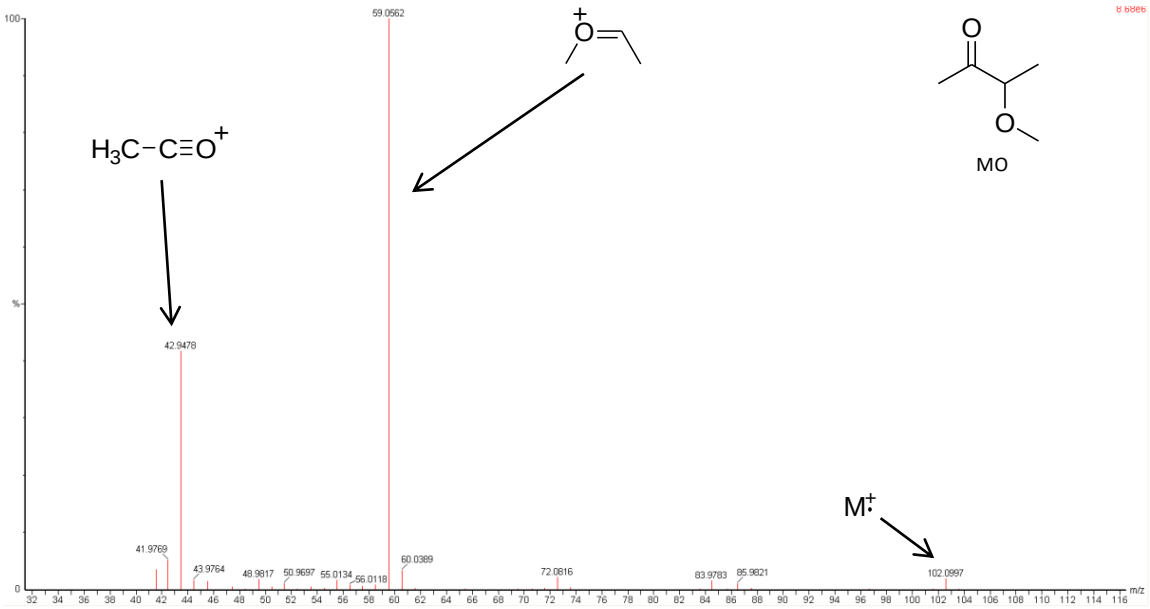
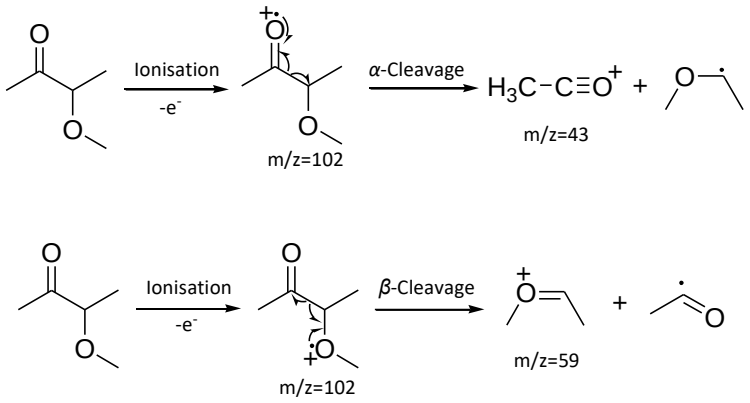
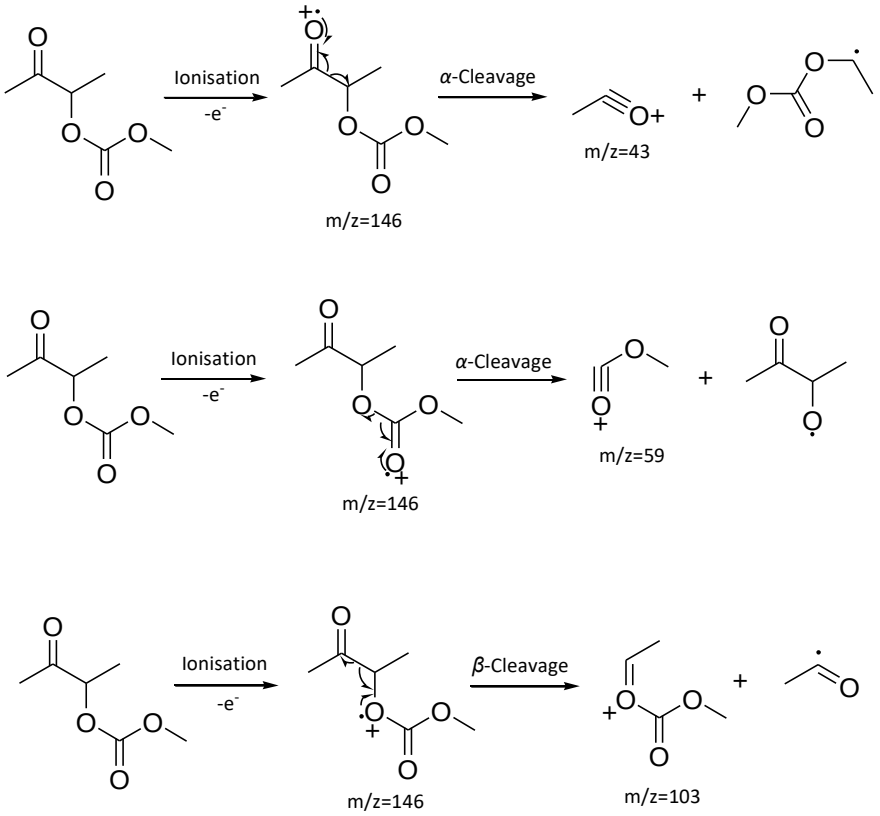


Fig. 5.5 The MS (EI) of MO



Scheme 5.1 The main cleavage mechanism of MO in the MS (EI)



Scheme 5.2 The main cleavage mechanism of MC in the MS (EI)

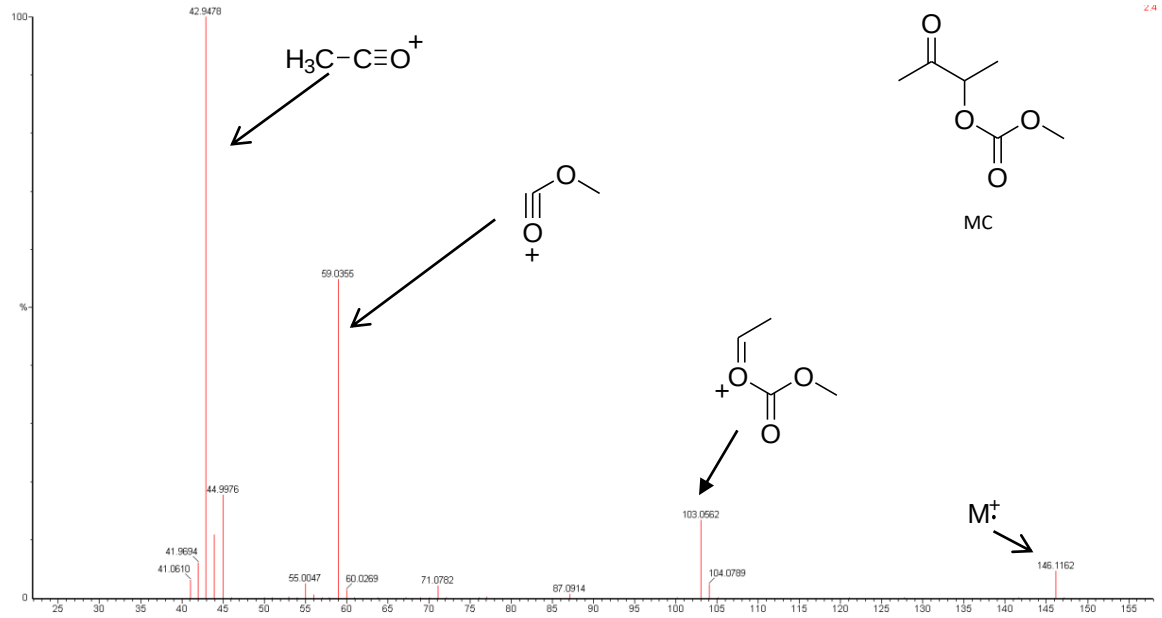
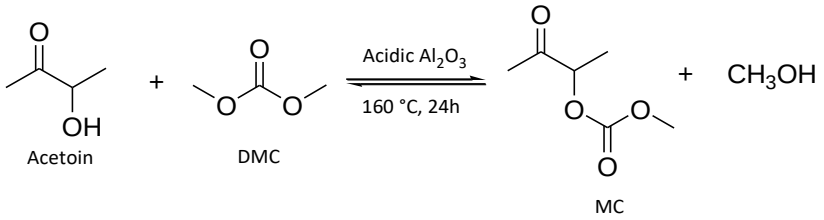


Fig. 5.6 The MS (EI) of MC



Scheme 5.3 The carboxymethylation reaction between acetoin and DMC

Scheme 5.3 gives the equation of synthesis of MC from acetoin and DMC. To investigate the complex by-products for the sodium bicarbonate catalysed reaction of acetoin and DMC (indicated by GC peaks at an approximate retention time of 23 min), following synthesis and filtration, the low boiling point (b.p.) materials were removed by rotary evaporator (Heidolph, VV2000) under 7 mbar at 85 °C. After the distillation, IR of the isolated product mixture was tested, and the results are illustrated in Fig. 5.7 and Table 5.1. The residue includes the compound represented by the main peaks of GC at a retention time of 23 min; therefore, this IR spectrum can provide some critical structural information for the unknown compound.

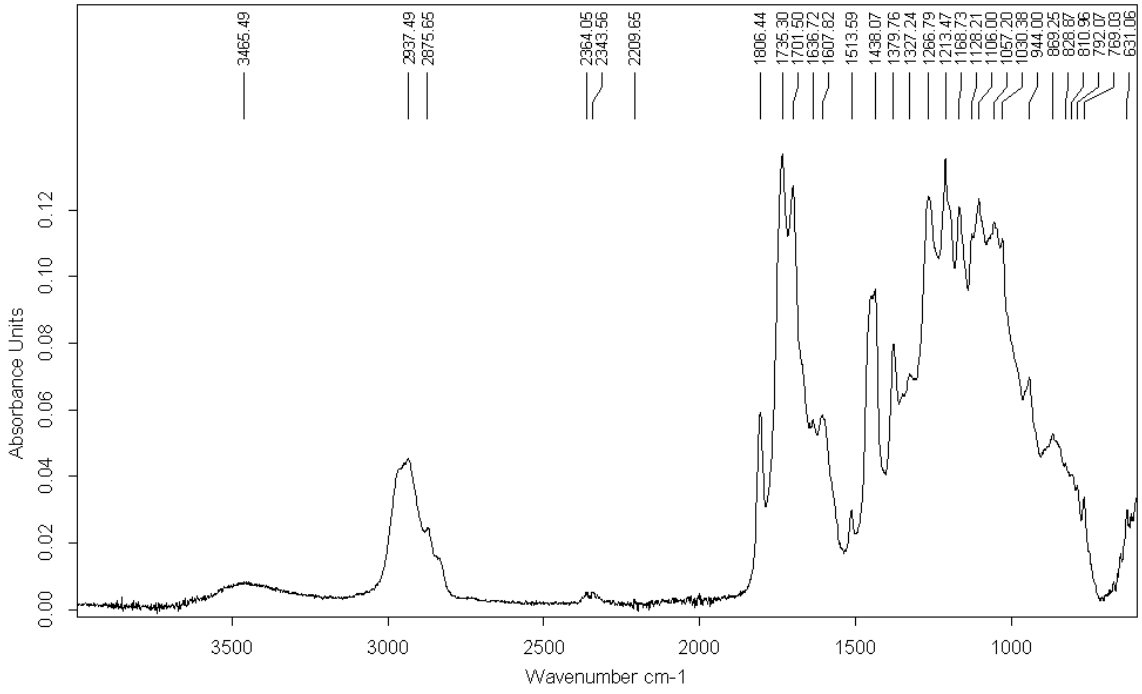


Fig. 5.7 IR of the distillation residue obtained from the synthesis of acetoin and DMC catalysed by sodium bicarbonate

Table 5.1 The IR analysis of the high b.p. by-products

Centre (cm^{-1}) of IR peaks	Assignment
3465	Hydroxyl group single bridge intermolecular O-H bonds stretching band
2937	Alkyl C-H stretching band
1735	Normal saturated ester C=O stretching band
1438	Methyl group C-H asymmetrical deformation band
1380	Methyl group C-H symmetrical deformation band
1267	Secondary alcohol C-O stretching band
1106	Alkyl secondary alcohol O-H bending band
1057	Hydroxyl group C-O stretching band

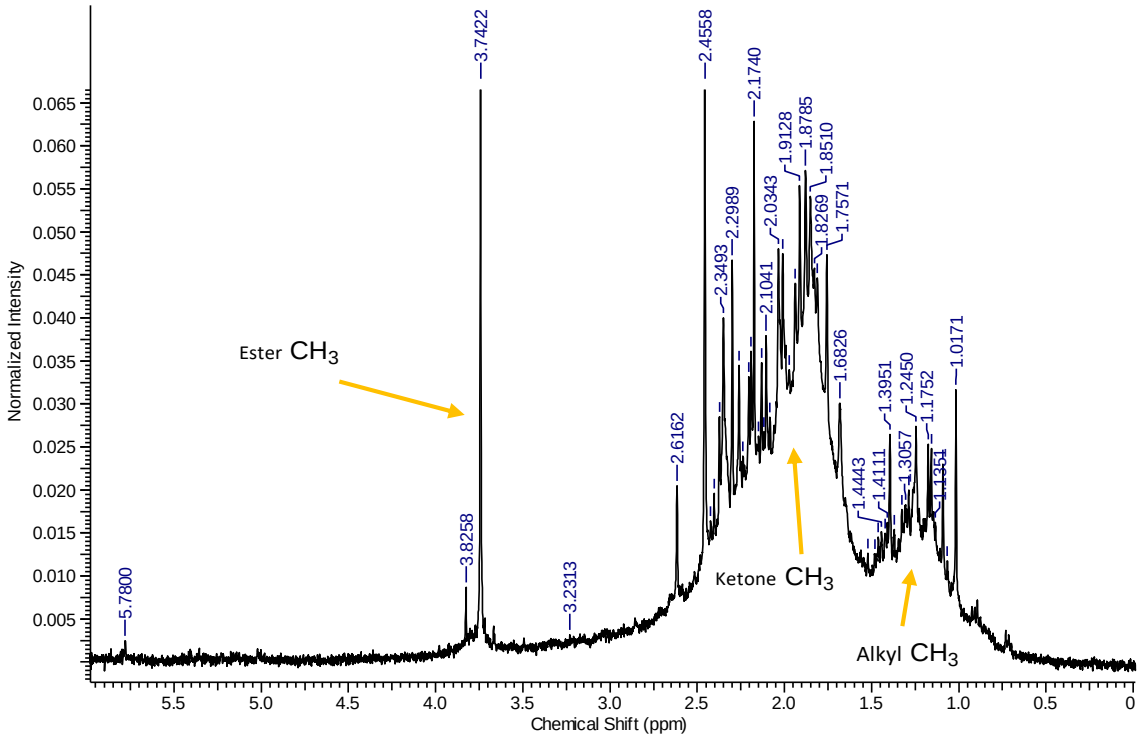


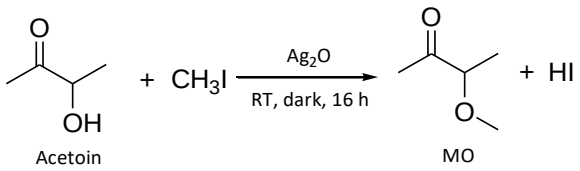
Fig. 5.8 ^{1}H NMR of mixture of high b.p. by-products

Fig. 5.8 exhibits the ^{1}H NMR result of the by-products, which demonstrates that the unknown compounds have intricate structures including methyl groups from various ester, ketone and alkyl chain. This result indicates that complex additional side reactions have occurred. Therefore, IR and ^{1}H NMR both indicated that the high b.p. by-products consist of complicated compounds, and more research is needed in the future to understand the structures of these by-products

and their formation mechanism.

5.3.3 Synthesis of MO from methyl iodide and acetoin catalysed by silver (I) oxide

To confirm the structure before purification process, MO was synthesised from methyl iodide and acetoin in the presence of silver (I) oxide (Scheme 5.4).



Scheme 5.4 The synthesis of MO from acetoin and methyl iodide catalysed by silver (I) oxide

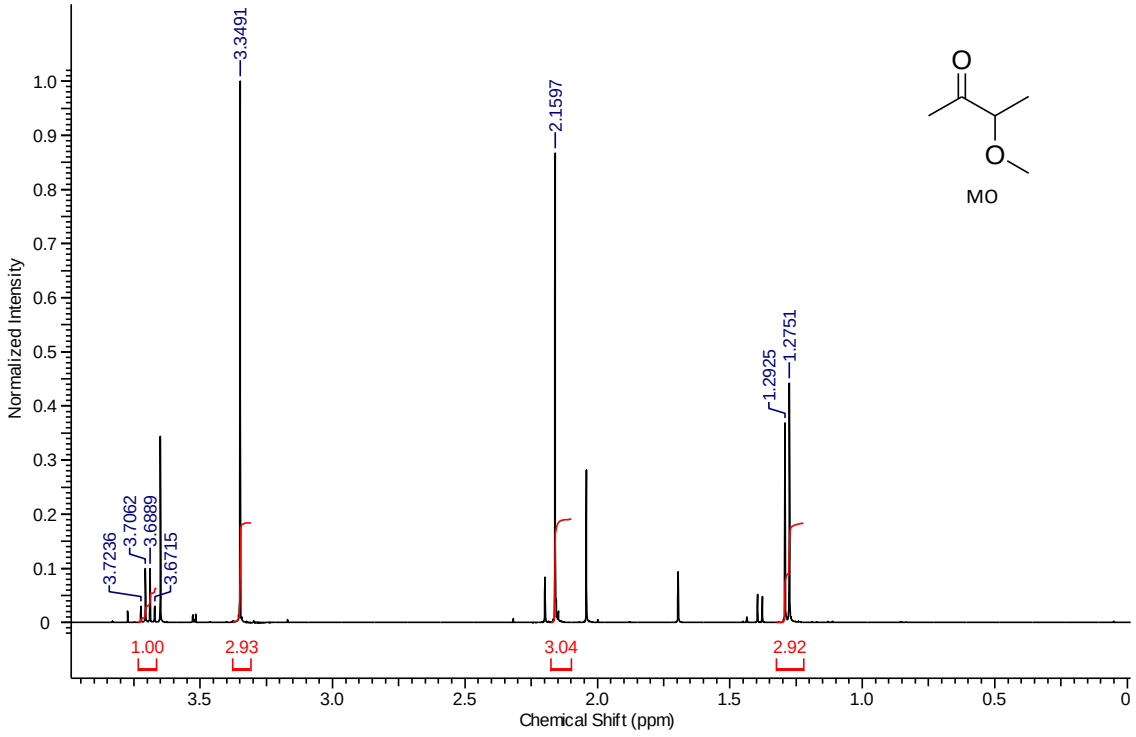


Fig. 5.9 The ^{1}H NMR of the product mixture obtained from methyl iodide synthesis

Experimental process: Into a 25 cm^{3} round-bottomed flask, 6 mmol acetoin, 9 mmol silver (I) oxide, 100 mmol DCM and 19 mmol methyl iodide were added, before sealing and stirring at room temperature in the dark. After 16 h, the reaction was stopped, and the reaction mixture was filtered. Finally, purification by short-path distillation equipment (BÜCHI Glass Oven B-585

Kugelrohr) was carried out, and the ^{1}H NMR and GC of the product mixture were both tested.

MO was proved to be synthesised successfully *via* the reaction of methyl iodide and acetoin by ^{1}H NMR (Fig. 5.9): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, J = 6.96 Hz, 3H, CHMe), 2.16 (s, 3H, CMe), 3.35 (s, 3H, OMe), 3.70 (q, J = 6.96 Hz, 1H, CHOMe) ppm.

Finally, the desired product synthesised from DMC and acetoin was confirmed to be MO *via* comparison to the main product produced from methyl iodide synthesis by GC.

5.3.4 The purification of MO by rectification

Isolated MO was synthesised *via* a one-step solvent-free process: To a high-pressure reactor 1.09 mol of acetoin was added followed by 1.09 mol DMC. To this 54.5 mmol *p*-toluenesulfonic acid (PTSA) was added before tightening and heating to 160 °C with agitation. After 2 h, the reaction was stopped and cooled to room temperature in an ice-bath and the reaction mixture was then filtered. Finally, the product mixture was rectified by a Vigreux distillation column, and 33.40 g

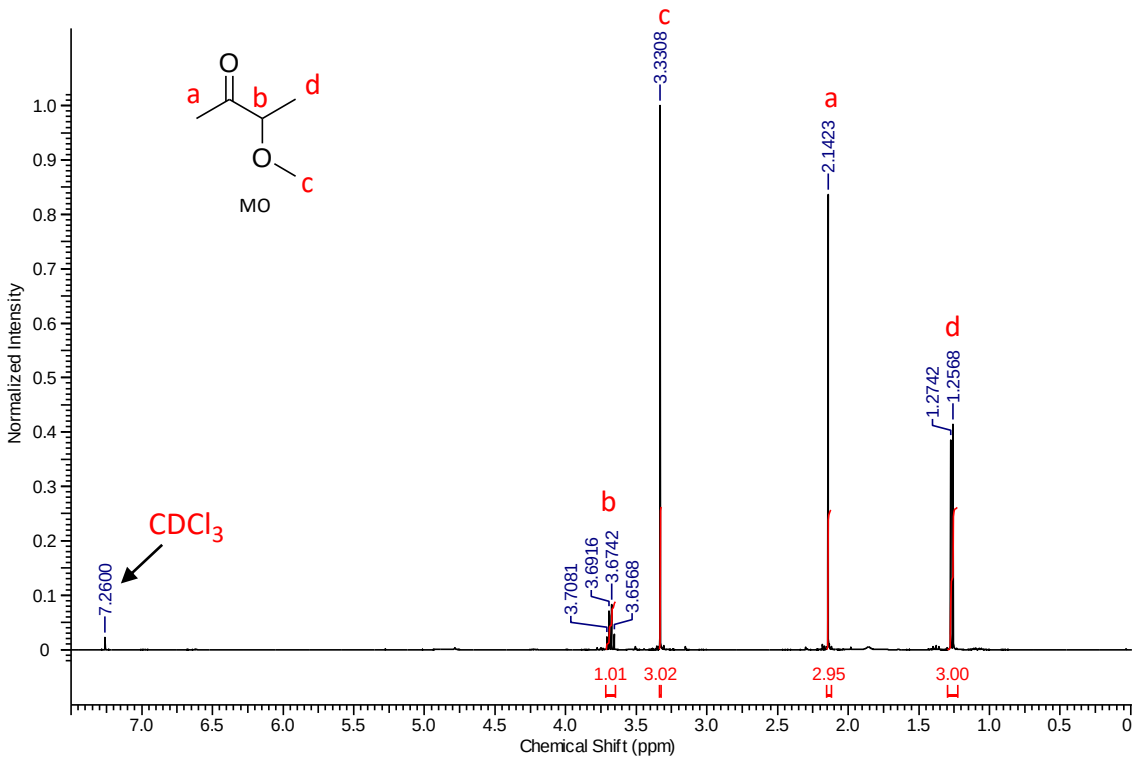


Fig. 5.10 The ^{1}H NMR of MO

MO (purity of 99% by GC, isolated yield of 30%) was obtained. GC, GC-MS and ^{1}H NMR (400 MHz) of MO were all analysed.

MO: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, J = 6.96 Hz, 3H), 2.14 (s, 3H), 3.33 (s, 3H), 3.68 (q, J = 6.60 Hz, 1H) ppm. GC-MS (relative intensity, 70 eV) m/z: 102 (M^+), 59 (100), 43.

By using the optimised reaction conditions, MO was purified by rectification again. However, the isolated yield of MO was only 6% with a purity of 98%. As such, an improvement in the isolated yield of MO will be necessary in the future, and industrially, much better distillation methodologies for MO are available.

5.3.5 The effect of catalytic loading on the synthesis of MO

0.5 mol Acetoin and 0.05 mol tetradecane were added to a high-pressure reactor followed by 0.5 mol DMC. To this, the limited loading of PTSA was added, prior to tightening and heating to 160 °C with agitation. After 2 h, the reaction was stopped and cooled to room temperature in an ice-bath. GC and ^{1}H NMR analysis of each of the reaction mixtures was carried out to identify the yield of MO.

5.3.6 The effect of mole ratio of DMC to acetoin on the synthesis of MO

To a high-pressure reactor was added 0.5 mol acetoin and 0.05 mol tetradecane followed by relevant DMC. To this, 0.025 mol PTSA was then added, before tightening and heating to 160 °C with agitation. After 2 h, the reaction was stopped and cooled to room temperature in an ice-bath. GC and ^{1}H NMR analysis of each of the reaction mixtures was carried out to identify the yield of MO.

5.3.7 The effect of reaction time on the synthesis of MO

To a high-pressure reactor was added 0.5 mmol acetoin and 0.05 mol tetradecane followed by 4 mol DMC. To this was then added 0.025 mmol PTSA before tightening and heating to 160 °C with

agitation. Samples at relevant reaction time were obtained, and their GC and ^{1}H NMR were tested to identify the yield of MO.

5.4 Chapter 3. Methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate as a new bio-based solvent

5.4.1 Synthesis and characterisation of MMC

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073), 6 mmol of solketal was added followed by 240 mmol DMC. To this 7.2 mmol potassium carbonate was added before heating to DMC reflux temperature with agitation. After 24 h, the reaction was stopped, cooled to room temperature and then filtered. Methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC) (purity of 99% by GC) was then isolated by distillation under reduced pressure (Heidolph, VV2000). The structure was analysed by GC, GC-MS, ^{1}H NMR and ^{13}C NMR.

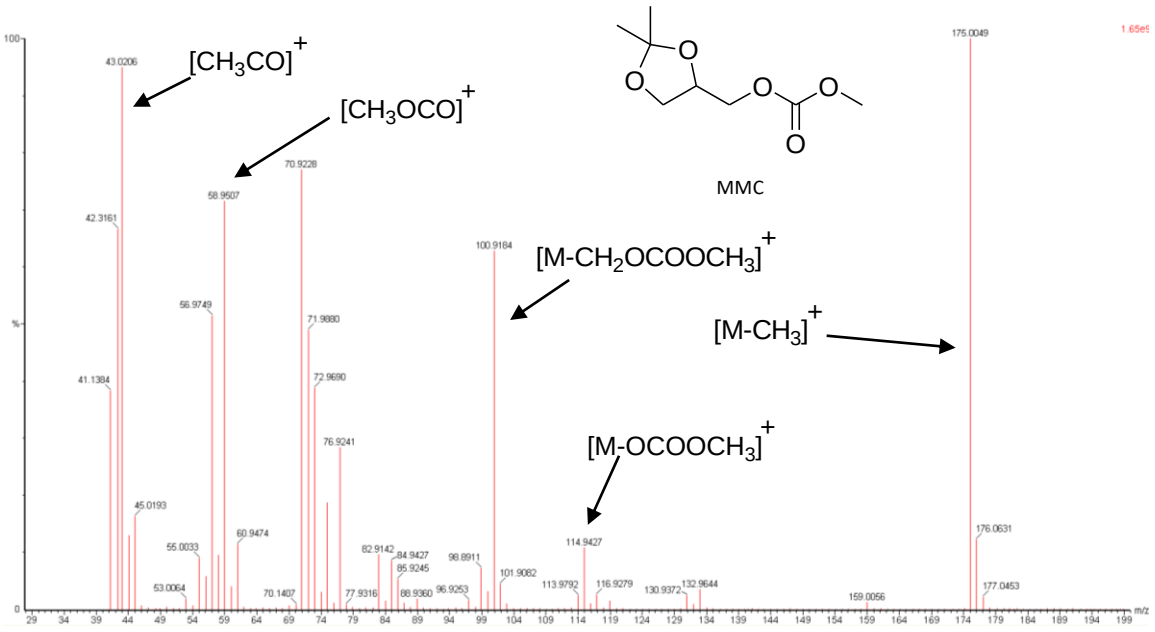
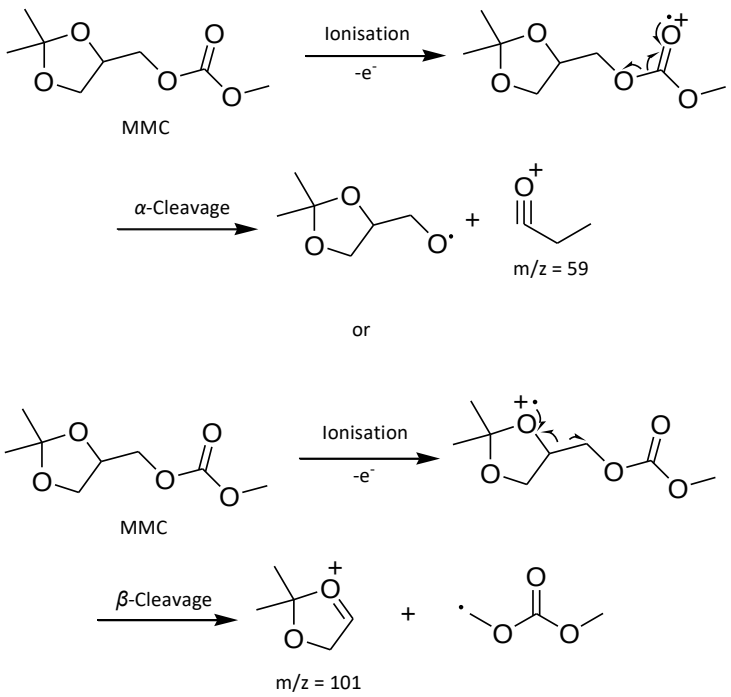


Fig. 5.11 The MS (EI) of MMC



Scheme 5.5 The main cleavage mechanism of MMC in the MS (EI)

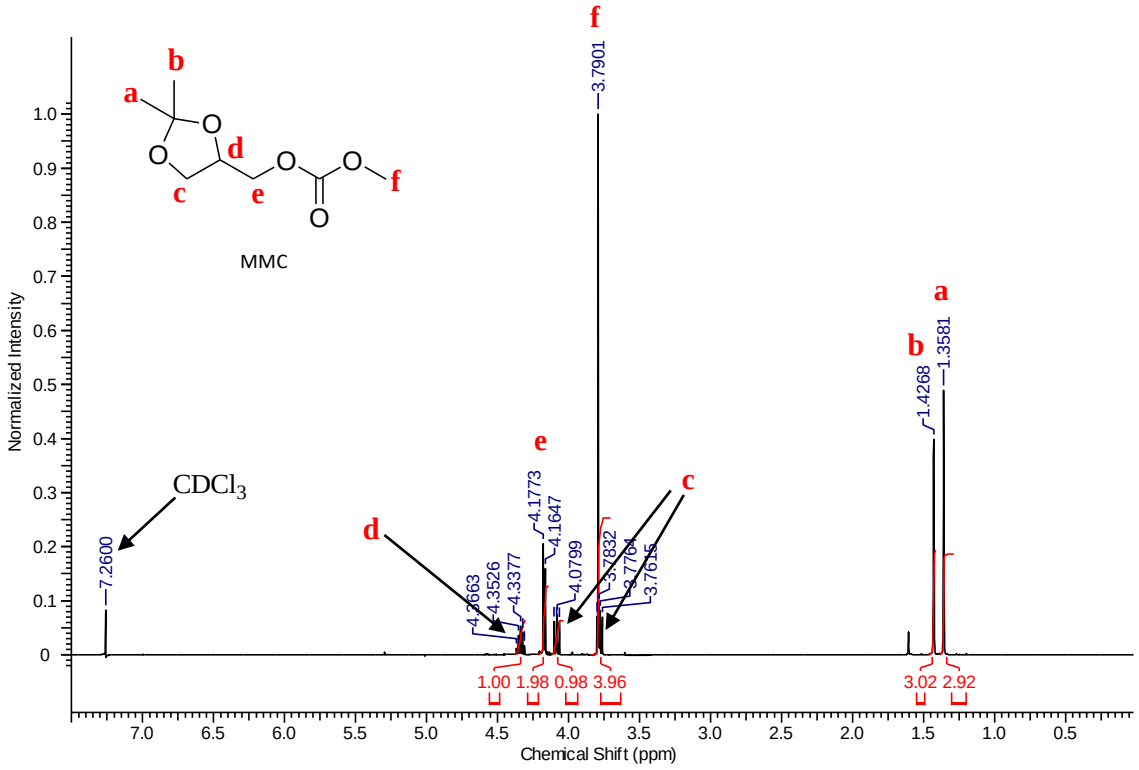


Fig. 5.12 The ^{1}H NMR of the isolated MMC

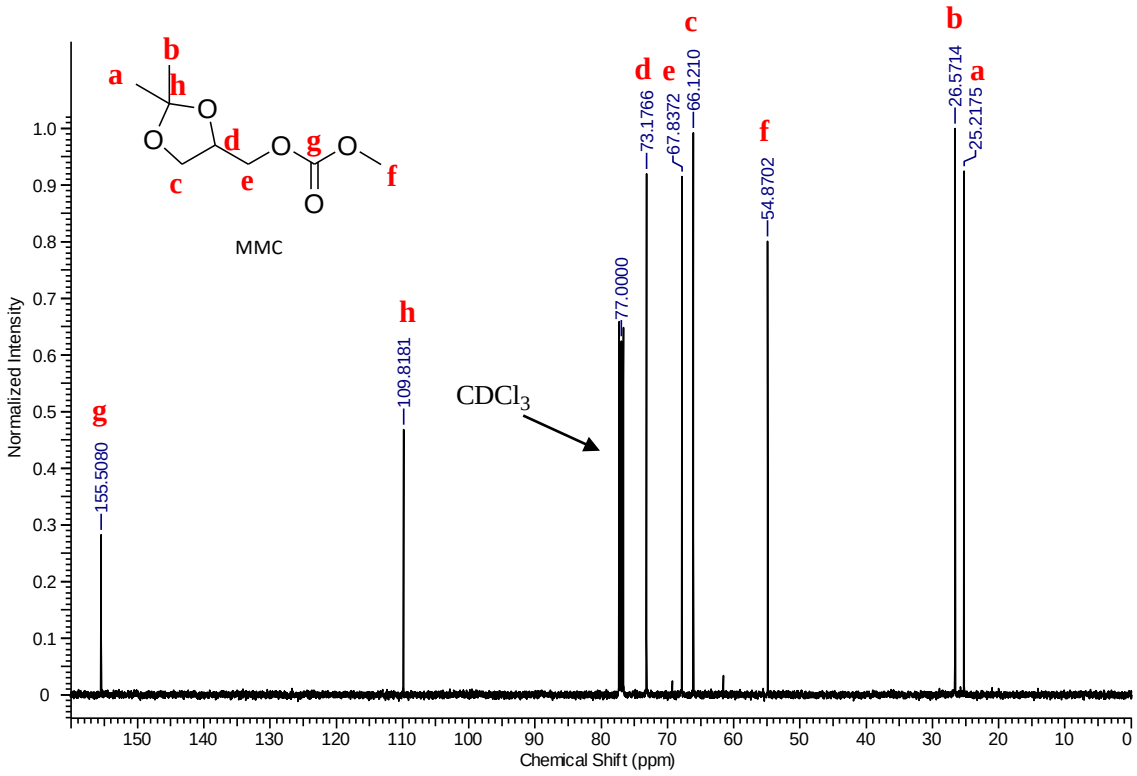


Fig. 5.13 The ^{13}C NMR of the isolated MMC

MMC: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.37-4.31 (m, 1H), 4.18-4.16 (m, 2H), 4.10-4.06 (m, 1H), 3.80-3.76 (m, 4H), 1.43 (s, 3H), 1.36 (s, 3H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 155.5, 109.8, 73.2, 67.8, 66.1, 54.9, 26.6, 25.2 pp. GC-MS (relative intensity, 70 eV) m/z: 175 (100), 133, 115, 101, 77, 71, 59, 57, 43. Protons and carbons of MMC are assigned on the ^{1}H NMR and ^{13}C NMR signals, respectively (Fig. 5.12 and Fig. 5.13). Scheme 5.5 shows the main cleavage mechanism of MMC in the MS.

5.4.2 The effect of the reaction time on the synthesis of MMC

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6 mmol solketal followed by 240 mmol DMC. To this was then added 7.2 mmol potassium carbonate before heating to DMC reflux temperature with agitation. GC and GC-MS were used to monitor the yield of MMC at relevant reaction time.

5.4.3 The effect of the catalytic loading on the synthesis of MMC

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was placed 6 mmol solketal followed by 240 mmol DMC. To this was then added corresponding potassium carbonate prior to heating to DMC reflux temperature with agitation. After 20 h, the reaction was stopped, cooled to room temperature and the reaction mixture was filtered. GC and GC-MS of the reaction mixture were tested.

5.4.4 The effect of the mole ratio of DMC to solketal on the synthesis of MMC

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was placed 6 mmol solketal followed by relevant DMC. To this was then added 0.006 mmol potassium carbonate before heating to DMC reflux temperature with agitation. After 20 h, the reaction was stopped, cooled to room temperature and the reaction mixture was filtered. GC and GC-MS of the reaction mixture were tested.

5.4.5 The synthesis and purification of MMC based on optimised reaction conditions

To a 200 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 40 mmol solketal followed by 800 mmol DMC. To this was then added 0.04 mmol potassium carbonate before heating to DMC reflux temperature with agitation. After 20 h, the reaction was stopped, cooled to room temperature and filtered. Finally, 6.94 g colourless MMC (purity of 99% by GC, 91% isolated yield) was then isolated by distillation under reduced pressure (Heidolph, VV2000).

5.4.6 The analysis of the by-product

Fig. 5.14 illustrates the MS (EI) of the by-product synthesised in the experiment of Section 3.2.3.3. This MS complies with the literature of diMMC.[306]

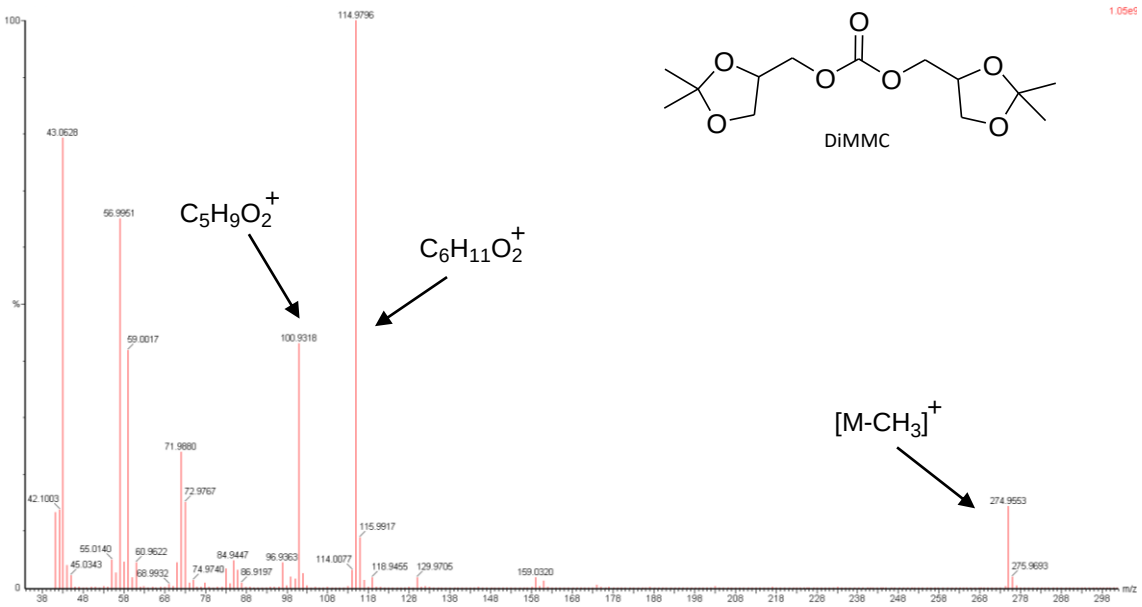
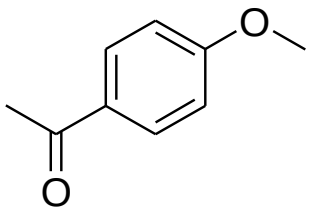


Fig. 5.14 The MS (EI) of diMMC

The fragment ions of diMMC can also be identified in Fig. 5.14 such as $C_5H_9O_2^+$ (m/z 101), $C_6H_{11}O_2^+$ (m/z 115) and $[M\text{-}CH_3]^+$ (m/z 275).

5.5 The solvent performances of MO/MMC in reactions

5.5.1 4-Methoxyacetophenone synthesised from the Friedel-Crafts reaction

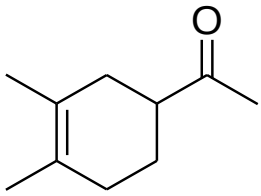


4-MAP

To a 3 cm^3 sample vial was placed 0.05 mmol anisole, 0.05 mmol iron (III) chloride, 0.05 mmol acetic anhydride, and 0.5 ml of the chosen solvent. The sample bottle was sealed for 2 hours and stirred by a roller (Stuart, roller mixer SRT6) at room temperature. Each experiment was carried out in duplicate. After 2 hours, an aliquot of the reaction was removed from the sample vial and analysed by GC and GC-MS.

4-Methoxyacetophenone (4-MAP): GC-MS (relative intensity, 70 eV) m/z: 150 (M^+), 135, 107, 92, 77, 64, 63, 62, 51, 50, 43 (100), 42. The product was also proved to be 4-MAP by comparing to commercial standard sample by GC.

5.5.2 1-(3,4-Dimethylcyclohex-3-enyl) ethanone synthesised from the Diels-Alder reaction



DE

To a 3 cm^3 sample bottle was placed 0.036 mmol anhydrous ytterbium(III) chloride, 0.5 ml limited solvent, 0.358 mmol 3-buten-2-one and 0.358 mmol diene. The argon gas protected sample bottle remained sealed for 16 hours and was stirred by a roller throughout (Stuart, roller mixer SRT6) at room temperature. Each experiment was repeated at least twice. After 16 hours, the sample was removed and analysed by GC and GC-MS. Following filtration of the reaction mixture, 1-(3,4-dimethylcyclohex-3-enyl) ethanone (DE) was isolated by distillation, and its GC, GC-MS, ^{1}H NMR and ^{13}C NMR were all analysed.

DE: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59-2.48 (m, 1H), 2.14 (s, 3H), 2.12-1.85 (m, 5H), 1.60 (s, 3H), 1.58 (s, 3H), 1.55-1.43 (m, 1H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 18.8, 19.0, 25.3, 27.9, 31.2, 33.0, 48.2, 123.9, 125.3, 211.8 ppm. GC-MS (relative intensity, 70 eV) m/z: 152 (M^+), 137, 119, 109 (100), 107, 95, 93, 91, 81, 79, 77, 67, 55, 43.

5.6 Chapter 4. The new developments in acidic DMC chemistry

5.6.1 General experimental procedure for the reaction of an alcohol or phenol with DMC at 90 °C

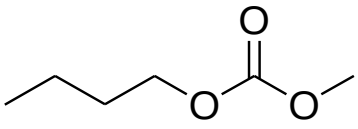
To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol limiting alcohol or phenol followed by 240.00 mmol DMC. To this the relevant acid was then added at limited loading before heating to reflux with agitation. After the required time (19 or 60 h), the reaction was stopped, cooled to room temperature and filtered. GC, GC-MS and ^1H NMR samples of the reactants in DMC were taken prior to removal of the solvent under reduced pressure (Heidolph, VV2000) to yield the crude product.

5.6.2 General experimental procedure for the reaction of alcohol or phenol with DMC at 160 °C

To a high-pressure reactor was placed 6.00 mmol limiting alcohol or phenol followed by 240.00 mmol DMC. To this was then added the relevant acid at related loading before heating to 160 °C. After 19 h, the reaction was stopped, cooled to room temperature in an ice-bath and filtered. GC, GC-MS and ^1H NMR samples of the reactants in DMC were taken before removal of the solvent under reduced pressure (Heidolph, VV2000) to yield the crude product.

5.6.3 Characterisation of the compounds obtained in Chapter 4

5.6.3.1 Synthesis of butyl methyl carbonate

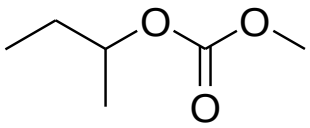


Butyl methyl carbonate

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol 1-butanol followed by 240.00 mmol DMC. To this was then added 0.3 mmol PTSA before heating to reflux with agitation. After 19 h, the reaction was stopped and then cooled to room temperature. DMC and methanol were then removed by reduced pressure (Heidolph, VV2000) to yield the crude product. This crude product was then washed with distilled water (3 x 10 cm^3), extracted with ethyl acetate (3 x 10 cm^3), and the organic phases combined and dried with magnesium sulphate. Removal of the solvent after filtering yielded the product, which was then analysed by GC-MS and ^{1}H NMR.

Butyl methyl carbonate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.32 Hz, 3H, CH_3), 1.36 (m, *J* = 7.36 Hz, 2H, CH_2), 1.61 (m, *J* = 7.32 Hz, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.10 (t, *J* = 6.60 Hz, 2H, CH_2) ppm. GC-MS (relative intensity, 70 eV) m/z: 103, 77, 73, 59, 56(100), 45, 41.

5.6.3.2 Synthesis of *sec*-butyl methyl carbonate

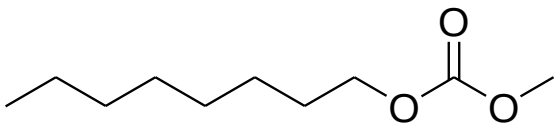


sec-Butyl methyl carbonate

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was placed 6.00 mmol 2-butanol followed by 240.00 mmol DMC. To this was then added 0.3 mmol aluminium chloride before heating to reflux with stirring. After 19 h, the reaction was stopped, cooled to room temperature and then filtered. DMC and methanol were then distilled off *via* reduced pressure (Heidolph, VV2000) to attain the desired product, which was then analysed by GC-MS and ^1H NMR.

sec-Butyl methyl carbonate: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.32 Hz, 3H, CH_3), 1.26 (d, J = 6.44 Hz, 3H, CH_3), 1.61 (m, 2H, CH_2), 3.76 (s, 3H, CH_3), 4.69 (m, J = 6.40 Hz, 1H, CH) ppm. GC-MS (relative intensity, 70 eV) m/z: 117, 103, 77, 73, 59(100), 57, 55, 45, 41.

5.6.3.3 Synthesis of methyl octyl carbonate

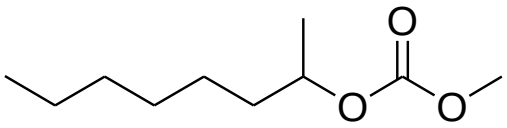


Methyl octyl carbonate

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol 1-octanol followed by 240.00 mmol DMC. To this was then placed 0.3 mmol aluminium chloride before heating to reflux with agitation. After 19 h, the reaction was stopped, cooled to room temperature and filtered. DMC and methanol were then eliminated by reduced pressure (Heidolph, VV2000) to obtain the desirable product, which was then analysed by GC-MS and ^1H NMR.

Methyl octyl carbonate: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 6.96 Hz, 3H, CH_3), 1.17-1.40 (m, 10H, CH_2), 1.63 (m, J = 6.56 Hz, 2H, CH_2), 3.74 (s, 3H, CH_3), 4.09 (t, J = 6.60 Hz, 2H, CH_2) ppm. GC-MS (relative intensity, 70 eV) m/z: 117, 112, 103, 97, 84, 77(100), 70, 59, 57, 55, 45, 43, 41.

5.6.3.4 Synthesis of methyl octan-2-yl carbonate

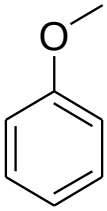


Methyl octan-2-yl carbonate

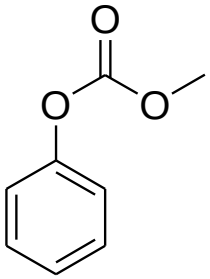
To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol 2-octanol followed by 240.00 mmol DMC. To this was then placed 0.3 mmol aluminium chloride before heating to reflux with stirring. After 19 h, the reaction was stopped, cooled to room temperature and the reaction mixture was filtered. DMC and methanol were then removed *via* reduced pressure (Heidolph, VV2000) to yield the desirable product, which was then analysed by GC-MS and ^{1}H NMR.

Methyl octan-2-yl carbonate: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.44 Hz, 3H, CH_3), 1.26 (d, J = 6.40 Hz, 3H, CH_3), 1.27-1.68 (m, 10H, CH_2), 3.75 (s, 3H, CH_3), 4.74 (m, J = 6.40 Hz, 1H, CH) ppm. GC-MS (relative intensity, 70 eV) m/z: 131, 129, 112, 103, 97, 83, 77, 70, 59(100), 55, 43, 41.

5.6.3.5 Synthesis of anisole and methyl phenyl carbonate



Anisole



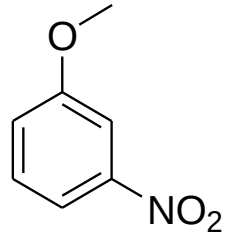
Methyl phenyl carbonate

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was placed 6.00 mmol phenol followed by 240.00 mmol DMC. And then 6.00 mmol aluminium chloride was added to the flask before heating to reflux with agitation. After 19 h, the reaction was stopped, cooled to room temperature and filtered. DMC and methanol were then removed under reduced pressure (Heidolph, VV2000) to obtain the product mixture, which was then analysed by GC, GC-MS and ^1H NMR.

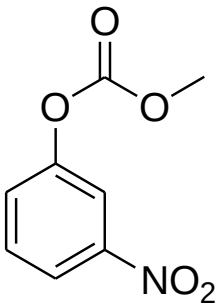
Anisole: GC-MS (relative intensity, 70 eV) m/z: 108 (M^+, 100), 93, 78, 65, 63, 51, 49, 43. The product was also confirmed as anisole *via* comparing to commercial standard sample by GC.

Methyl phenyl carbonate: GC-MS (relative intensity, 70 eV) m/z: 152(M^+), 108, 93. 78(100), 73, 65, 59, 51, 44. The product was also confirmed as methyl phenyl carbonate *via* comparing to commercial standard sample by GC.

5.6.3.6 Synthesis of 3-nitroanisole and methyl 3-nitrophenyl carbonate



3-Nitroanisole



Methyl 3-nitrophenyl carbonate

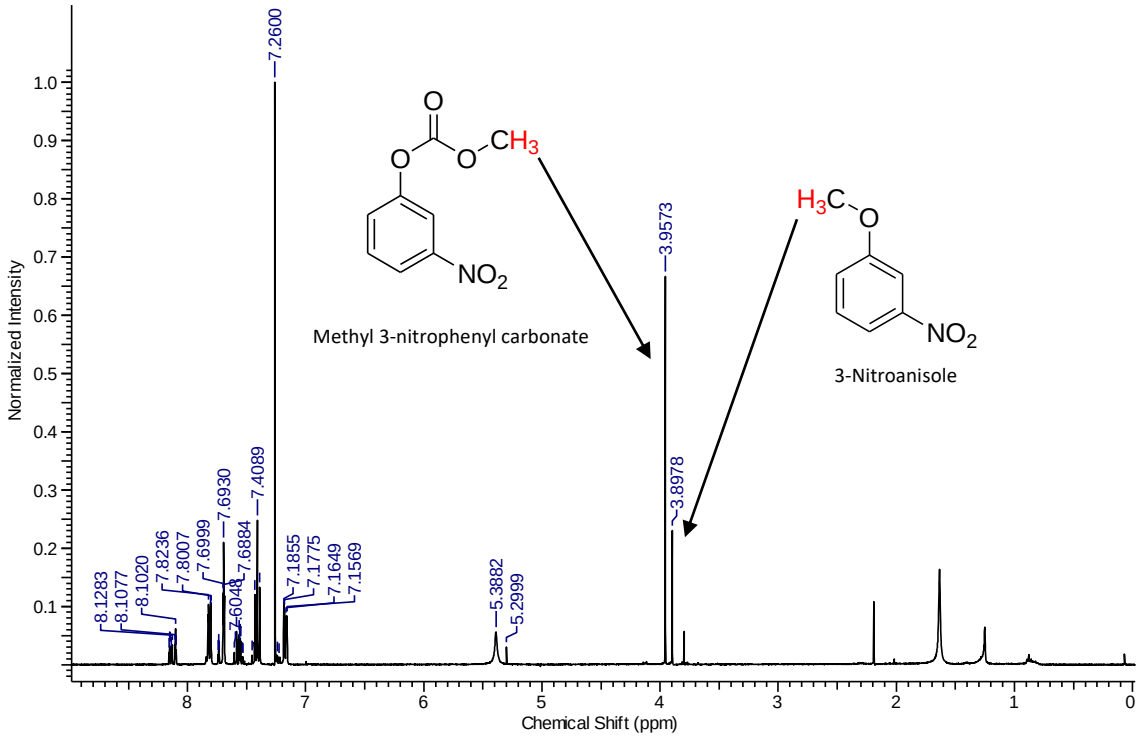


Fig. 5.15 ^{1}H NMR of product mixtures of 3-nitrophenol, 3-nitroanisole and methyl 3-nitrophenyl carbonate

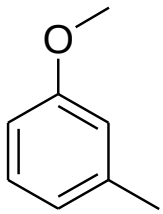
To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol 3-nitrophenol followed by 240.00 mmol DMC. To this was then placed 6.00 mmol aluminium chloride before heating to reflux with agitation. After 19 h, the reaction was stopped, cooled to room temperature and filtered. DMC and methanol were then eliminated under reduced pressure (Heidolph, VV2000) to attain the product mixture, which was then analysed by GC, GC-MS and ^1H NMR.

The ^1H NMR result is illustrated in Fig. 5.15, where the main peaks. in the range of 0.000 ppm to 2.500 ppm, were from the 3-nitrophenol starting material.

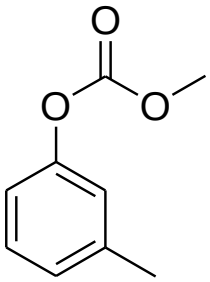
3-Nitroanisole: GC-MS (relative intensity, 70 eV) m/z: 153 (M^+), 137, 123, 107, 95, 92, 77(100), 64, 50. The product was also proved to be 3-nitroanisole *via* comparing to commercial standard sample by GC.

Methyl 3-nitrophenyl carbonate: GC-MS (relative intensity, 70 eV) m/z: 197(M^+), 181, 153, 139, 122, 107, 95, 92(100), 77, 64, 59, 50, 44.

5.6.3.7 Synthesis of 3-methylanisole and methyl *m*-tolyl carbonate



3-Methylanisole



Methyl *m*-tolyl carbonate

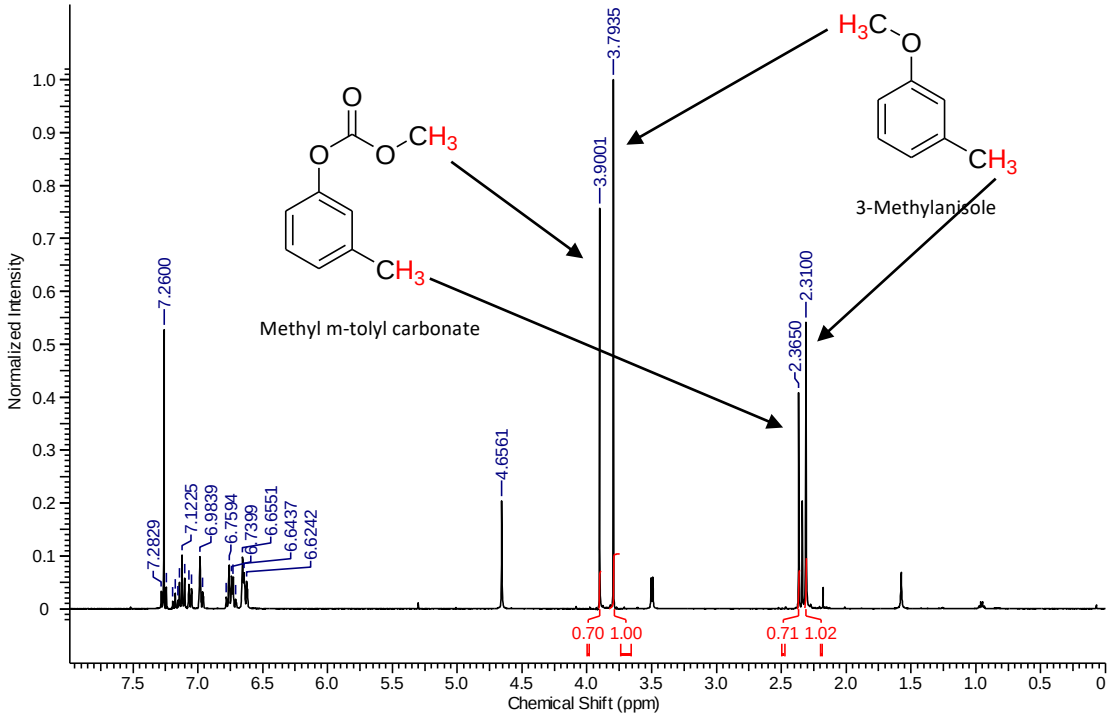


Fig. 5.16 ^{1}H NMR of product mixtures of *m*-cresol, methyl *m*-tolyl carbonate and 3-methylanisole

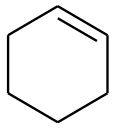
To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was placed 6.00 mmol *m*-cresol followed by 240.00 mmol DMC. To this was then added 6.00 mmol aluminium chloride before heating to reflux with stirring. After 19 h, the reaction was stopped, cooled to room temperature and filtered. DMC and methanol were then distilled off under reduced pressure (Heidolph, VV2000) to attain the product mixture, which was then analysed by GC, GC-MS and ^1H NMR.

The ^1H NMR result is illustrated in Fig. 5.16, where main peaks, in the range of 0.000 ppm to 2.000 ppm, were from the *m*-cresol starting material.

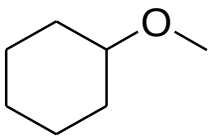
3-Methylanisole: GC-MS (relative intensity, 70 eV) m/z: 122(M^+, 100), 107, 91, 89, 79, 77, 65, 51. The product was confirmed as 3-methylanisole *via* comparing to commercial standard sample by GC.

Methyl *m*-tolyl carbonate: GC-MS (relative intensity, 70 eV) m/z: 166(M^+), 122, 107, 91(100), 77, 65, 59, 51, 44.

5.6.3.8 Synthesis of cyclohexene and methoxycyclohexane



Cyclohexene



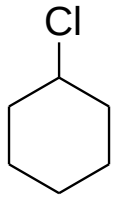
Methoxycyclohexane

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was placed 6.00 mmol cyclohexanol followed by 240.00 mmol DMC. To this was then added 6.00 mmol iron (III) chloride before heating to reflux with stirring. After 19 h, the reaction was stopped, cooled to room temperature and filtered. The reaction mixture was then analysed by GC and GC-MS.

Cyclohexene: GC-MS (relative intensity, 70 eV) m/z: 82(M^+), 67(100), 54, 41. The product was confirmed as cyclohexene *via* comparing to commercial standard sample by GC.

Methoxycyclohexane: GC-MS (relative intensity, 70 eV) m/z: 114(M^+), 85, 82, 71(100), 67, 58, 55, 45, 43, 41. The GC retention time of this compound and methoxycyclohexane synthesised from cyclohexane and methyl iodide catalysed by silver (I) oxide was identical.

5.6.3.9 Synthesis of chlorocyclohexane

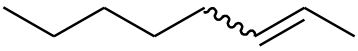


Chlorocyclohexane

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol cyclohexanol followed by 240.00 mmol n-heptane. To this was then placed 6.00 mmol iron (III) chloride before heating to reflux with agitation without adding any molecular sieves. After 19 h, the reaction was stopped, cooled to room temperature and filtered. The reaction mixture was then analysed by GC and GC-MS.

Chlorocyclohexane: GC-MS (relative intensity, 70 eV) m/z: 118(M^+), 83(100), 67, 62, 55, 51, 41. The product was also proved to be chlorocyclohexane *via* comparing to commercial standard sample by GC.

5.6.3.10 Synthesis of 2-octene and 3-octene



2-Octene

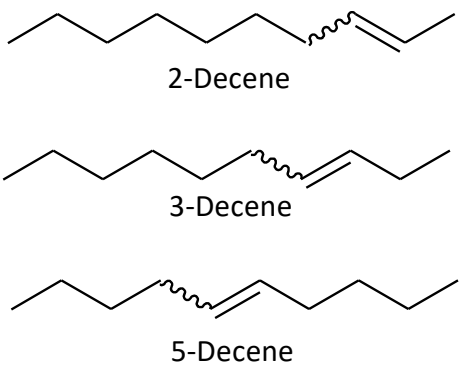
3-Octene

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol 2-octanol followed by 240.00 mmol DMC. To this was then added 6.00 mmol iron (III) chloride before heating to reflux with stirring. After 19 h, the reaction was stopped, cooled to room temperature and filtered. The reaction mixture was then analysed by GC and GC-MS.

2-Octene: GC-MS (relative intensity, 70 eV) m/z: 112(M^+), 97, 84, 83, 70, 56, 55(100), 53, 41. This mass spectrum (EI) of 2-octene was also in accordance with the standard mass spectrum provided by NIST library (Ver. 2.0).

3-Octene: GC-MS (relative intensity, 70 eV) m/z: 112(M^+), 97, 84, 83, 79, 77, 70, 69, 67, 56, 55(100), 53, 41. This mass spectrum (EI) of 3-octene was also in accordance with the standard mass spectrum provided by NIST library (Ver. 2.0).

5.6.3.11 Synthesis of 2-decene, 3-decene and 5-decene



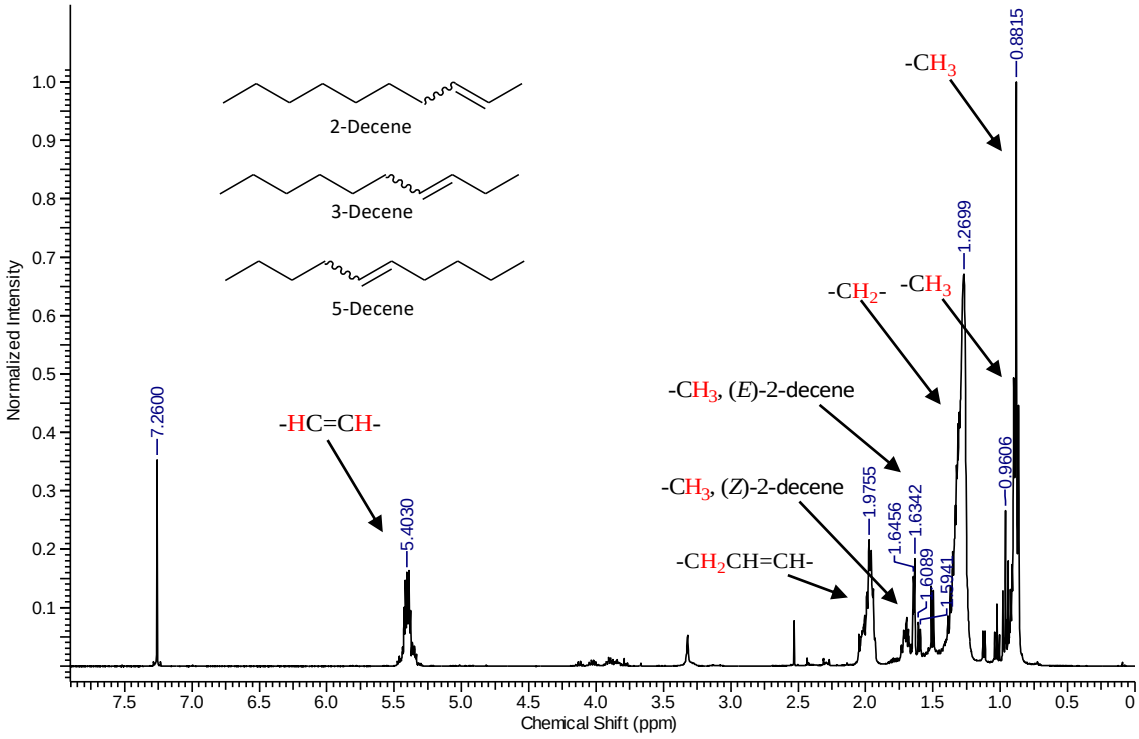


Fig. 5.17 ^{1}H NMR of products mixture of dehydration reaction of 2-decanol

To a 100 cm^{3} round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol 2-decanol followed by 240.00 mmol DMC. To this was then placed 6.00 mmol iron (III) chloride before heating to reflux with stirring. After 19 h, the reaction was stopped, cooled to room temperature and filtered. DMC and methanol were then eliminated by reduced

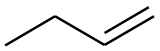
pressure (Heidolph, VV2000) to attain the product mixture, which was then analysed by GC, GC-MS and ^{1}H NMR. The ^{1}H NMR result is illustrated in Fig. 5.17.

2-Decene: GC-MS (relative intensity, 70 eV) m/z: 140(M^{+}), 112, 111, 98, 97, 84, 70, 69, 56(100), 55, 43. This mass spectrum (EI) of 2-decene was also in accordance with the standard mass spectrum provided by NIST library (Ver. 2.0).

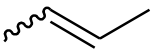
3-Decene: GC-MS (relative intensity, 70 eV) m/z: 140(M^{+}), 112, 111, 110, 98, 97, 85, 84, 71, 70, 69, 56, 55(100), 51, 43. This mass spectrum (EI) of 3-decene was also in accordance with the standard mass spectrum provided by NIST library (Ver. 2.0).

5-Decene: GC-MS (relative intensity, 70 eV) m/z: 140(M^{+}), 112, 111, 99, 98, 97, 91, 84, 83, 70, 69, 67, 65, 56, 55(100), 51, 42. This mass spectrum (EI) of 5-decene was also in accordance with the standard mass spectrum provided by NIST library (Ver. 2.0).

5.6.3.12 Synthesis of 1-butene and 2-butene



1-Butene



2-Butene

To a 100 cm^3 round bottom flask placed on a multi-point reflux reactor (Radleys, RR98073) was added 6.00 mmol 2-butanol followed by 240.00 mmol DMC. To this was then placed 6.00 mmol iron (III) chloride before heating to reflux with agitation. The dehydration process of 2-butanol with stoichiometric iron (III) chloride was carried out in a closed system. Any gases produced during the reaction were collected after 19 h with a 10 cm^3 Luer lock gas tight syringe (SGE Analytical Science) for gas phase GC-MS analysis.

1-Butene: GC-MS (relative intensity, 70 eV) m/z: 56(M^+), 55, 53, 51, 50, 41(100), 39, 38, 37. This mass spectrum (EI) of 1-butene was also in accordance with the standard mass spectrum provided by NIST library (Ver. 2.0).

2-Butene: GC-MS (relative intensity, 70 eV) m/z: 56(M^+, 100), 55, 54, 53, 52, 51, 50, 49, 41, 40, 39, 38, 37. This mass spectrum (EI) of 2-butene was also in accordance with the standard mass spectrum provided by NIST library (Ver. 2.0).

Chapter 6 Thesis conclusions and future work

6.1 Conclusions

In summary, this research focussed on the development of a new bio-based solvent 3-methoxybutan-2-one (MO). This solvent demonstrated suitable properties for the replacement of halogenated solvents such as dichloromethane (DCM). Another novel bio-derived medium methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate (MMC) was also synthesised via dimethyl carbonate (DMC) chemistry. This also demonstrated some promise as a bio-derived solvent. However, the Ames test results for this molecule exhibited some mutagenicity. This highlighted the importance of toxicological testing at an early stage of solvent development. Finally, the scope of DMC chemistry has been expanded to include acid-catalysed reactions of different aliphatic alcohols and phenols.

Chapter 2, after the initial screening of HSPiP software, the successful synthesis of MO (with a yield of 95%) from bio-based platform molecule acetoin and green methylation agent DMC was achieved. MO provides a good approximation to the polarity of halogenated solvents, as assessed using both Kamlet-Taft (KT) and Hansen solubility parameters (HSPs). Significantly, MO did not exhibit any mutagenicity in a preliminary Ames test, while peroxide testing highlighted the limited formation of peroxide after 210 days (less than 1 $mg \cdot dm^{-3}$). The low viscosity, melting point and low boiling point make MO a potential substitution solvent for DCM. However, this solvent does have the disadvantage that it cannot be easily separated from water, unlike DCM. MO was comparable to DCM in the Friedel-Craft synthesis but not for the Diels-Alder reaction. It is envisaged that bio-based medium such as MO will assist the replacement of those common solvents, which are deemed unacceptable under legislation such as REACH.

Chapter 3 explored a synthesis methodology of MMC from bio-based solketal and green carboxymethylation agent DMC after the initial screening of HSPiP software. MMC was attained with a yield of 91% and has similar KT and HSPs parameters to a wide range of common aprotic solvents. A peroxide test demonstrated that MMC does not form hazardous peroxide compounds over a period of 224 days. Friedel-Crafts and Diels-Alder reactions both demonstrated MMC gives reasonable performance compared to a wide range of traditional aprotic solvents. These results indicated that MMC could be a potential bio-based medium for

the replacement of conventional petroleum based solvents in the future. Unfortunately, it appears that MMC may pose a chronic toxicity hazard based on Ames test, and this result serves as an important warning that the objective to create new green solvents must be to substitute environmentally damaging, toxic and hazardous solvents and that solvents must be proven as such to be accepted.

Chapter 4 used Brønsted and Lewis acids as catalysts or reagents in the presence of alcohols/phenols and DMC as a new area of dialkyl carbonate chemistry. In comparison with more commonly used base catalysis, acid catalysts have many advantages such as lower market price, lower hazard and lower energy of production. Additionally, the acid-catalysed reaction will enable more substrates to be available in dialkyl carbonate chemistry as well as significantly expanding the number of catalysts. At 90 °C, both Brønsted and Lewis acids have promoted carboxymethylation of alcohols with near quantitative conversion and selectivity. Methylation or carboxymethylation of phenols was also achieved. The high activity of aluminium chloride at low loadings demonstrates significant promise, however, further work is needed to improve the reusability of this catalyst. Stoichiometric loading of iron (III) chloride or sulphuric acid leads to the dehydration of secondary alcohols, with better conversion in DMC than in n-heptane. Moreover, iron (III) chloride and DMC were found to be a suitable system for methylation of cyclohexanol. At 160 °C, the conversion and selectivity of secondary aliphatic alcohol improve, but no methylation product is produced, and *tert*-Butanol did not react under acidic conditions. The control experiments provided valuable evidence that the acid catalysts play a vital role in this DMC chemistry.

6.2 Future work

6.2.1 For Chapter 2

The future work of the bio-based solvent MO is needed to be carried out. Firstly, the isolated yield of MO solvent is necessary to be improved from 30% to at least 90%. In industry, much better purification methodologies are available to purify MO such as rectifying tower which has much higher number of theoretical plates than the lab-based rectifying column, thus MO will be

purified in industrial scale. Moreover, PTSA, used in the synthesis of MO, is a petroleum-based catalyst since it is synthesised *via* the sulphonation of toluene,[307] as such it will be replaced by *p*-cymene sulphonic acid (PCSA)[308] which is a more sustainable catalyst derived from citrus waste. The risk of formation of peroxide of MO is needed to be evaluated by more precise titration method,[309] and stabilisers, such as butylated hydroxytoluene (BHT), will be added in MO in order to investigate its antioxidant ability. Although no mutagenicity of MO was found in this project, however, a full set of toxicity tests are still needed to study its toxicology such as Ames test with S9 microsomal activation and animal test. Additionally, the stability of MO in acidic or basic conditions will be investigated.

6.2.2 For Chapter 3

Based on Chapter 3, although MMC is a bio-based solvent, it is not a green solvent since it exhibits mutagenicity. The future work will focus on developing other new bio-based solvents. More bio-based medium will be synthesised from bio-based platform molecules and DMC to fill up the gaps in the Kamlet-Taft solvent map. More potential bio-based platform molecules are also needed to be explored and developed. Additionally, other possible green reaction reagents are required to be studied and applied in synthesising new bio-based solvents. Significantly, toxicology tests will be carried out for any new bio-derived medium in the early stage of the study.

6.2.3 For Chapter 4

This project opened a new area of acid-catalysed dialkyl carbonate chemistry, which highlights that many future works are necessary. Firstly, computational quantum chemistry based on density functional theory (DFT)[310] will be used to analyse the mechanism of acid-catalysed DMC reactions such as reaction pathway, activation energy and transition state. In addition, the reactivity of more substrates, such as amine and thiol, in acidic DMC chemistry are also needed to be screened. Other dialkyl carbonates are necessary to be further investigated in the presence of acid catalysts. Moreover, aluminium chloride and iron (III) chloride can be substituted by

heterogeneous catalysts such as ion-exchanged clays with strong Lewis acidic site Al^{3+},[311,312] or more sustainable bio-based catalyst PCSA. The performances of these heterogeneous acid catalysts will be assessed in DMC reactions. The mechanism that DMC offered better conversion in the dehydration reaction of secondary alcohol than n-heptane will also be investigated in the future.

Glossary

List of abbreviations and symbols

DMC	Dimethyl carbonate
^{13}C NMR	Carbon-13 nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
2D	Two dimension
2-MeTHF	2-Methyl tetrahydrofuran
2-NF	2-Nitrofluorene
3D	Three dimension
4-MAP	4-Methoxyacetophenone
4-NQO	4-Nitroquinoline-*N*-oxide
b.p.	Boiling point
$B_{AC}2$	Bimolecular, base-catalysed, acyl cleavage and nucleophilic substitution
$B_{AL}2$	Bimolecular, base-catalysed, alkyl cleavage and nucleophilic substitution
BHT	Butylated hydroxytoluene
c.p.	Crystallisation point
DCM	Dichloromethane
DE	1-(3,4-Dimethylcyclohex-3-enyl) ethanone
DFT	Density functional theory
Diene	2,3-Dimethylbuta-1,3-diene
DiMMC	(4,4-Dimethyl-1,3-dioxolan-2-yl) methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate
DL	Detection limit
DMAc	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethyl sulphate
DMSO	Dimethyl sulfoxide
DSC	Differential scanning calorimetry
DTG	Differential thermogravimetric
E	Total energy of vaporisation

E1	Unimolecular elimination
E_D	Dispersion cohesive energy
E_H	Electron exchange energy
EHS	Environmental, health and safety
EI	Electron ionisation
E_P	Polar cohesive energy
EPA	Environmental Protection Agency
EU	European Union
FT-IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GC-FID	Gas chromatography with a flame ionisation detector
GC-MS	Gas chromatography-mass spectrometry
GVL	*γ*-Valerolactone
HBA	Hydrogen bond accepting
HBD	Hydrogen bond donating
His^-	Mutational *Salmonella typhimurium*
His^+	Prototrophic *Salmonella typhimurium*
HSAB	Hard-Soft Acid-Base
HSPiP	Hansen Solubility Parameters in Practice
HSPs	Hansen solubility parameters
ICTA	Nomenclature Committee of the International Confederation for Thermal Analysis
InCHI	IUPAC International Chemical Identifier
IR	Infrared spectroscopy
IS	Internal standard
KT	Kamlet-Taft
LCA	Lifecycle assessment
LSER	Linear solvation energy relationship
LUMO	Lowest unoccupied molecular orbital
m.p.	Melting point

m/z	Mass-to-charge ratio
MC	Methyl 3-oxobutan-2-yl carbonate
MMC	Methyl (2,2-dimethyl-1,3-dioxolan-4-yl) methyl carbonate
MO	3-Methoxybutan-2-one
MOFs	Metal-organic frameworks
MS	Mass spectrometry
Mwt	Molecular weight
NA	4-Nitroaniline
NMP	1-Methyl-2-pyrrolidone
NN	*N*,*N*-Diethyl-4-nitroaniline
NR	Nile red
NREL	National Renewable Energy Laboratory
NTP	National Toxicology Program
PCSA	*p*-Cymene sulphonic acid
PTSA	*p*-Toluenesulfonic acid
R_0	Interaction radius
Ra	Hansen distance
RAPEX	Rapid Alert System for Dangerous Non-food Products
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
RED	Relative energy difference
R_f	Response factor
$ScCO_2$	Supercritical CO_2
SMILES	Simplified molecular-input line-entry system
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
SVHCs	Substances of very high concerns
TBD	1,5,7-Triazabicyclo [4.4.0] dec-5-ene
TG	Thermogravimetric
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran

TOF	Time of flight
UV	Ultraviolet
UV-vis.	Ultraviolet-visible
VOC	Volatile organic compound
α	Hydrogen bond donating ability
β	Hydrogen bond accepting (HBA) ability
δ	Hildebrand solubility parameter
δ_0	Polarisability correction term
δ_D	Hansen dispersion cohesion solubility parameter
δ_H	Hansen hydrogen bonding cohesion solubility parameter
δ_P	Hansen polar cohesion solubility parameter
λ_{max}	Maximum wavelength
ν_{max}	Wavenumbers at maximum absorbance
π^*	A combination of dipolarity and polarisability
ρ	Density

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