DEVELOPING PLATFORM CHEMICALS FROM RENEWABLE RESOURCES

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DEVELOPING PLATFORM CHEMICALS FROM

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

The Department of Energy has listed 5-hydroxymethylfurfural (HMF) and 2,5-furandicarboxylic acid (FDCA) as two of the twelve building blocks derived from cellulosic biomass. HMF can serve as a renewable platform for the production of fuels and chemicals. Our research goal is to develop novel methods for the conversion of renewable resources to feedstock chemicals for polymer synthesis. The Diels-Alder reaction, the cycloaddition of alkenes and dienes, has become one of the most important synthetic methods used in organic chemistry. We were interested in carrying out Diels-Alder reactions with derivatives of HMF. Naphthalene analogs of terephthalic acid were synthesized by reacting HMF derivatives with benzyne which could lead to the formation of bio-based polyethylene terephthalate (PET) analogs.

ACKNOWLEDGMENTS

I wish to first thank my advisor Dr. Mukund Sibi for his guidance while completing my degree. I have grown not only as a chemist but as a person as well under your direction. Thank you for your time and support throughout my time as a graduate student through its many ups and downs.

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I also express gratitude and thanks to the faculty and staff of the Department of Chemistry for all the time and effort you put into our program, especially Wendy, Linda, Dionna, Dave, Dan, and Dr. John Bagu.

DEDICATION

I dedicate this to the love of my life, Kevin; thank you for all of your support, encouragement and understanding from the beginning. I can't imagine doing graduate school without you. I thank you from the bottom of my heart for being there beside me while perusing my degree. I know I can always count on you to make me laugh. You mean so much to me and I look forward to beginning the next chapter of our lives together.

To my parents, I want to express the deepest gratitude for everything you have done in my life. Your selfless devotion to my upbringing, endless support and encouragement, and dedication means so much to me.

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LIST OF ABBREVIATIONS

°C .....Degree Celsius

^{13}C NMR .....Carbon Nuclear Magnetic Resonance

^{1}H NMR .....Proton Nuclear Magnetic Resonance

12-MPA.....12-Molybdophosphoric Acid

4ÅMS .....4-Angstrom Molecular Sieves

[BMIM]Cl .....1-Butyl-3-Methylimidazolium Chloride

[EMIM]Cl .....1-Ethyl-3-Methylimidazolium Chloride

acac .....Acetylacetonate

Ar .....Aryl

BG .....1,4-Butylene Glycol

BHETP .....Bis(2-Hydroxyethyl) Terephthalate

BHEFDC.....Bis(Hydroxyethyl)-2,5-Furandicarboxylate

BHMF .....2,5-Bis(Hydroxymethyl)Furan

Bn.....Benzyl

Bz .....Benzoyl

Calc'd.....Calculated

$CDCl_3$.....Deuterated Chloroform

CMF .....5-(Chloromethyl) Furfural

CPM .....Crystalline Porous Materials

CPO.....Chloroperoxidase

CYP3A4.....Cytochrome P450 3A4

DCM .....Dichloromethane

DFF 2,5-Diformylfuran

DMA .....*N*,*N*-Dimethyl Acetamide

DMF .....2,5-Dimethyl Furan

DMSO.....Dimethyl Sulfoxide

DPP-IV.....Dipeptidyl Peptidase IV

DS .....Dodecyl Sulfate

EDG .....Electron Donating Group

EG .....Ethylene Glycol

EMF 5-Ethoxymethyl-2-Furfural

EL.....Ethyl Levulinate

ESI.....Electrospray Ionization

Et.....Ethyl

Et_2O.....Diethylether

Equiv.....Equivalents

EWG .....Electron Withdrawing Group

FDCA.....2,5-Furan Dicarboxylic Acid

FDMC Furan-2,5-Dimethylcarboxylate

FFCA.....5-Formyl-2-Furancarboxylic Acid

FFA .....Furfuryl Alcohol

FMO.....Frontier Molecular Orbital Theory

FT-IR.....Fourier-Transform Infrared Spectroscopy

GC.....Gas Chromatography

GHL .....γ-Hexalactone

GVL .....γ-Valerolactone

h.....Hour

HMF.....5-Hydroxymethylfurfural

HMFCA .....5-Hydroxymethyl-2-Furancarboxylic Acid

HmfH .....*Cupriavidus Basilensis* Oxidoreductase

HMMF 2-Hydroxy-Methyl-5-Methylfuran

HOMO .....Highest Occupied Molecular Orbital

HPA.....Heteropoly Acid

HPLC .....High Performance Liquid Chromatography

HRMS .....High Resolution Mass Spectrometry

HT .....Hydrotalcite

Hz.....Hertz

Imd…… Imidazole

i-Pr.....Isopropyl

J.....Coupling Constant, Hz (NMR)

LA .....Lewis Acid

LED.....Light-Emitting Diode

LUMO.....Lowest Unoccupied Molecular Orbital

MA .....Maleic Anhydride

Me .....Methyl

MFF.....Methyl-5-Formyl-2-Furoate

MHz .....Megahertz

MIBK .....Methylisobutylketone

Min.....Minute

mL.....Milliliter

MOF.....Metal-Organic Frameworks

Mol.....Moles

Mol. Wt.....Molecular Weight

NaOH .....Sodium Hydroxide

NHC .....N-Heterocyclic Carbene

Naph.....Naphthyl

OBMF .....5,5’(Oxy-Bis(Methylene))Bis-2-Furfural

OTf.....Trifluoromethanesulfonate (Triflate)

PBSF .....Poly(Butylene Succinate Furandicarboxylate)

PBF .....Poly(Butylene 2,5-Furandicarboxylate)

PEF.....Poly(Ethylene 2,5-Furandicarboxylate)

PHF .....Poly(Hexylene 2,5-Furandicarboxylate)

PMO.....Porous Metal Oxides

POF .....Poly(Octylene 2,5-Furandicarboxylate)

PTF.....Poly(Trimethylene 2,5-Furandicarboxylate)

PET .....Polyethylene Terephthalate

Ph .....Phenyl

PLE .....Pig Liver Esterase

PPL.....Porcine Pancreatic Lipase

Prod.....Product

pTSA.....Para-Toluenesulfonic Acid

R.....Alkyl Group

rt .....Room Temperature

SA .....Succinic Acid

TBAC.....Tetrabutylammonium Chloride

TBDPS .....*tert*-Butyldiphenylsilyl

TBT.....Tetrabutyl Titanate

Temp .....Temperature

T_g.....Glass Transition Temperature

THF.....Tetrahydrofuran

TLC.....Thin Layer Chromatography

TMS .....Trimethylsilyl or Tetramethylsilyl (NMR)

TPA .....Terephthalic Acid

Ts.....*p*-Toluenesulfonyl (Tosylate)

X.....Variable Atom Within Ring

ZSM-5 .....Zeolite Socony Mobil–5

δ.....Chemical Shift in Parts-Per-Million

CHAPTER 1. HYDROXYMETHYLFURFURAL: A CHEMICAL PLATFORM FROM BIOMASS

1.1. Introduction

Based on the current environmental and political issues regarding our dependence on petroleum, a major focus in the scientific community is concentrating on new technologies for the conversion of renewable materials, such as biomass, into sources of energy and chemicals. Fossil fuels that include oil, coal and natural gas, are the source of 86% of the total energy and 96% of the organic chemicals produced.[1] The chemical industry is based on limited chemical building blocks: methanol, benzene, toluene, xylene, ethene, and butadiene.[2] Biomass has the potential to serve as a platform for the fuel and chemical industries. Biomass is composed of a broad class of compounds including carbohydrates, lignins, proteins, and fats.[3] Biomass stands out as a potential source for the fuel and chemical industries due to its abundance, renewability and carbon neutrality.[4] Currently biomass and other renewable energy sources such as wind, solar and tide represent only 0.9% of the total energy used.[5] Much of the current research is focusing on using lignocellulose, which is the most abundant renewable biomass, or cellulose, the most abundant organic compound, making up 33% of all plant matter.[6] However, the Department of Energy has also listed 5-hydroxymethylfurfural (HMF) and 2,5-furan dicarboxylic acid (FDCA) as 2 of the 12 building blocks derived from sugar.[7] This chapter will focus on the different methods for the synthesis of HMF and FDCA and include some reactions that use HMF and FDCA.

1.2. Synthesis of 5-hydroxymethylfurfural

Since the late 19th century, 5-hydroxymethylfurfural (HMF) **1** has been of interest to many researchers.[8] HMF can serve as a renewable platform for the production of fuels and chemicals. The derivatives 2,5-furan dicarboxylic acid, 2,5-furfuryldiamine, 2,5-furfuryldiisocyanate and 5-hydroxymethyl furfurylidenester are suitable starting materials for polymeric materials. Polyurethanes display very high resistance to thermal treatments.[9] Kevlar-like polyamides exhibit liquid crystal behavior.[9] Polyconjugated polymers of these furan-based molecules possess good electrical conductivity.[9] Due to HMF's ability to serve as an intermediate in a wide range of applications, it has been called a "sleeping giant".[10] The triple dehydration of hexose, fructose or glucose, is the widely accepted method for the synthesis of HMF. Substrates other than hexoses that can be used for the synthesis of HMF include oligosaccharides and polysaccharides. The dehydration reactions can occur in either aqueous or non-aqueous conditions. Compared to aqueous media, the dehydration of hexoses to HMF under non-aqueous conditions is found to be more efficient based on yield.[11] Glucose and fructose are sources for the production of HMF; however, each presents its own challenges. Glucose is desirable because of its abundance and low price, but fructose is readily converted to HMF. Glucose must isomerize to fructose before the dehydration can occur.[12] The dehydration of fructofuranose to HMF has been demonstrated in several different media including water, organic solvents, multiphase systems, ionic liquids and enzymatically. Figure 1.1 shows the name and structure of the many different derivatives of HMF. This section will focus on the different methods for the synthesis of HMF.

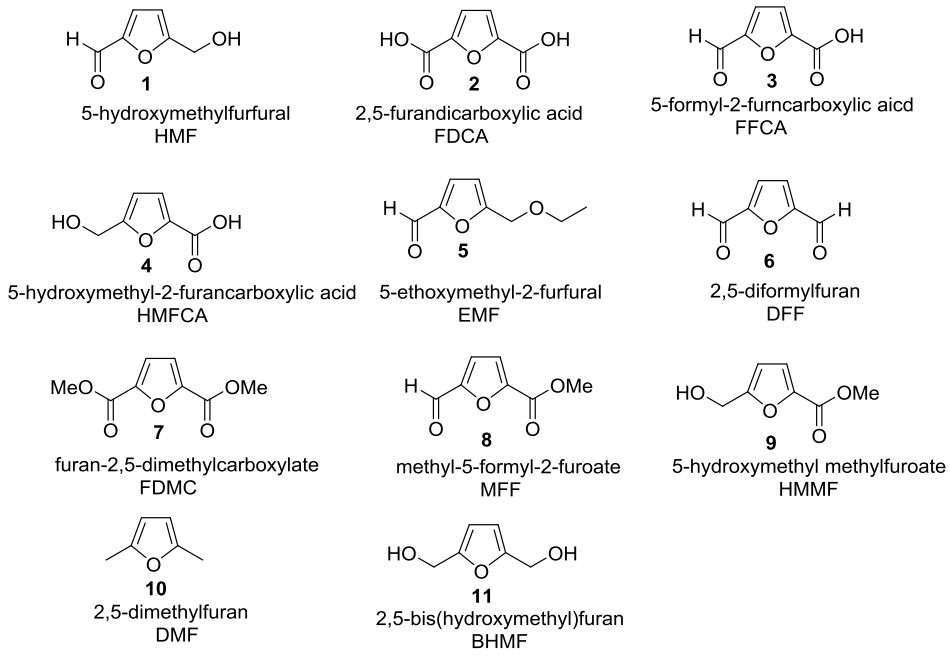
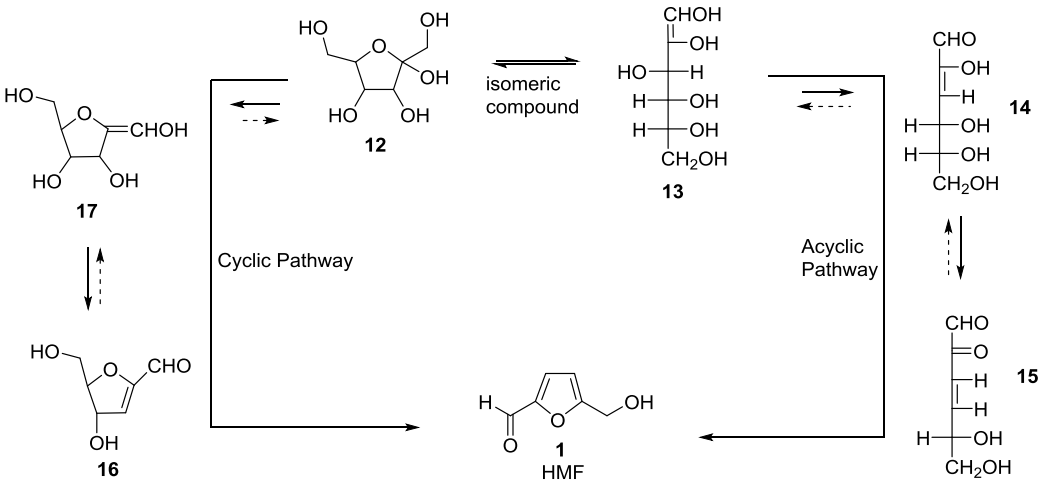


Figure 1.1. HMF based derivatives

1.2.1. Hexose dehydration

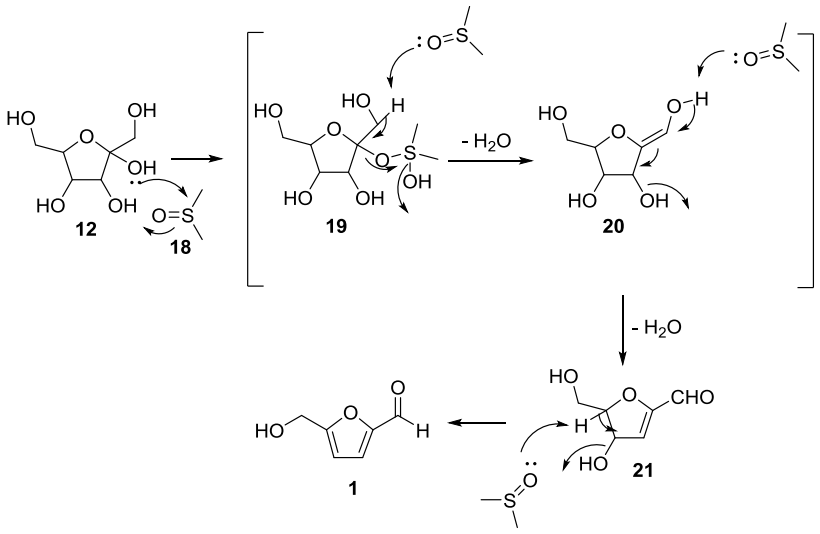
The first mechanism for the dehydration of fructose to HMF was proposed by Haworth and Jones.[13] Work completed by van Dam et al.[14], Kuster[15], and Antal et al.[16] proposed the dehydration of hexoses went through two possible pathways, cyclic or acyclic, as shown in Scheme 1.1. Evidence to support the acyclic pathway, were the fructofuranosyl intermediate or through a 1,2-enediol mechanism.[17,18,19] In support of the cyclic pathway, Antal et al.[20] and Newth[21] gave this evidence: 1) conversion of 2,5-anhydro-D-mannose to HMF, 2) easy formation from fructose but challenging formation from glucose, and 3) lack of carbon-deuterium bond formation from D_2O in the keto-enol tautomerism present in the open chain pathway.



Scheme 1.1. Possible pathways for the dehydration of hexoses

1.2.2. Dehydration in non-aqueous solvents (DMSO)

Dimethyl sulfoxide (DMSO) is a polar aprotic solvent useful in the dehydration of hexose to HMF. As of today, DMSO is the only solvent to efficiently promote dehydration of hexoses and limit unwanted side reactions while generating HMF in high yields.[22] Amarasekara and coworkers were the first to identify a key intermediate (4R,5R)-4-hydroxy-5-hydroxymethyl-4,5-dihydrofuran-2-carbaldehyde **21** in the dehydration of D-fructose to HMF as shown in Scheme 1.2.[23] To initiate the dehydration of fructose to HMF, the C_2 hydroxyl was activated by the electrophilic (sulfur) end of DMSO and the oxygen on DMSO hydrogen bonded with a hydrogen atom on C_1 on fructose; this eliminated the first water molecule due to the proton transfer and oxygen transfer of DMSO.[11] The enol intermediate formed through the oxygen exchange between DMSO and the hydroxyl on the anomeric center of fructose and removal of a hydrogen from C_1.[11] The oxygen on the DMSO promoted the removal of the remaining two water molecules.[11]

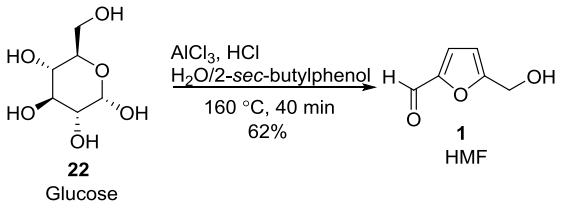


Scheme 1.2. Mechanism for the dehydration of α–furanose/β–furanose to HMF in DMSO

1.2.3. Synthesis of HMF in multiphase systems

Dumesic and coworkers have developed a multiphase system for the production of HMF.[24] The dehydration of fructose occurred in the aqueous phase which contained fructose, DMSO, a hydrophilic polymer and the acid catalyst. The organic phase used for the HMF extraction contained methylisobutylketone (MIBK) and 2-butanol.[24] The optimal system produced HMF in 77% yield at 92% conversion.[24] In a later work by Román-Leshkov and Dumesic, different types of extracting solvents for the dehydration of fructose in a biphasic system in the presence of sodium chloride were explored.[2] They found solvents that contained four carbon atoms such as 2-butanol, produced the highest HMF selectivity of 85% at 423K.[2] Increasing the reaction temperature from 423K to 453K improved HMF selectivity for both 2-butanol and THF systems (85% to 90% and 83% to 89% respectively).[2] Another important finding was that the addition of sodium chloride to the aqueous phase improved the partitioning of HMF into the extracting phase by the "salting-out effect" which increased the yield of HMF.[2]

The production of HMF from glucose using a combination of Lewis and Brønsted acids in a biphasic reactor with an alkyl phenol solvent was recently reported. In a biphasic system using $AlCl_3$ and HCl as catalysts, HMF was produced in a 62% yield (Scheme 1.3).[25] The formation of HMF proceeds by the tandem pathway involving the isomerization of glucose to fructose and the subsequent dehydration of fructose to HMF. The organic phase extracts contained 97% of the HMF produced, while both the Lewis and Brønsted acids remained in the aqueous phase.



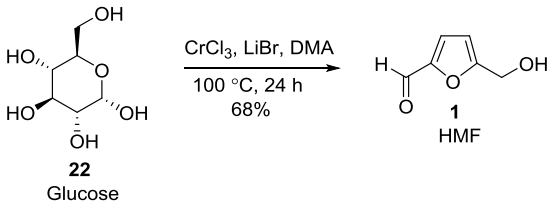
22
Glucose

1
HMF

Scheme 1.3. Formation of HMF from glucose

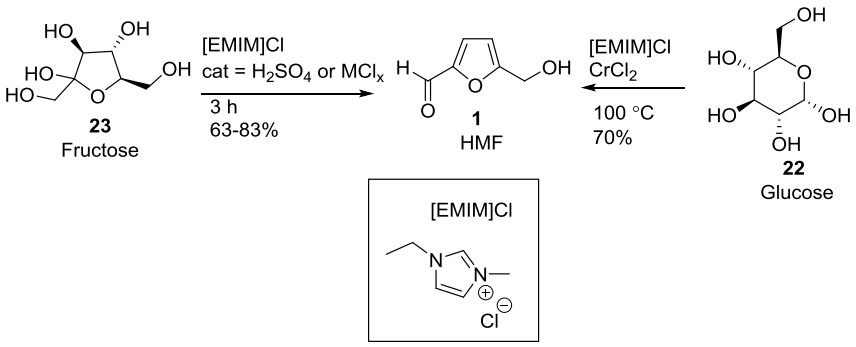
1.2.4. Synthesis of HMF in ionic liquids

Ionic liquids provide an acidic site which accelerates the isomerization of glucose. Ionic liquids are a suitable solvent for the synthesis of HMF because of their inherent properties, such as low vapor pressure, good thermal stability, range of tunable hydrophobicity/hydrophilicity and their industrial applications.[26] Binder and Raines produced HMF with 48% and 54% yields from untreated biomass and purified cellulose respectively, using a $CrCl_2$ catalyst in *N*,*N*-dimethyl acetamide (DMA) solvent containing LiCl and 1-ethyl-3-imidazolium chloride ([EMIM]Cl) as depicted in Scheme 1.4.[27]



Scheme 1.4. Synthesis of HMF from glucose

Zhang and coworkers explored the concept of using 1-ethyl-3-methylimidazolium chloride [EMIM]Cl.[28] Ethyl outperformed or performed as well as octyl or butyl solvent systems.[26] The use of mineral acids performed as expected; a yield of 80% was achieved when 18% H_2SO_4 was used.[26] The use of metal halides catalyzed the dehydration of fructose at 80°C and produced HMF yields in the range of 63-83%; however not all metal halides were effective such as $LaCl_3$ and $MnCl_2$ (Scheme 1.5).[14] When changing the substrate to glucose only one catalyst $CrCl_2$ gave high HMF yields.[26]



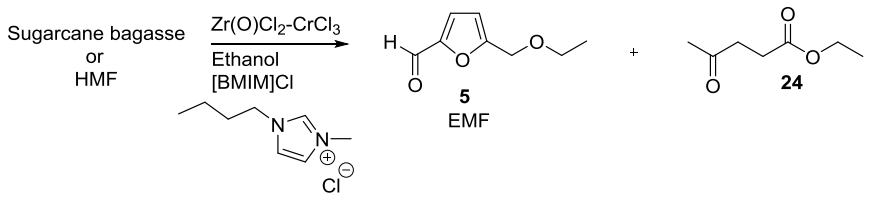
Scheme 1.5. Comparing HMF production from glucose and fructose

A later report by Zhang et al. produced 58% HMF from cellulose using two metal chloride catalysts $CuCl_2$ and $CrCl_2$ in ionic liquids.[29] Moreau and coworkers explored the use of mordenites in the dehydration of fructose.[30] They found that in the presence of mordenites, both fructose conversion and HMF selectivity were increased.[30] The conversion of cellulose to HMF

was produced in a one-pot reaction using a Brønsted-Lewis surfactant-combined heteropoly acid (HPA), $Cr[(DS)H_2PW_{12}O_{40}]_3$ (DS = dodecyl sulfate) in a 53% yield.[31]

In ionic liquids, 48% and 60% HMF yields were achieved using a $CrCl_2$-NHC-carbene/zeolite and combined $CrCl_2/RuCl_3$ catalytic systems.[32,33] The cellulose transformation was reported to proceed by hydrolysis of cellulose using zeolite followed by the resulting glucose dehydration using NHC-$CrCl_2$.[32] In the hydrolysis reaction, a 4:1 M ratio of $CrCl_2/RuCl_3$ was used at 120 °C for two hours.[33]

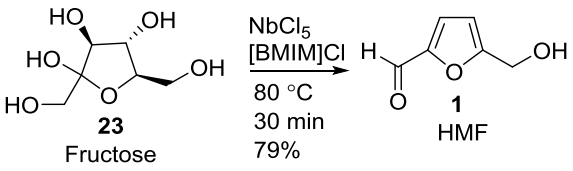
The aforementioned reactions used thermal heating as the energy source. Microwave assisted reactions could be another source of energy for the synthesis of HMF. In a reaction medium of ionic liquids, microwave-assisted synthesis of HMF from cellulose was performed. This rapid synthesis occurred in a 62% yield in two minutes.[34] The synthesis of HMF from cellulose and sugarcane bagasse was investigated under microwave-assisted heating. The most effective catalyst was $Zr(O)Cl_2/CrCl_3$ combined catalyst, producing HMF yields of 57% and 42% from cellulose and sugarcane bagasse respectively.[35] In the presence of 1-butyl-3-methylimidazolium chloride ([BMIM]Cl), HMF yields were improved due to the increased chloride ions concentration, which favors cellulose hydrogen bond disruption.[35] The combined $Zr(O)Cl_2/CrCl_3$ catalyst also effectively converted sugarcane bagasse and HMF into a mixture of 5-ethoxymethyl-2-furfural (EMF) **5**, a promising biofuel, and ethyl levulinate (EL) **24** with 90% EMF selectivity as shown in Scheme 1.6.[35]



Scheme 1.6. Synthesis of EMF from sugarcane bagasse and HMF

Chidambaram and Bell reported that heteropoly acids effectively catalyzed the dehydration of glucose to HMF. After three hours, using 12-molybdophosphoric acid (12-MPA) as the catalyst, in a mixture of [EMIM]Cl and acetonitrile, 98% conversion and 99% selectivity for HMF was achieved.[36] This high selectivity for HMF was higher than observed using liquid acids.[36] Upon hydrogenation of HMF in a mixture of [EMIM]Cl and acetonitrile promoted by Pd/C produced 2,5-dimethyl furan (DMF), in higher yields.[36] DMF has been gaining interest as a biofuel. DMF energy density is 40% greater than ethanol, making it comparable to gasoline.[37,38,39] DMF is less volatile than ethanol due to the higher boiling point 93 °C compared to 78 °C for ethanol.[40]

Multiple metal chlorides in ionic liquids were investigated for the dehydration of fructose to HMF. Niobium pentachloride was found to be an effective catalyst for the dehydration of fructose to HMF (Scheme 1.7).[41] Other Group V metal chlorides like VCl_3 and $TaCl_5$ showed potential good yields; however, formation of humins resulted in slightly lower yields than reacting with $NbCl_5$.

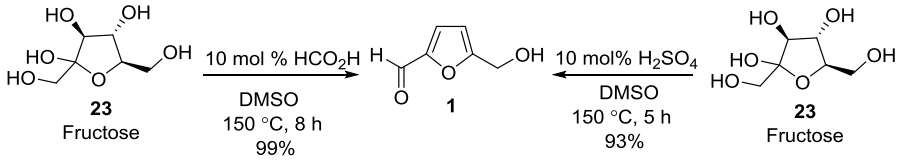


Scheme 1.7. Dehydration of fructose using niobium pentachloride

1.2.5. Synthesis of HMF using catalysts

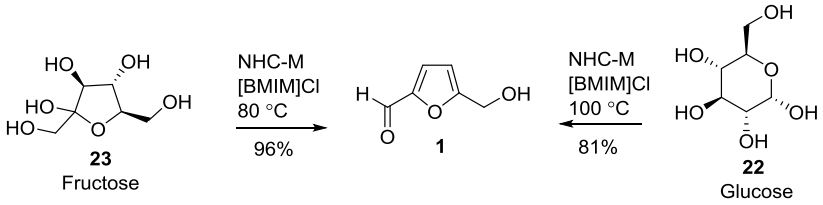
Brønsted acids as well as Lewis acids are known to catalyze the dehydration of fructose to HMF. In a review by Lewkowski, nearly a hundred inorganic and organic compounds were named as a possible catalyst for the synthesis of HMF. The catalysts were grouped into five categories: organic acids, inorganic acids, salts, Lewis acids, and others.[8]

Thananattanachon and Rauchfuss[42] explored the use of organic acids in the conversion of fructose to HMF. They found that the addition of organic acids accelerated HMF formation and that side reactions in DMSO were reduced as compared to water. In comparing sulfuric acid and formic acid as catalysts, reactions with formic acid took slightly longer and required a higher temperature than sulfuric acid.[42] However, the yield when using a formic acid/DMSO mixture was 99% compared to 93% with the sulfuric acid/DMSO mixture as displayed in Scheme 1.8.[42] They also found that oxalic acid and acetic acid catalyzed the formation of HMF from fructose with a 99% yield as well.[42]



Scheme 1.8. Formation of HMF from different acids

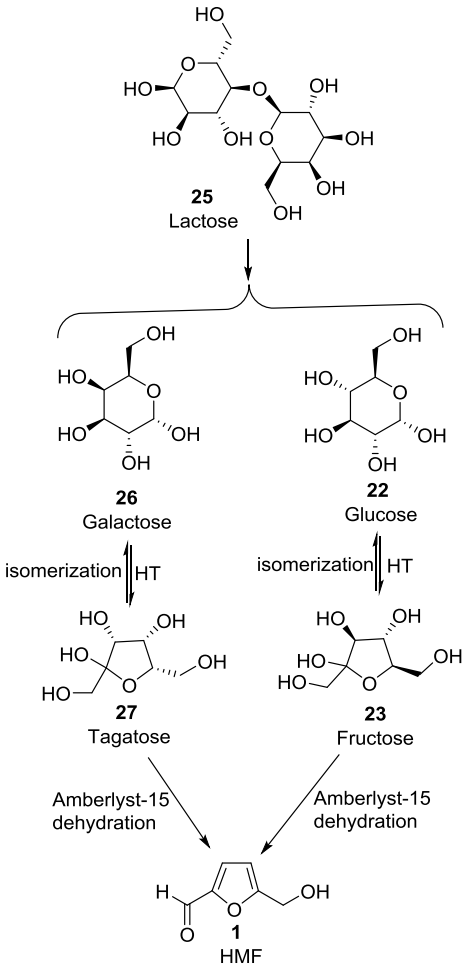
Ebitani[43] and coworkers produced HMF from both monosaccharaides (glucose and fructose) and disaccharides (sucrose - a disaccharide of glucose and fructose and cellobiose - a disaccharide of glucose) by a one-pot synthesis using a solid Amberlyst-15 acid and hydrotalcite base.[43] They reported high selectivity and conversion for simple monosaccharaides (>99% conversion and 76% HMF selectivity with fructose and 73% conversion and 58% HMF selectivity with glucose) and high selectivity for the disaccharides (58% conversion and 93% HMF selectivity for sucrose and 52% conversion and 67% HMF selectivity for cellobiose).[43] Based on Zhang[28] and coworkers findings that transition metals were good catalysts for the conversion of HMF from sugars, Ying[12] and coworkers used an N-heterocyclic carbene (NHC)/metal complex as the catalyst for the dehydration of sugars. They found that the catalyst with the most bulky NHC ligand such as 1,3-bis(2,6-diisopropylphenyl)imidazolylidene and 1,3-bis(2,6-diisopropyl)phenylimidazolinylidene produced the highest yields of 96% from fructose and 81% from glucose (Scheme 1.9).[12] In a recent report, a new catalytic system which incorporated an enzyme and acid catalysis produced HMF with a 63% yield.[44] The isomerization of glucose to fructose was assisted by immobilized glucose isomerase in the presence of sodium tetraborate.[44] This is the key step in producing high yields of HMF.



Scheme 1.9. Production of HMF from fructose and glucose

Lactose **25** is a disaccharide of glucose **22** and galactose **26**, upon isomerization with a base catalyst, fructose **23** and tagatose **27** were formed, and then further dehydration with an acid

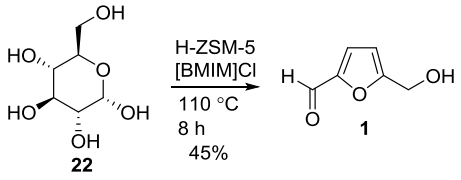
catalyst gave HMF. The yield of HMF from glucose is much higher than that of galactose at all temperatures (Scheme 1.10).[45] This is explained by the stereochemical configuration of galactose; consequently, there is inefficient dehydration of tagatose into HMF. Galactose and tagatose are less reactive than glucose and fructose.



Scheme 1.10. Synthesis of HMF from lactose

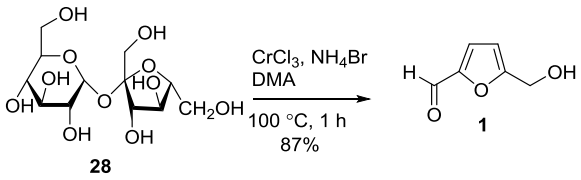
A 45% isolated yield was achieved when an acidic zeolite, H-ZSM-5, catalyzed the dehydration of glucose to HMF in [BMIM]Cl (Scheme 1.11).[46] Further experiments showed that

tetrabutylammonium chloride (TBAC) was a more convenient, inexpensive and non-toxic solvent to work with than [BMIM]Cl. TBAC gave HMF yields in 50-55% yields.



Scheme 1.11. H-ZSM-5 zeolite as a catalyst for the conversion of glucose to HMF

Recent work demonstrated that NH_4Br is an effective promoter for the conversion of glucose and fructose to HMF.[47] Using a catalyst system of $CrCl_3$ and NH_4Br at 100 °C for one hour in DMA an 87% yield of HMF from sucrose **28** was achieved (Scheme 1.12).

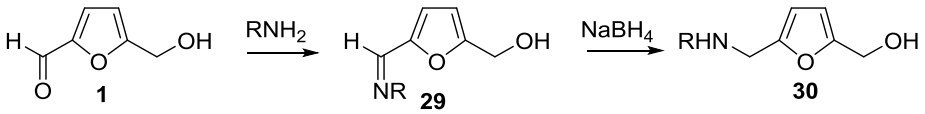


Scheme 1.12. Conversion of sucrose to HMF

1.2.6. Reactions involving HMF

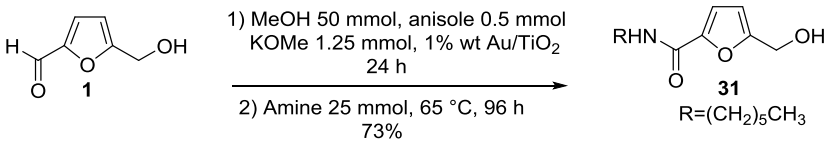
In organic synthesis, reductive amination is used frequently. In recent work done by Cukalovic and Stevens, a library of compounds containing a hydroxymethyl and an aminomethyl moiety were produced (Scheme 1.13).[48] The method was a straightforward, one-pot, two-step reductive amination, followed by a reduction with sodium borohydride. In an aqueous medium, aliphatic amines produced good results; complete conversion to imines and imine reduction took place in just a few hours.[48] Up to 50% conversion was produced when aromatic imines were

used in aqueous solutions. Methanol also gave poor results for aromatic amines; however, aliphatic amines showed improved reaction times, only 45 minutes in methanol compared to four hours needed for completion in water.[48]



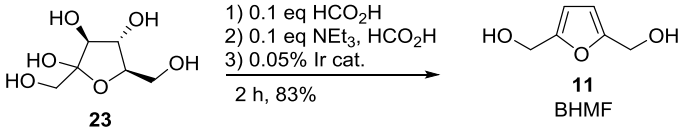
Scheme 1.13. Synthesis of HMF based amines

The production of amides **31** by the aerobic oxidative coupling of alcohols or aldehydes using supported gold and base as the catalyst was highly effective.[49] HMF was oxidized to the corresponding amide through the synthesis of a methyl ester in a 73% yield (Scheme 1.14).



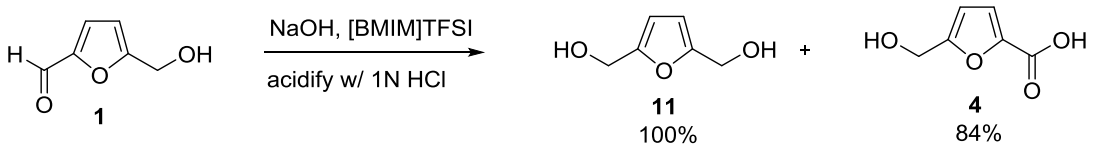
Scheme 1.14. HMF derived amide synthesis

In a one-pot process, fructose **23** can be converted into 2,5-bis(hydroxymethyl)furan (BHMF) **11** in an 83% yield.[42] Formic acid acts initially as the acid catalyst for the dehydration and subsequently as the hydrogen donor for hydrogenation as displayed in Scheme 1.15.[42]



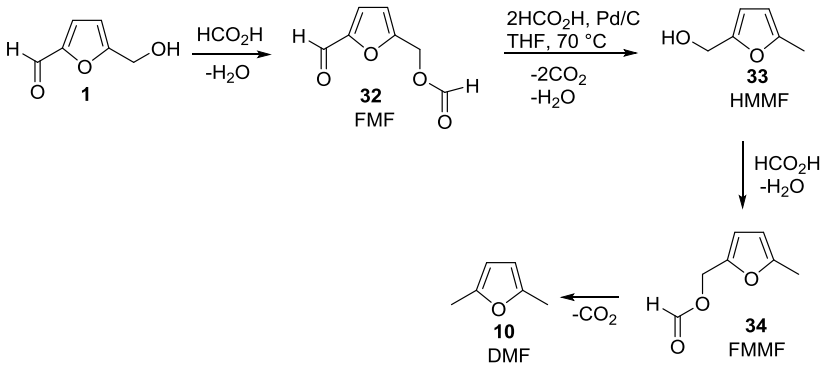
Scheme 1.15. Synthesis of 2,5-bis(hydroxymethyl)furan from fructose

An effective and eco-friendly Cannizzaro reaction of HMF has been developed for the simultaneous synthesis of both BHMF **11** and HMFCA **4** using ionic liquids as the reaction media in good to high yields (Scheme 1.16).[50] Key steps to this process include: the Cannizzaro reaction of HMF using ionic liquids, recovery and recycling of the ionic liquids and acid-base extraction to isolate both products.



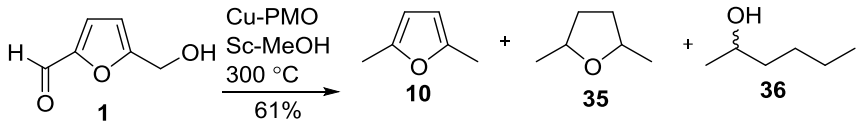
Scheme 1.16. Cannizzaro reaction of HMF to BHMF and HMFCA

Thananattanachon and Rauchfuss produced DMF **10** in an overall 51% yield by heating HMF, formic acid with Pd/C catalyst at 70 °C (Scheme 1.17).[51] Formic acid played a key role in both the hydrogenation and hydrogenolysis. This formation of DMF is believed to proceed through intermediates 2-hydroxy-methyl-5-methylfuran (HMMF) **33** and monoformate ester (FMMF) **34**.



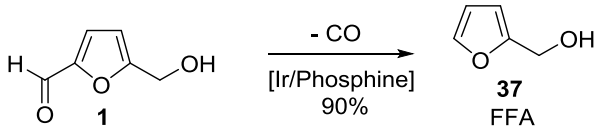
Scheme 1.17. One-pot synthesis of DMF

In recent work, Cu-doped porous metal oxides (PMO) converted HMF into valuable chemicals DMF **10**, dimethyltetrahydrofuran **35**, and 2-hexanol **36** in supercritical methanol by hydrogen transfer.[52] The three products were produced in a 61% yield at 300 °C for two hours (Scheme 1.18). Under milder reaction temperatures, DMF was obtained in a 50% yield.



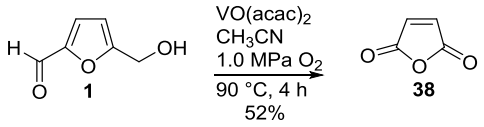
Scheme 1.18. One-pot reduction of HMF in supercritical methanol

The highly selective decarbonylation of HMF **1** to furfuryl alcohol (FFA) **37** was achieved in greater than 90% yields using an iridium phosphine catalyst in the presence of compressed carbon dioxide (Scheme 1.19).[53]



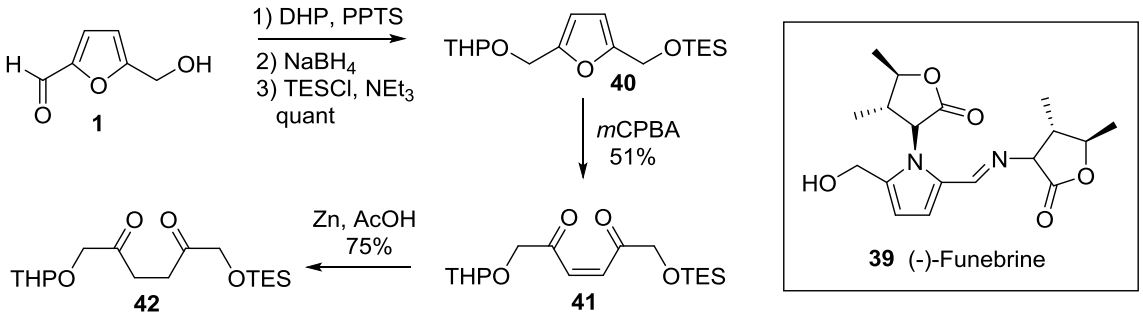
Scheme 1.19. Catalytic decarbonylation of HMF

HMF was converted to maleic anhydride (MA) **38** in 52% yield by the selective oxidation with molecular oxygen using $VO(acac)_2$ as the catalyst in liquid phase (Scheme 1.20).[54] The conversion of HMF and yields of MA were significantly increased with increasing the oxygen pressure. Acetonitrile and acetic acid were solvents that favored the formation of MA **38** over DFF **6**. The carbon-carbon bond cleavage occurred due to the hydroxymethyl group of HMF rather than the aldehyde group.



Scheme 1.20. Synthesis of maleic anhydride

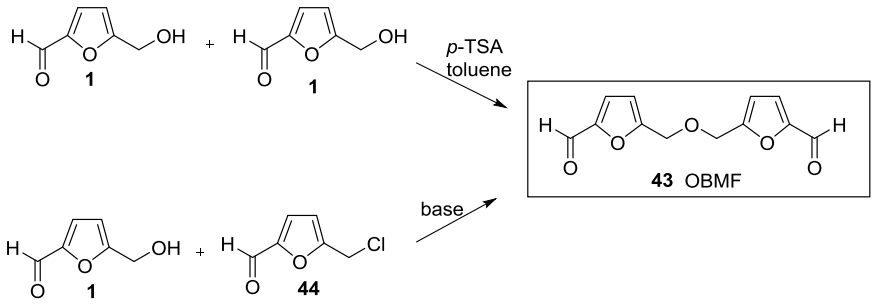
(-)-Funebrine **39** was isolated in 1984 from the flowers of *Quararibeafunebris*.[55] Funebrine is based on the highly functionalized γ-butyrolactone core. To date, only two total syntheses have been reported.[55] HMF was used in the total synthesis of Funebrine. First step was the protection of the hydroxyl group, followed by the reduction of the aldehyde to the corresponding alcohol, which was further protected with TES **40**. Anhydrous *m*CPBA oxidized the furan ring which produced the enone **41**. Upon further reduction with Zn/AcOH, the unsymmetrical 1,4-diketone **42** was produced (Scheme 1.21).[55]



Scheme 1.21. Steps in the total synthesis of (-)-Funebrine involving HMF

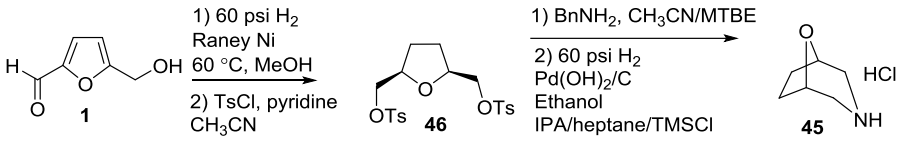
The synthesis of 5,5'(oxy-bis(methylene))bis-2-furfural (OBMF) **43** has been receiving interest in the preparation of imine-based polymers and in the preparation of hepatitis antiviral precursors.[56] Reacting OBMF and 1,4-diaminobenzene results in a polymer that exhibits high glass transition temperature (300 °C) and high thermal and electrical conductivity.[56] The hepatitis application is produced by reacting OBMF with 4-amino-pyridine in the presence of

para-toluenesulfonic acid (pTSA) followed by a reduction with KBH_4.[57] Two different methods have been reported in literature for the synthesis of OBMF, 1) the etherification of two HMF molecules in organic solvent with an organic catalyst to obtain 72% yield[58,59,60] and 2) Williamson reaction between HMF and 5-chloro-methyl-2-furfural **44** (Scheme 1.22).[57] High conversion and selectivity of OBMF was achieved using molecular sieves with Brønsted and Lewis acid sites. Mesoporous materials such as Al-MCM-41 and Sn-MCM-41 performed better than the zeolites.[56] Al-MCM-41 bearing a Brønsted acid site performed better than a homogeneous acid catalyst such as pTSA.[56] Trifluorotoluene as the solvent generated the highest yield of OBMF of 99%.[56]



Scheme 1.22. Synthetic routes to OBMF

A four step synthesis generated 8-oxo-3-aza-bicyclo[3.2.1]octane hydrochloride **45** in 53% yield starting from HMF (Scheme 1.23).[61] This synthesis comprised a Raney nickel reduction followed by a protection, and finally a cyclization with benzylamine. Pearlman's catalyst helped in the hydrogenolysis of the N-benzyl group.[61]

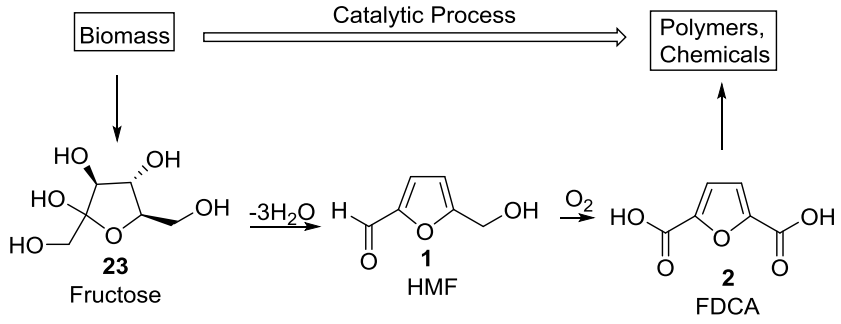


Scheme 1.23. Synthesis of 8-oxo-3-aza-bicyclo[3.2.1]octane hydrochloride

1.3. Synthesis of 2,5-furan dicarboxylic acid

2,5-Furan dicarboxylic acid (FDCA) also known as dehydromucic acid, is an oxidized furan derivative. The early preparations of FDCA used mucic or saccharic acids with concentrated hydrobromic acid solution, giving poor yields of 20-30%.[62] In 1953, the synthesis of FDCA (74% yield) by the oxidation of methyl 5-formyloxymethyl-2-furoate with 65% nitric acid was reported by Moldenhauer.[62] Based on the difficult purification techniques, it was more convenient to esterfy and distill. Upon saponification, the desired diacid was produced in a 45% yield.[62] In 1973, FDCA was first reported in human urine.[63] A healthy human produces between 3-5 mg/day.[63] FDCA can also be obtained by the oxidation of HMF. FDCA is chemically very stable and is a promising platform for biomass derived analogues, because of its potential as a terephthalic acid replacement. Terephthalic acid (TPA) is used in the manufacturing of poly(ethyleneterephtalate) (PET), which is used in various polyesters, plastics, fine chemicals, pharmaceuticals, and agrochemicals (Scheme 1.24).[64] Products produced from FDCA may be possible alternatives for the petroleum-based industry. Current applications of FDCA include the preparation of furanic-modified amine based derivatives for polyureas, and polyester polyols for the manufacturing of corrosion and flame resistant coatings,[65] which are used in small amounts in fire foams.[52,66] Another application of FDCA is the use as a fungicide[67] and in medicine for the removal of kidney stones.[66] FDCA has been identified as one of the 12 building block compounds that can be produced from sugars. The first synthesis of FDCA was the

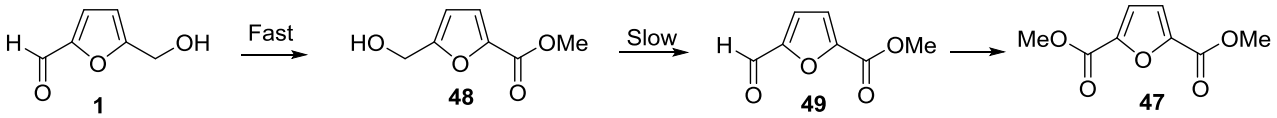
reaction of mucic acid with hydrobromic acid.[8] Numerous reports have been made changing the dehydrating agent.[8]



Scheme 1.24. Pathway for chemical products from renewable resources

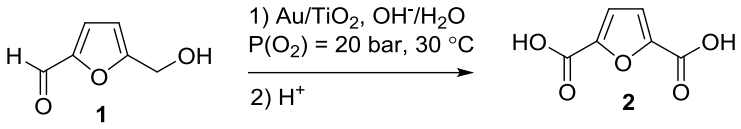
1.3.1. Oxidation of HMF

HMF can be oxidized into FDCA. The synthesis requires high temperature, high pressure, metal salts, and organic solvents.[8] Gold has become an excellent catalyst for selective oxidation with molecular oxygen when dispersed on nanoparticles. Christensen et al. transformed HMF directly into furan-2,5-dimethylcarboxylate (FDMC) **47** in excellent 98% yield in 3 hours.[68] Pure FDMC was easily attained because FDMC can be purified by sublimation in contrast to FDCA.[68] In just a few hours, HMF can readily be oxidized to 5-hydroxymethyl methylfuroate (HMMF) **48** at a pressure of 1 atmosphere of oxygen. This confirmed the aldehyde moiety was oxidized much faster than the hydroxymethyl side chain.[68] Upon raising the temperature, the alcohol can be oxidized to an aldehyde forming methyl-5-formyl-2-furoate (MFF) **49,** which can be oxidized to the ester FDMC **47** (Scheme 1.25).[68]



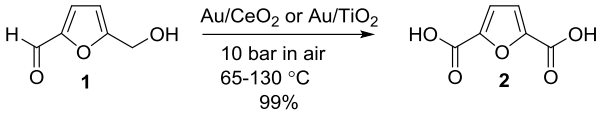
Scheme 1.25. Proposed oxidation pathway of HMF to FDMC

Riisager et al. produced FDCA in a 71% yield with complete HMF conversion in an aqueous solution over an Au/TiO_2 catalyst; however it required 20 equivalents of base as shown in Scheme 1.26.[69]



Scheme 1.26. Oxidation of HMF to FDCA

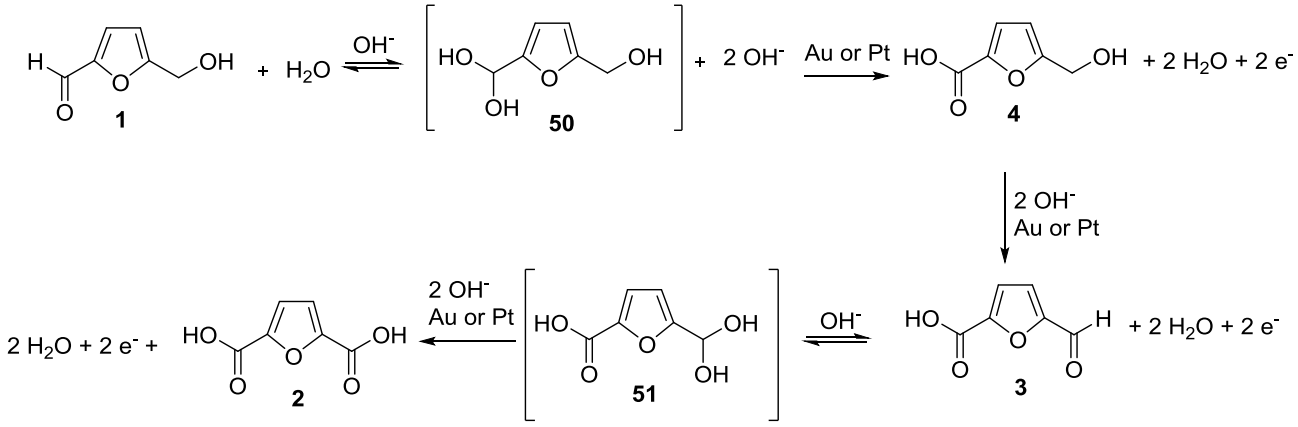
In recent work done by Casanova et al. HMF was oxidized to FDCA with gold nanoparticles in water, under mild conditions (65-130 °C, 1.0MPa air) as depicted in Scheme 1.27.[65] They found that Au-CeO_2 and Au-TiO_2 were the best performing catalysts. Comparing Au-CeO_2 and Au-TiO_2, Au-CeO_2 gave higher activity and selectivity for FDCA.[65].



Scheme 1.27. HMF oxidation to FDCA

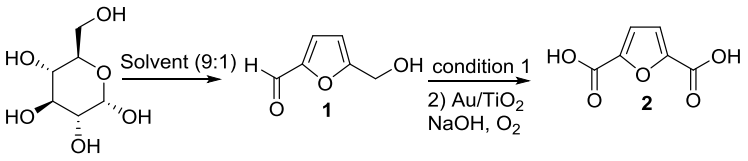
The oxidation of HMF to FDCA is a sequential reaction where the aldehyde side chain is rapidly oxidized by the solvent (Scheme 1.28).[70] The mechanism started with the fast oxidation of HMF into 5-hydroxymethyl-2-furancarboxylic acid (HMFCA) **4** via formation of a

hemiacetal **50**, followed by the rate limiting step, the oxidation of HMFCA to FDCA.[65] Following this step, hydroxide ions from the water with a metal catalyst promote O-H and C-H bond activation on the alcohol side chain to the aldehyde than further oxidation to the acid. Results from labeling experiments, indicate that hydroxide ions from water acts as the oxygen source rather than molecular oxygen.



Scheme 1.28. Proposed mechanism for HMF oxidation to FDCA

The synthesis of FDCA from glucose in different solvent systems was recently investigated.[71] The highest obtained overall yield was 50% when THF was the solvent. The yields were lower when using γ-valerolactone (GVL) and γ-hexalactone (GHL), 38% and 35%, respectively (Table 1.1).

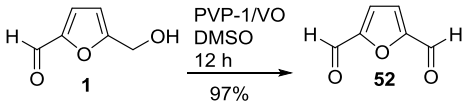


Entry	Solvent	Condition 1[a]	Yield **2** (%)
1	$THF:H_2O$	distillation	50
2	$GVL:H_2O$	extraction	38
3	$GHL:H_2O$	extraction	35

[a] Work up of HMF

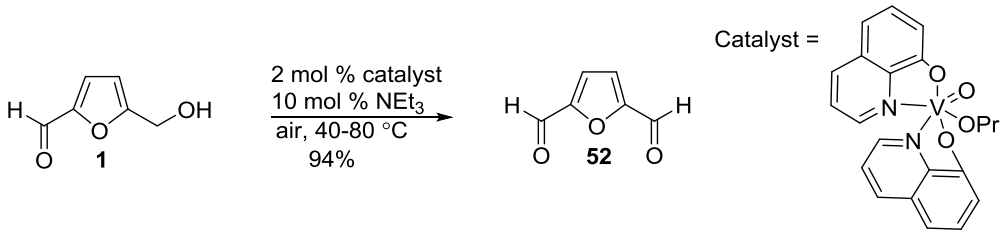
Table 1.1. FDCA synthesis from glucose

A variety of oxidants have been used for the oxidation of HMF to FDCA, however only a few use oxygen, the most economical oxidant. The few reported methods for the oxidation of HMF with oxygen are with heterogeneous platinum catalysts. Partenheimer and coworkers reported the first example of catalytic aerobic HMF oxidation catalyzed with a homogeneous metal/bromide system (Co/Mn/Zr/Br).[72] The application of metal salts comprising of transition-metal acetates and a bromide source, $Co(OAc)_2/HBr/Mn(OAc)_2$, is commonly known as Amoco Mid-Century (MC) catalyst.[73] They found that HMF can be oxidized to 2,5-diformylfuran (DFF) **52** and FCDA with 57 and 60% isolated yields, respectively.[72] Navarro et al. produced DFF from HMF in a >99% selectivity.[74] This method used vanadyl-pyridine complexes in both homogeneous and heterogeneous forms in several solvents including toluene, trifluorotoluene and DMSO (Scheme 1.29). A drawback to this method was the very high catalyst loading (mol substrate/mol metal = 10).[74]



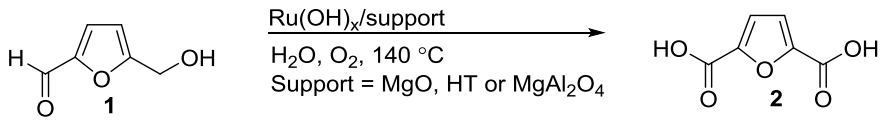
Scheme 1.29. Production of DFF from HMF

The oxidation of benzylic, allylic, and propargylic alcohols was shown to be catalyzed by 8-quinolinate vanadium complex. HMF containing an allylic alcohol was oxidized to DFF in a 94% yield (Scheme 1.30).[75]



Scheme 1.30. Oxidation of HMF using vanadium complex

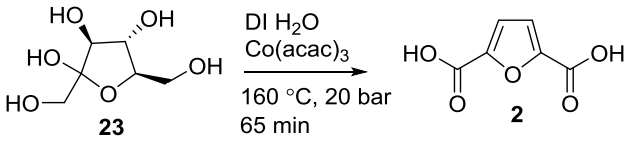
Riisager et al. explored ruthenium hydroxide supported by magnesium-based materials spinel ($MgAl_2O_4$), magnesium oxide, and hydrotalcite (HT).[76] All three catalysts effectively catalyzed the oxidation of HMF to FDCA in water without the addition of base. Both the HT and MgO supports dissolved partially resulting in Mg^{2+} ions, making the system basic; however, the spinel remained stable throughout the reaction which allowed the oxidation to occur under a base free condition.[76] Their data suggests the initial competitive oxidation to be relatively slow compared to the subsequent oxidation of DFF or HMFCA.[76] For the selective, aerobic oxidation of HMF to FDCA, heterogeneous ruthenium-based catalysts were used according to a later report by Riisager et al (Scheme 1.31).[77] The yield of FDCA after 6 hours was 38%; consequently, after 18 hours the yield increased to 60%.[77] Ceria-supported catalysts effectively oxidized HMF, which is in line with the previous work done by Corma et al.[77]



Scheme 1.31. Oxidation of HMF using ruthenium based catalysts

Hydrotalcite-supported gold nanoparticle catalyst (Au/HT) was found to oxidize HMF to FDCA with excellent conversion 99% and selectivity 99% in water at 368 K under an ambient oxygen pressure without any addition of homogeneous base.[64] HT consists of layered clays with HCO_3^- and OH^- groups on the surface and is known for high activity base catalyzed reactions such as aldol condensation, Knoevenagel condensation and transesterification. In addition, metals supported on HTs function as excellent catalysts for alcohol oxidation. Without any loss of activity or selectivity, the catalyst could be reused three times.[64]

Noble metal catalysts such as carbon or alumina-supported platinum have been found to be effective for the oxidation of HMF to FDCA.[7] When the pH was controlled, HMF was favorably oxidized to the diacid.[54] Ribeiro and Schuchardt explored a very efficient bifunctional acidic and redox catalyst, cobalt acetylacetonate encapsulated in sol-gel silica.[78] They produced FDCA **2** with 99% selectivity with 72% conversion from D-fructose **23** at 160 °C under 2.0 MPa air (Scheme 1.32).[78]



Scheme 1.32. Synthesis of FDCA from fructose

The oxidation of HMF over Pt/Pb catalysts was investigated by Gaset et al.[79] They found the need for high pH for the reaction to succeed. Another interesting finding was the oxidation of HMF to FDCA occurred in two stages; first the aldehyde side chain was oxidized to a carboxylic acid. After the production of HMFCA, the second stage oxidized the hydroxymethyl side chain, resulting in the production of FDCA.[79]

Davis et al. explored the rate and product formation for HMF oxidation over supported metal catalysts, Pt/C, Pd/C, Au/C, and Au/TiO_2.[80] The rate of HMF oxidation using gold catalysts was an order of magnitude greater than Pt or Pd under standard conditions (295 K, 690 kPa O_2, 0.15 M HMF, 0.3 M NaOH).[80] However, the gold catalysts produced the intermediate HMFCA, oxidation of the aldehyde side chain of HMF. Gold as the catalyst, produced 92% and 8% selectivity for HMFCA and FDCA, respectively.[80] It is interesting to note, that both Pt and Pd could activate the alcohol side chain and were effective at oxidizing HMFCA to FDCA.[80] High pressures of oxygen and high concentrations of base were required for the oxidation of FDCA from HMFCA when using gold catalysts; furthermore, the effect of base was more important than the pressure of oxygen.[80] FDCA selectivity of 79% and 71% were achieved by Pt/C and Pd/C respectively.[80]

Lilga et al. oxidized HMF in basic, neutral and acidic solutions.[81] High yields and selectivity of FDCA were achieved in basic solutions. Using stoichiometric amounts of aqueous Na_2CO_3, with air, over supported platinum metals like Pt/C and Pt/Al_2O_3 produced near quantitative yields of FDCA.[81] FFCA was favored over FDCA when lower platinum loading was used. For example, 93% conversion and 83% selectivity for FFCA was achieved when 5% Pt/C was used; however, when decreasing the liquid hourly space velocity, the FDCA selectivity and

HMF conversions increased, 80% and 100% respectively.[81] Neutral solution reactions were slower and incomplete. Due to the fact, that inorganic supports absorb less than carbon supports, inorganic supports with very low surface areas and relatively high metal loadings were the most effective catalysts for the synthesis of FDCA.[81] Complete HMF conversion and high selectivity (up to 98%) was achieved from Pt/ZrO_2 catalysts.[81] FDCA is relatively insoluble in water; however, carboxylic acid solvents such as acetic acid/water mixtures increased the solubility. The preferred product DFF was formed in about 70% selectivity.[81] The oxidation of the primary alcohol of HMF produced FFCA in an 85% yield under a TEMPO-mediated oxidation.[82]

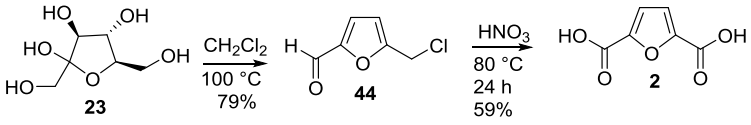
Metal permanganates including lithium, sodium, magnesium, calcium, strontium, cesium, zinc and silver were investigated for the oxidation of HMF. In the presence of potassium permanganate in a basic solution under bubbling oxygen, FDCA was produced in an 89% yield.[83]

Vuyyuru and Strasser performed a comparison study on chemical catalysis and electrochemical catalysis comparing the effect of pH, the effect of oxygen pressure and the effect of the nature of the metal catalyst.[40] At high pH, ($pH \geq 13$), the aldehyde moiety oxidizes faster to the carboxylic acid relative to the alcohol moiety. The oxidation of the alcohol is slow due to the stabilizing electron effects of the furan ring and formyl group.[40] The yields for FDCA increased with time by oxidizing both the aldehyde and the alcohol groups, 80% yield of FDCA after 8 hours of reaction time.[40] At low pH, the formation of FDCA was significantly reduced; consequently, an increase in pH increased the formation of FDCA, as well as the solubility.[40] The effect of pressure influenced the FDCA yield; higher pressure proceeded with higher FDCA yields. The increased oxygen pressure increased the amount of available dissolved oxygen for

the oxidation of HMF.[40] Comparing the different metal nanoparticle catalysts, gold was superior. Gold effectively oxidized HMF with a yield of 80% FDCA.[50] Ru, Rh, and Pd showed low activity for HMF oxidations.[40]

Kröger et al. developed a concept of "*in situ* oxidation of HMF".[84] This was performed by working in a two-phase system water/methyl isobutyl ketone (MIBK). The water phase produced HMF and the oxidation reaction took place in MIBK.[84] Oxidation products reached 50% maximum selectivity. The product yield of FDCA was 25%.[84]

Dehydration of carbohydrates can lead to 5-(chloromethyl) furfural (CMF) **44** which can be oxidized to FDCA **2** in 59% yield (Scheme 1.33).[85] CMF can be used for other transformations as well, including hydrolysis to HMF, reduction to (5-methylfuran-2-yl)methanol and reductive amination to symmetrical furan diamines.

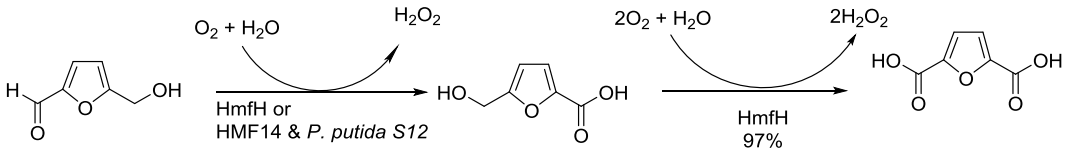


Scheme 1.33. CMF oxidation to FDCA

1.3.2. Enzymatic conversions to FDCA

Chemical processes tend to have harsh reaction conditions. However biotransformations typically proceed under milder conditions and commonly require fewer toxic chemicals.[86] The first reported enzyme to catalyze the oxidation of HMF was chloroperoxidase (CPO) from *Caldariomyces fumago*, which is a heme peroxidase, containing iron(III)protoporphyrin(IX) as the prosthetic group.[87] However this process leads to incomplete HMF oxidation. The oxidation of HMF by CPO and hydrogen peroxide proceeds with 60-74% selectivity to DFF, with a major

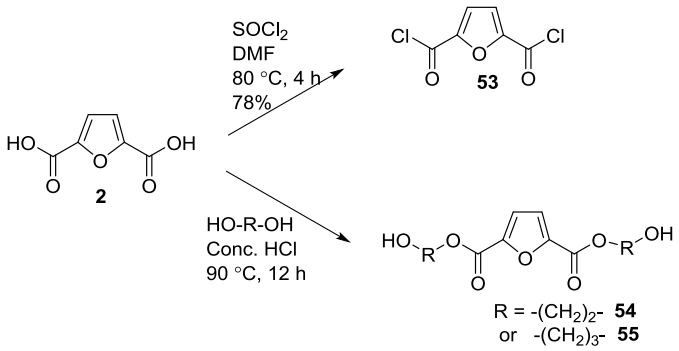
byproduct of HMFCA **4** and a minor byproduct of 5-formyl-2-furancarboxylic acid (FFCA) **3**.[87] With the incomplete oxidation and mixture of products, this biocatalyst was insufficient.[88] A new promising biocatalyst *Cupriavidus basilensis* oxidoreductase HmfH has been reported.[88] The oxidation of HMF proceeded in two steps. The first step can be catalyzed by either *C. basilensis* oxidoreductase HmfH or by a specific aldehyde dehydrogenases in *C. basilensis* HMF14 and *P. putida S*12; however the second step is only oxidized by HmfH (Scheme 1.34).[88] Koopman et al. produced FDCA from HMF with a 97% yield using a whole-cell biotransformation.[88]



Scheme 1.34. Schematic representation of the oxidation of HMF to FDCA

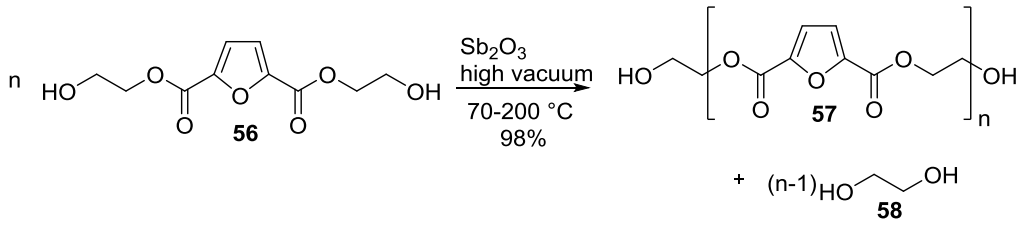
1.3.3. Reactions incorporating FDCA

Based on FDCA, 2,5-furandicarbonyl dichloride **53** and polyesters were synthesized using Fischer esterification under mild conditions (Scheme 1.35).[89]



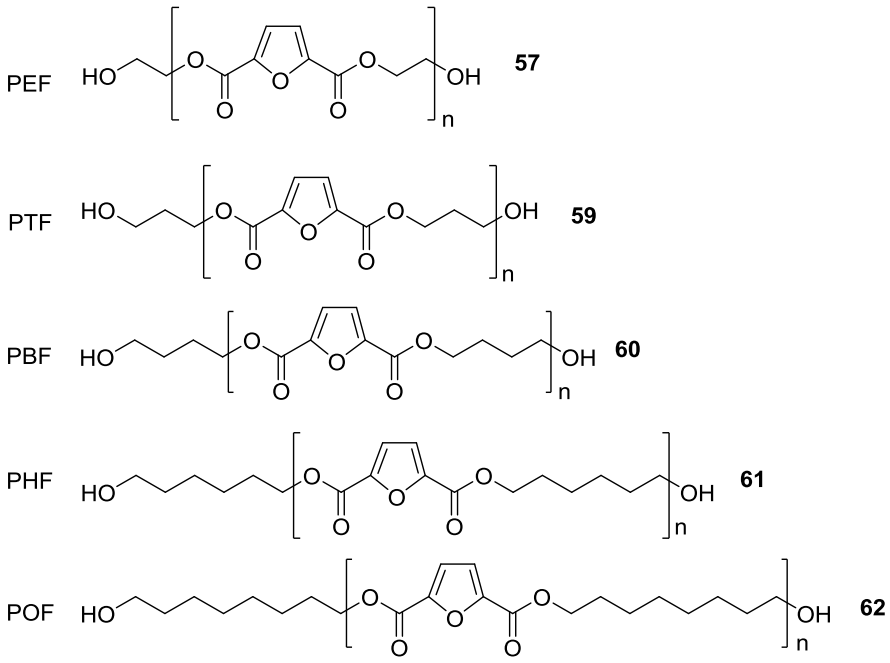
Scheme 1.35. Synthesis of polyesters from FDCA

The synthesis of poly(ethylene 2,5-furandicarboxylate) (PEF) **57** was explored by various synthetic pathways including 1) the polycondensation of furandicarbonyl dichloride and ethylene glycol, 2) transesterification of the dimethyl ester with excess ethylene glycol followed by polytransesterification and 3) the polytransesterification of the diester diol.[90] The best route was the polytransesterification of the diester diol producing PEF **57** in 98% yield (Scheme 1.36).



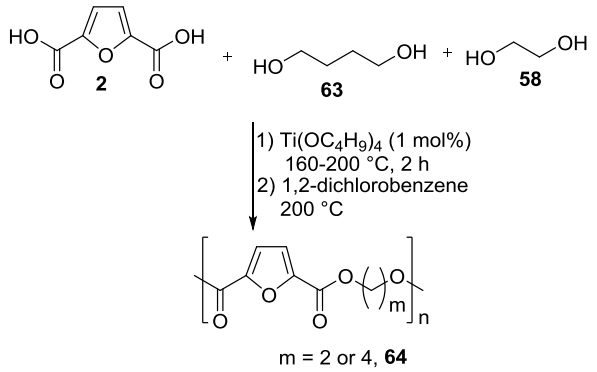
Scheme 1.36. Synthesis of PEF

Starting from ethylene glycol, 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, and 1,8-octanediol, a series of furan based polyesters including poly(ethylene 2,5-furandicarboxylate) (PEF) **57**, poly(trimethylene 2,5-furandicarboxylate) (PTF) **59**, poly(butylene 2,5-furandicarboxylate) (PBF) **60**, poly(hexylene 2,5-furandicarboxylate) (PHF) **61**, and poly(octylene 2,5-furandicarboxylate) (POF) **62** were synthesized via direct esterification (Scheme 1.37).[91]



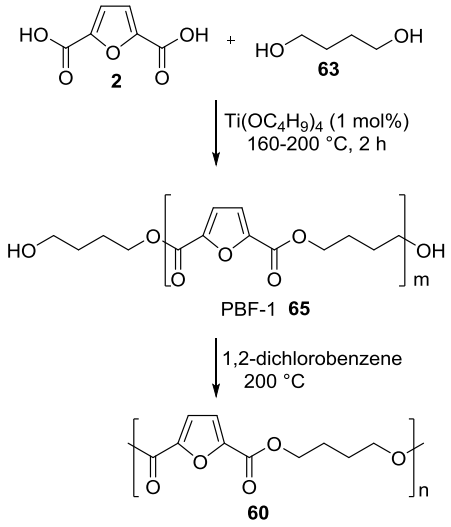
Scheme 1.37. Structures of PEF, PTF, PBF, PHF, and POF

Novel furan containing copolyesters were synthesized by polytransesterification of FDCA and ethylene glycol (EG) **58** and 1,4-butylene glycol (BG) **63**.[92] Excess **58** and **63** were used for complete conversion of all carboxylic groups into ester linkages. In order to remove any excess EG or BG, 1,2-dichlorobenzene was added as it will form azeotropes. The product consisted of milk white fibrous copolyesters with the name PEF/PBF-*x* **64** was achieved in high yields. It was determined that EG was less reactive than BG based on kinetic studies; the reactivity of diols with FDCA increased with a longer carbon chain (Scheme 1.38).



Scheme 1.38. Synthesis of copolyesters PEF/PBF-*x*

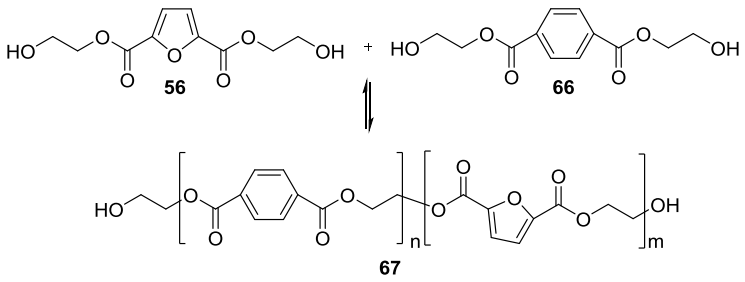
Upon esterification of FDCA and 1,4-butylene glycol **63**, poly(butylene 2,5-furandicarboxylate) (PBF) **60** was synthesized in 93% yield.[93] The synthesis proceeds through an intermediate PBF-1 **65** which has both ends completely capped with hydroxybutylene group (Scheme 1.39). Based on NMR studies, the stages of polymerization were easily detected.



Scheme 1.39. Synthesis of PBF

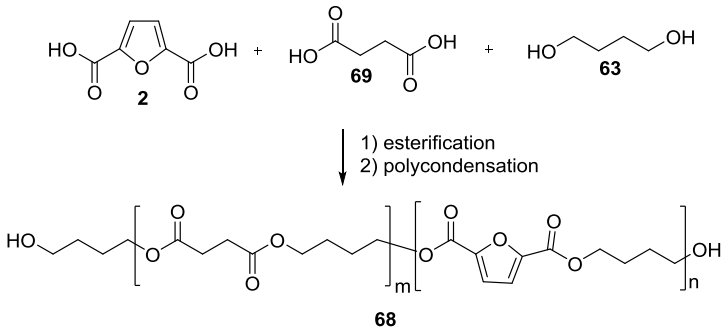
The random copolymerization reactions of bis(2-hydroxyethyl) terephthalate (BHETP) **66** and bis(hydroxyethyl)-2,5-furandicarboxylate (BHEFDC) **56** using different monomeric feed

ratios was recently reported.[94] Incorporating 20% of the renewable furan units PET-ran-PEF 4/1 **67** showed similar properties to commercial PET (Scheme 1.40).



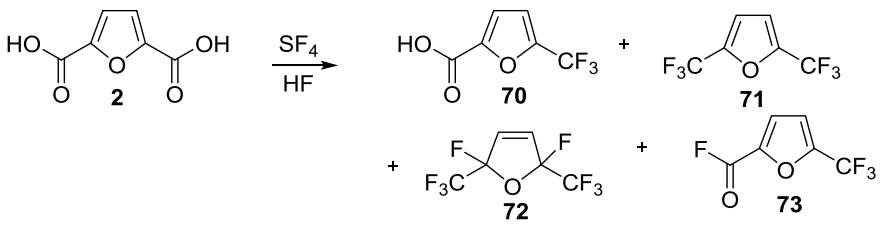
Scheme 1.40. Copolymerization reaction of BHETP and BHEFDC

By direct esterification and polycondensation, the synthesis of poly(butylene succinate-co-butylene furandicarboxylate) (PBSF) **68** was recently reported from FDCA, succinic acid (SA) **69**, and 1,4-butylene glycol **63** using tetrabutyl titanate (TBT) or TBT/La(acac)$_3$ as the catalyst.[95] The molecular weight, composition, T_g and crystallinity effect the mechanical properties of PBSF **68** (Scheme 1.41).



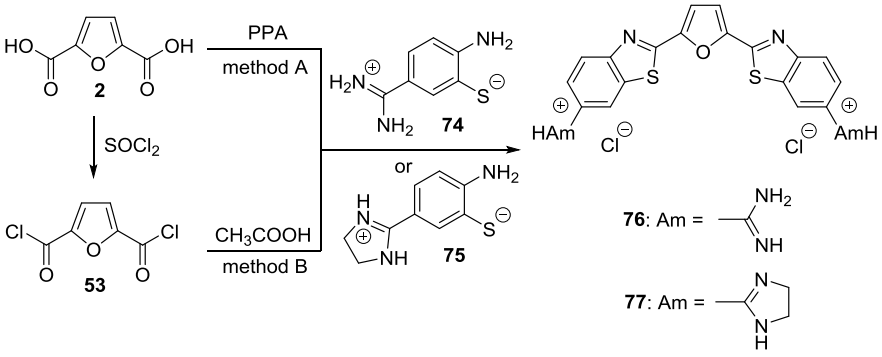
Scheme 1.41. Synthesis of PBSF

Fluorination of FDCA with sulfur tetrafluoride in the presence of anhydrous hydrogen fluoride produced mono **70** and bis(triflroromethyl)furans **71** (Scheme 1.42).[96]



Scheme 1.42. The fluorination of FDCA with sulfur tetrafluoride

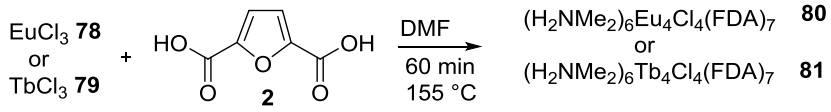
A new synthetic approach of amidino **74** and 2-imidazolinyl-substituted 2-aminothiophenol **75** was developed for the synthesis of bisamidino dibenzothiazolyl compounds **76** and **77**.[97] Method A incorporated the condensation of FDCA and amidino-substituted 2-aminothiophenole **74** in polyphosphoric acid in poor to moderate yields 30-60% of the desired compound **76** as a hydrochloride salt. Method B increased the product yield to 72-80% by using diacyl chlorides **53** in acetic acid with the amidino-substituted 2-aminothiophenole **74** (Scheme 1.43). Compounds **76** and **77** showed a strong antiproliferative effect on all the tested cell lines.[97]



Scheme 1.43. Diamidino-substituted derivatives of dibenzothiazolyl furans

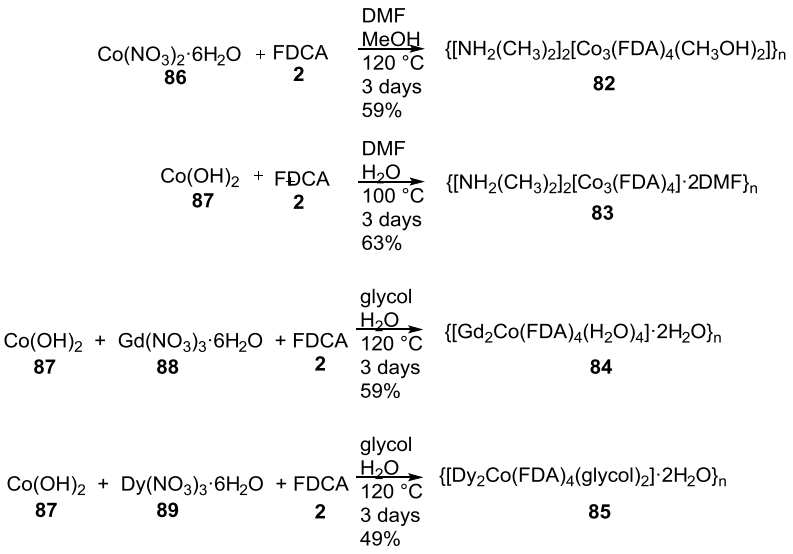
New europium (Eu) **78** and terbium (Tb) **79** complexes were synthesized with FDCA and characterized in the solid state. The synthesis generated compounds with the general formula $(H_2NMe_2)_6Ln_4Cl_4(FDA)_7$ (Ln = Eu, Tb) **80** and **81** (Scheme 1.44).[98] Both complexes exhibit

line-like luminescence characteristic of the lanthanide upon ligand centered excitation, consequently both cases the ligand acts as an antenna. However, due to low efficiency, both complexes are not suitable for LED applications. After drying, the compounds were produced in 59% and 64% yields for europium and terbium, respectively.



Scheme 1.44. Synthesis of lanthanide(III) complex

Four new metal-organic frameworks (MOFs) based on linear homo/heterotrinuclear nodes with FDCA were synthesized.[99] The building blocks of the four MOFs are all linear trinuclear clusters stabilized by the carboxylic groups; however, the three-dimensional frameworks are all different. The MOFs {[$NH_2(CH_3)_2$]$_2$[Co_3(FDA)$_4$(CH_3OH)$_2$]}n, **82** {[$NH_2(CH_3)_2$]$_2$[Co_3(FDA)$_4$]·2DMF}n, **83** {[Gd_2Co(FDA)$_4$(H_2O)4]·2H_2O}n, **84** {[Dy_2Co(FDA)$_4$(glycol)$_2$]·2H_2O}n **85** were synthesized in 59%, 63%, 59% and 49% yields, respectively (Scheme 1.45).[99]

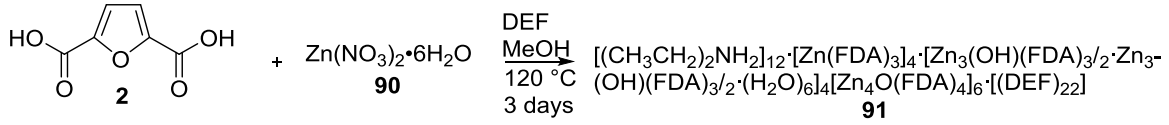


Scheme 1.45. Synthesis of MOFs

Three anionic porous MOFs were synthesized solvothermally using Zn(II), FDCA and DMF at different reaction temperatures.[100] The first compound, $[Zn_{1.5}(FDA)_2(Me_2NH_2)]\cdot x$G (G=guest) was synthesized at 90 °C, has a two-dimensional sheet structure. The second compound, $[Zn_3(FDA)_4(Me_2NH_2)]\cdot x$G was synthesized at 120 °C, has a three-dimensional structure as well as the third compound, $[Zn_{1.5}(FDA)_2(Me_2NH_2)]\cdot x$G, which was synthesized at 160 °C. Increasing the temperature changed the local environment around the zinc center. This is the first reported example where simultaneous control over both dimensionality and supramolecular isomerism was achieved by changing the temperature.[100]

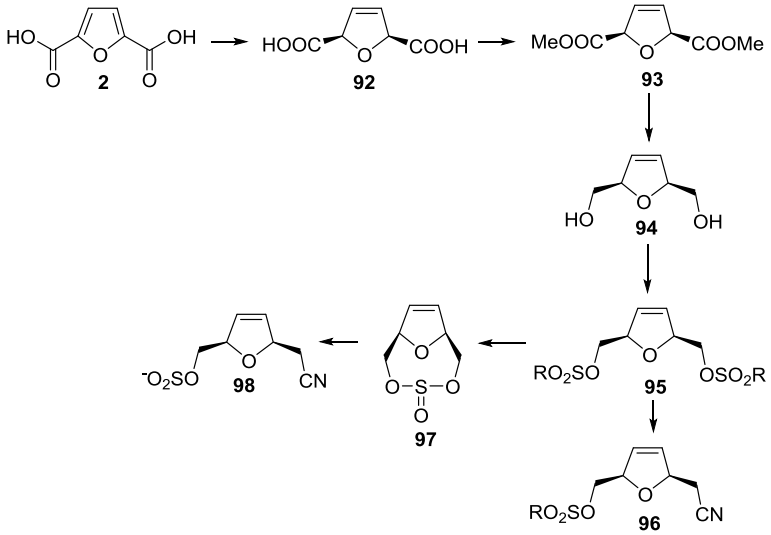
The first reported example of two types of frameworks present in the same material was recently reported.[101] The new material CPM-7 (crystalline porous materials) **91** was produced by a solvothermal reaction of $Zn(NO_3)_2\cdot 6H_2O$ **90** and FDCA **2** (Scheme 1.46). CPM-7 structure is built from four different building blocks, a Zn_4O tetramer, two $Zn_3(OH)$ trimers and a Zn monomer. Of the two crystallographicallly different trimers, one consists of no water (trimer 1) the other has water (trimer 2). Due to the presence of water in trimer 2, the Zn is six-coordinated

compared to four-coordinated in trimer 1. CPM-7 consists of two types of polyhedral cages: a sodalite cage from the tetramers and a cubic cage from the trimers.[101]



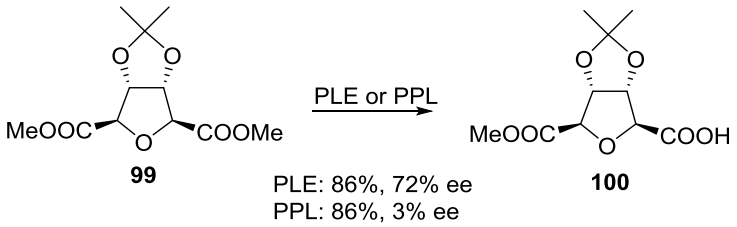
Scheme 1.46. Synthesis of CPM-7

Using FDCA as the starting material to prepare C-nucleosides has proven ineffective.[102] It was thought that by reducing cis-2,5-dihydrofuran-2,5-carboxylate **93** to the corresponding diol **94**; the diol could be tosylated or mesylated to the disulfonates. The next step of the reaction with cyanide ion to form **96** failed. So attention was switched to making the cyclic sulfate function **97**, which had anticipated advantages of favorable geometry for backside S_N2 attack and the cyclic compound would only monocyanoate **98** (Scheme 1.47). However, the desired product did not form due to the attack on sulfur preferred carbon or elimination of bridgehead hydrogen was faster than the substitution reaction.[102]



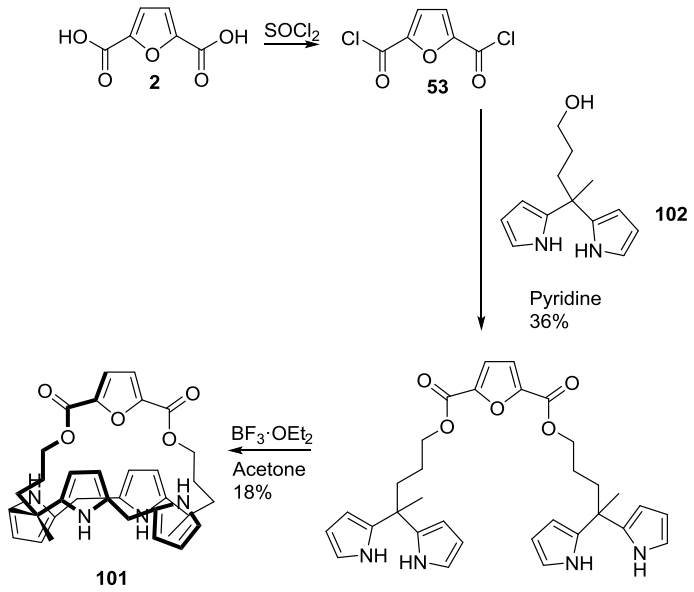
Scheme 1.47. Proposed route to C-nucleosides

Hydrolytic enzymes pig liver esterase (PLE) and porcine pancreatic lipase (PPL) catalyzed hydrolysis of diesters **99** with enantiotopic selectivity (Scheme 1.48).[103] These products **100** could serve as possible precursors for the sugar moieties of C-nucleosides.



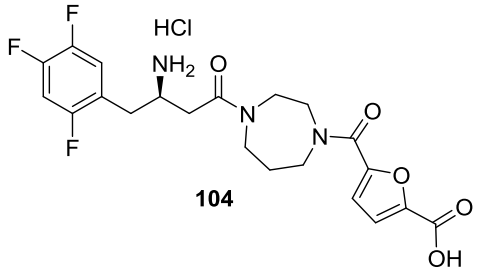
Scheme 1.48. PLE and PPL catalyzed hydrolysis of different diesters

The synthesis of furan-strapped calix[4]pyrrole **101** was synthesized from FDCA in an overall 18% yield (Scheme 1.49).[104] In the solid state, the furan-strapped calix[4]pyrrole, which contains two methanol molecules, adopts a 1,2-alternate conformation.



Scheme 1.49. Synthesis of the furan-strapped calix[4]pyrrole

Several homopiperazine derivatives **104** were synthesized with acid moiety and were found to be potent inhibitors of dipeptidyl peptidase IV (DPP-IV), with no CYP 3A4 inhibition (Scheme 1.50).[105] The derivative with FDCA gave an IC_{50} value of 260 nM.



Scheme 1.50. Homopiperazine derivative based on FDCA

1.4. Conclusion

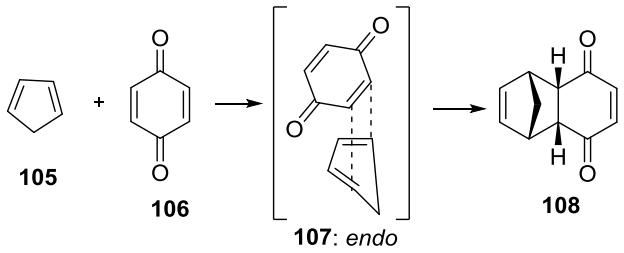
HMF is considered to be one of the most promising platform molecules that can be converted into a wealth of interesting chemicals. HMF has been known as a product from hexose dehydration for over 100 years. With the growing number of publications in the recent years, improvements have been made in understanding the mechanism and kinetics of the dehydration process to HMF. By applying different solvent types, extraction methods, and bifunctional catalyst systems, the synthesis of HMF has improved.

FDCA, identified as one of the twelve building blocks, has great potential as a terephthalic acid replacement. The oxidation of HMF to FDCA is a sequential reaction where the aldehyde side chain is rapidly oxidized than the alcohol side chain is oxidized. FDCA can be used in the synthesis of polymers and metal organic frameworks.

CHAPTER 2. HMF BASED DIELS-ALDER REACTIONS

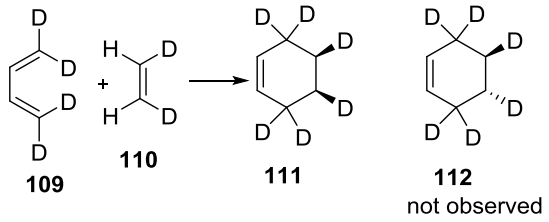
2.1. Introduction

The Diels-Alder reaction, the cycloaddition of alkenes and dienes, has become one of the most important synthetic methods used in organic chemistry. It is named after Professor Otto Paul Hermann Diels and his research student, Kurt Alder, who discovered and developed the reaction in 1928 and later received the Noble Prize in 1950. The reaction of cyclopentadiene **105** and quinone **106** resulted in the [4+2] cycloaddition product **108** (Scheme 2.1).[106] The Diels-Alder reaction has been exploited in numerous dimensions including inter- and intramolecular, heteroatom, and with various catalyzed reactions.



Scheme 2.1. The discovery of the Diels-Alder reaction

The Diels-Alder reaction adopts a concerted pathway; consequently, the transition structure of the diene must adopt the *s-cis* conformation. The approach of the diene and dienophile is approximately in parallel planes.[107] With respect to both the diene and dienophile, the reaction is a stereospecific *syn* (suprafacial) addition. Many substituted dienes and dienophiles have been investigated to demonstrate the stereospecific addition, including the simplest example of ethene **110** and butadiene **109** with isotope labeling (Scheme 2.2).[108]



Scheme 2.2. Isotopic labeling experiment

There are two possible stereochemical orientations with respect to the diene, *endo* and *exo*, when a substituted dienophile is present. In the *exo* transition state **113**, the substituent is orientated away from the π orbitals of the diene. The *endo* transition state **114** has the substituent orientated toward the π system.[107] These two orientations are illustrated in Figure 2.1.

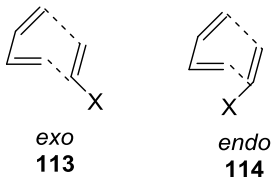
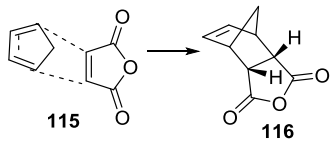


Figure 2.1. Transition structures for the Diels-Alder reaction

When substituted dienes are present, the two transition states lead to two different stereoisomeric products. When an electron withdrawing group (EWG) substituent such as a carbonyl group is present on the dienophile, the *endo* means of approach is usually preferred; this preference is referred to as the Alder rule. The Alder rule is a good rule of thumb to initially follow for the predication for the stereochemistry of the Diels-Alder reaction; however, frequently a mixture of both stereoisomers is formed or the *exo* product predominates. The *endo* product is often the more sterically congested. An example of a more sterically congested product **116** is the addition of dienophiles to cyclopentadiene as shown in Scheme 2.3.[107]



Scheme 2.3. Diels-Alder reaction favoring the *endo* stereoisomer

The Diels-Alder reaction has a strong electronic substituent effect. It has been known for a long time that when the dienophile contains one or more EWGs the reactions proceed efficiently and rapidly; this is favored even more when the diene also contains an electron donating group (EDG). Some of the most reactive dienophiles are quinones, maleic anhydride and nitroalkenes. Nitriles, ketones, and α,β-unsaturated esters are also effective dienophiles.[107] The reaction between unfunctionalized dienes and dienophiles is quite slow. For example, the reaction of cyclopentadiene and ethane occurs around 200 °C.[109] Diene reactivity is increased with EDG substituents.

When the diene is electron-poor, the best dienophiles are electron-rich alkenes such as vinyl ethers and enamines. Such reactions are called inverse electron demand Diels-Alder reactions and best understood in terms of frontier orbital theory (FMO). Electron rich dienes have high energy highest occupied molecular orbital (HOMO) that interact strongly with the lowest unoccupied molecular orbital (LUMO) of the electron poor dienophile. When the substituent pattern is reversed and the diene is electron poor, the strongest interaction is between the dienophile HOMO and the LUMO of the diene. Using the FMO approach, the reactivity and regioselectivity of the Diels-Alder reaction can be predicted for a wide range of diene-dieneophile combinations (Figure 2.2).[107]

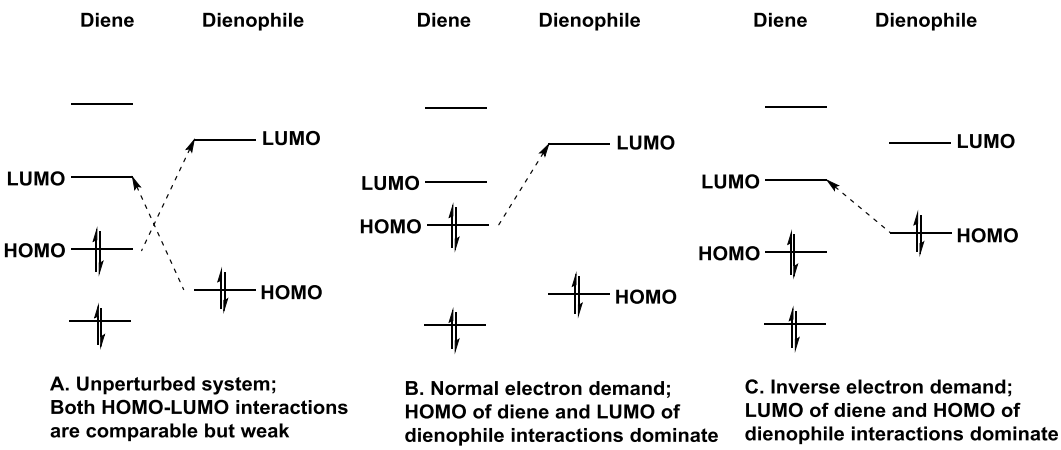
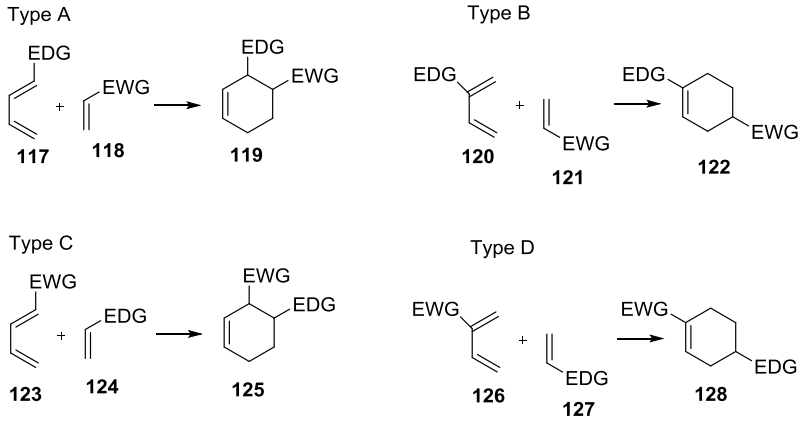


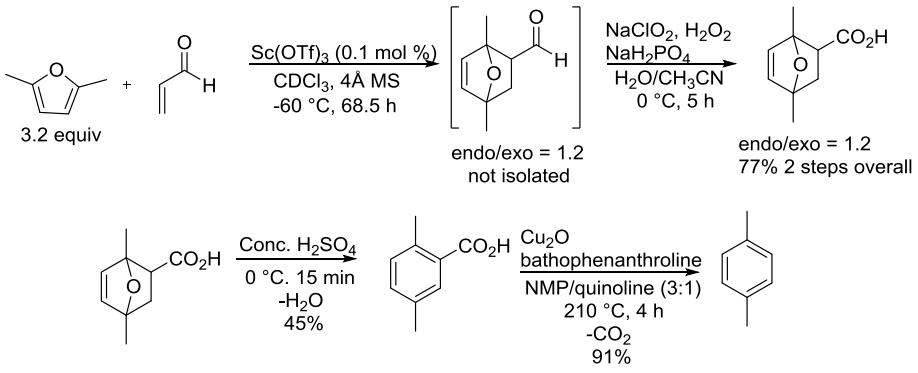
Figure 2.2. FMO interactions for Diels-Alder reactions

The nature of the substituents on the diene and dienophile determine the regioselectivity of the Diels-Alder reaction. Scheme 2.4 displays the preferred regiochemistry for various substitution patterns.[107] Case A and B arise from the combination of an electron donor diene and an electron acceptor dienophile. The frontier orbitals will be the diene HOMO and the dienophile LUMO for cases A and B. Inverse electron demand Diels-Alder reactions give rise to case C and D; the pairing of the diene LUMO and the dienophile HOMO is the strongest interaction.[107]



Scheme 2.4. Regioselectivity of the Diels-Alder reaction

An example of a Diels-Alder reaction using a derivative of HMF was reported by Toste.[110] DMF **10** and acrolein which can be produced from glycerol, a side product of biodiesel production, were converted into a key intermediate *p*-xylene (Scheme 2.5). The synthesis consisted of a sequential Diels-Alder reaction, oxidation, dehydration and decarboxylation. Although the reaction required low temperature, which presents a limitation economically for industrial scale, the bio-derived *p*-xylene was obtained in a 34% overall yield over four steps.



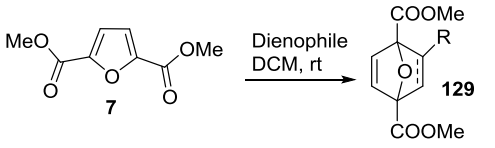
Scheme 2.5. Bio-derived *p*-xylene synthesis

2.2. Results and discussion

Our research goal was to develop novel methods for the conversion of renewable resources to feedstock chemicals for polymer synthesis. We were interested in examining Diels-Alder reactions with derivatives of HMF using different dienophiles such as ethyl vinyl ether, phenylacetylene, trimethylsilylacetylene, and ethoxy ethyne. These dienophiles were chosen because they are electron rich. An electron poor diene such as dimethyl-2,5-furandicarboxylate would be needed for a matched case. This type of Diels-Alder reaction would be an inverse electron demand reaction, since the diene is electron poor and the dienophile is electron rich.

Both alkene and alkyne dienophiles were examined. Alkyne dienophiles have an advantage over alkene dienophiles in that the Diels-Alder product gives the dihydro compound.

We first evaluated the Diels-Alder reaction of the furan diene and the dienophile with and without molecular sieves (Table 2.1). The presence of molecular sieves did not affect reaction, since starting material was fully recovered with or without molecular sieves. The energetics of this reaction were not met and starting material was recovered.



Entry[a]	Dienophile	4ÅMS	Yield (%)[b]
1	130	yes	NR
2	130	no	NR
3	131	yes	NR
4	131	no	NR
5	132	yes	NR
6	132	no	NR
7	133	yes	NR
8	133	no	NR

[a] Reactions performed under argon, monitored by TLC [b] isolated yields

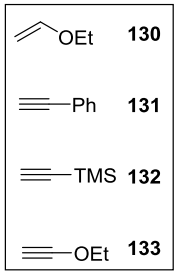
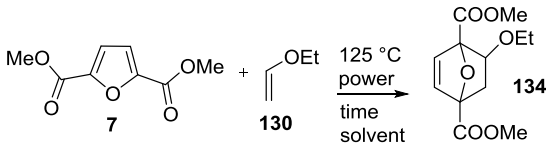


Table 2.1. Basic Diels-Alder reaction

The use of microwave heating was explored next. Microwave chemistry has its advantages over conventional heating. Microwave chemistry can significantly increase the reaction rate of various liquid-phase chemical transformations, due to the instant volumetric heating of the reaction medium when compared to conventional methods. Microwave chemistry also provides better conversion, selectivity and yield, achieves greater reproducibility, and helps for cleaner and greener production of chemicals.[111] Table 2.2 shows the different microwave conditions tested with vinyl ethyl ether. Changing the power or time did not do anything for the reaction. Starting material was recovered.

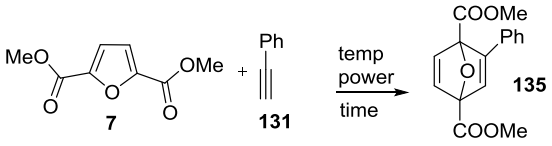


Entry	Power (W)	Time (min)	Solvent	Yield (%)[a]
1	300	10	DCM	NR
2	300	20	DCM	NR
3	300	60	DCM	NR
4	150	180	DCM	NR
5	300	60	neat	NR
6	300	180	neat	NR

[a] isolated yields

Table 2.2. Microwave testing with ethyl vinyl ether

Since no product formed, the focus was shifted to a different dienophile, phenylacetylene. Different microwave conditions were explored. However, no product was formed (Table 2.3).



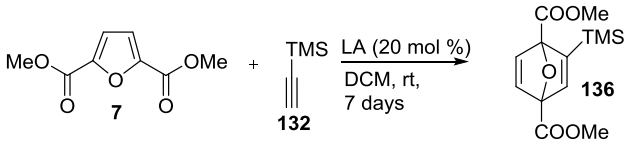
Entry	Power (W)	Time (h)	Temp (° C)	Yield (%)[a]
1	300	2	125	NR
2	300	5	125	NR
3	300	15	90	NR
4	150	15	90	NR

[a] isolated yields

Table 2.3. Microwave conditions for phenylacetylene

Since no product formed under microwave conditions, the focus switched to Lewis acid catalysts. Our focus at first was mainly on environmentally friendly Lewis acids like indium and bismuth, to enhance the "green" aspect of this chemistry. To investigate the substrates thoroughly, a Lewis acid scope was performed. The goal was to get the derivatives of HMF to react in a Diels-Alder fashion. Table 2.4 shows the Lewis acid and molecular sieve screening. To our surprise, no combination of these Lewis acids or molecular sieves generated any product;

starting material was only present. The reaction was monitored every twelve hours, and finally stopped after seven days of no product formation.

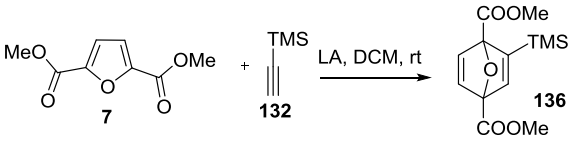


Entry[a]	LA	4Å MS	Yield (%)[b]
1	$In(OH)_3$	no	NR
2	$In(OH)_3$	yes	NR
3	$In(OTf)_3$	no	NR
4	$In(OTf)_3$	yes	NR
5	$InBr_3$	no	NR
6	$InBr_3$	yes	NR
7	$BiCl_3$	no	NR
8	$BiCl_3$	yes	NR

[a] Reactions performed under argon, monitored by TLC [b] isolated yields

Table 2.4. "Green" Lewis acid screening

Since the "green" Lewis acids did not catalyze the reaction, other Lewis acids were investigated such as copper acetate, copper iodide, and aluminum chloride (Table 2.5). Just as before, these Lewis acids did not catalyze the formation of product.

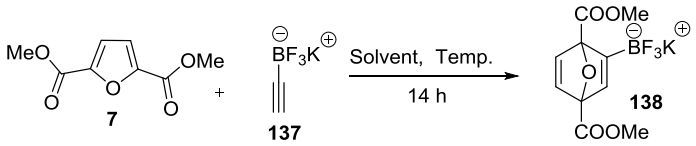


Entry[a]	Lewis Acid	Yield (%)[b]	Entry	Lewis Acid	Yield (%)[b]
1	$Cu(OAc)_2$	NR	11	$Y(OTf)_3$	NR
2	CuI	NR	12	$Yb(OTf)_3$	NR
3	$YbCl_3 \cdot 6H_2O$	NR	13	$Mg(OTf)_2$	NR
4	$CeCl_3 \cdot 7H_2O$	NR	14	$Zn(OTf)_2$	NR
5	$Ce(OTf)_3$	NR	15	$In(OOCCH_3)_3$	NR
6	$La(OTf)_3$	NR	16	$Dy(OTf)_3$	NR
7	$AlCl_3$	NR	17	$Nd(OTf)_3$	NR
8	$TiCl_4$	NR	18	$Pr(OTf)_3$	NR
9[c]	$Ti(OEt)_4$	NR	19	$Gd(OTf)_3$	NR
10	$Sc(OTf)_3$	NR	20	$Hf(OTf)_4$	NR

[a] Reactions performed under argon, monitored by TLC [b] isolated yields [c] transesterfication occured

Table 2.5. Lewis acid screening

A final attempt was made to react **7** with a different dienophile, potassium ethynyltrifluoroborate **137**. This dienophile is electron rich, pairing with an electron poor diene, resulting in an inverse electron demand Diels-Alder reaction. This dienophile was chosen because if the Diels-Alder reaction proceeded, then the product could be used in cross coupling reactions. Table 2.6 shows the temperature and solvent screening for this combination of diene and dienophile.

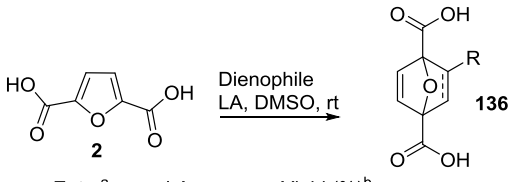


Entry[a]	Solvent	Temp. (°C)	Yield (%)[b]
1	MeOH	reflux	NR
2	MeOH	rt	NR
3	DCM	reflux	Degrad.
4	DCM	rt	NR
5	DMSO	reflux	NR
6	DMSO	rt	NR

[a] Reactions performed under argon, monitored by TLC [b] isolated yields

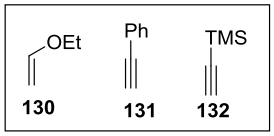
Table 2.6. Solvent and temperature screening

With a thorough Lewis acid and microwave chemistry scope, it can be concluded that the FDMC **7** does not react with the given dienophiles. So the focus switched to a different diene, FDCA. FDCA **2** was tested with the same Lewis acids as **7** with the different dienophiles **130**, **131**, and **132** (Table 2.7).



Entry[a]	LA	Yield (%)[b]
1	$Y(OTf)_3$	NR
2	$Yb(OTf)_3$	NR
3	$Mg(OTf)_2$	NR
4	$Zn(OTf)_2$	NR
5	$In(OOCCH_3)_3$	NR
6	$Sc(OTf)_3$	NR
7	$Nd(OTf)_3$	NR
8	$Gd(OTf)_3$	NR
9	$Pr(OTF)_3$	NR
10	$Dy(OTf)_3$	NR

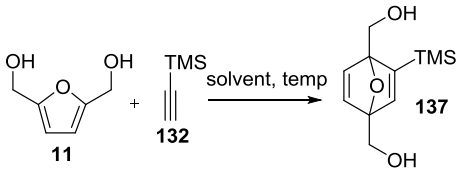
Dienophiles



[a] Reactions performed under argon, monitored by TLC [b] isolated yields

Table 2.7. Lewis acid scope with FDCA

Based on the negative results, the diene was changed to the diol **11**. A solvent screening was performed as seen in Table 2.8. No product was formed, starting material was recovered. The reaction may not have worked since both the diene and dienophile are electron rich.



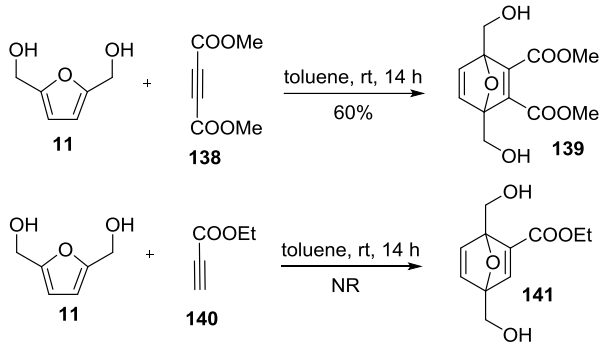
Entry[a]	Solvent	Temperature (°C)	Yield (%)[b]
1	DCM	45	NR
2	Benzene	220	NR
3	Mesitylene	220	NR
4	Toluene	90	NR

[a] Reactions performed under argon, monitored by TLC [b] isolated yields

Table 2.8. Solvent screening

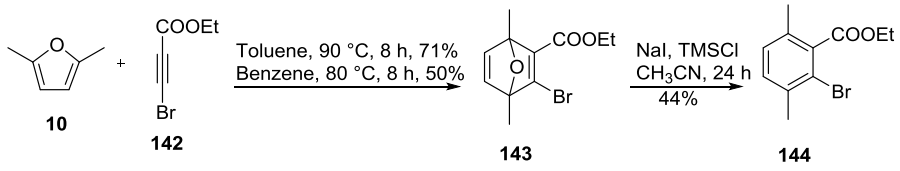
A comparison study was done on dienophiles having one or two electron withdrawing groups. The Diels-Alder reaction of **11** and **138** is reported in literature.[112] Having two electron

withdrawing groups was required for the reaction with the diol as displayed in Scheme 2.6. The two EWGs made the triple bond more electron poor, which reacted with electron rich **11**.



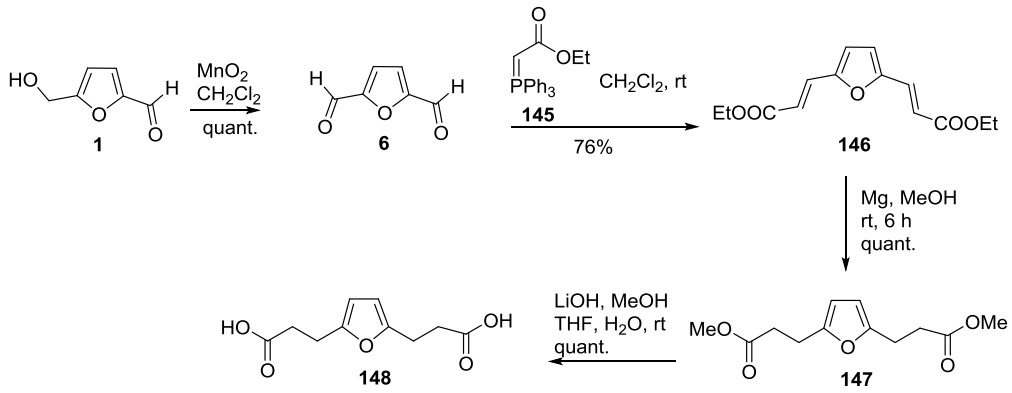
Scheme 2.6. Electron withdrawing group comparison

Another combination of diene and dienophile was explored. An electron rich diene **10** was paired with the electron poor dienophile **142** for a normal electron demand Diels-Alder reaction. In comparing solvents, toluene gave a higher yield than benzene (Scheme 2.7). It is interesting to note that the bromine is present throughout these transformations, which is beneficial as it can be converted into other functional groups.



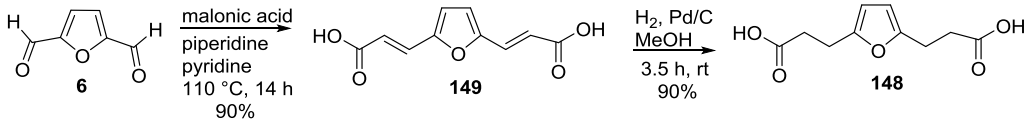
Scheme 2.7. Solvent screening

Another goal was to prepare C-10 diacids for the synthesis of polymers. The previous method included oxidation of HMF **1** to DFF **6**, a Wittig reaction to form **146**, then upon reduction and transesterfication gave **147**. Base hydrolysis afforded the C-10 diacid **148** (Scheme 2.8).



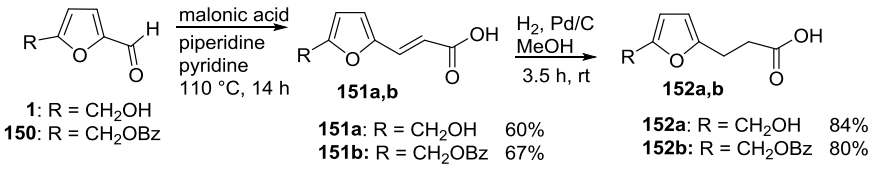
Scheme 2.8. Previous method for C-10 diacids

An alternative method for the generation of C-10 products is the Perkin condensation of DFF **6** with malonic acid.[113] This new method requires one less step than the previous method. The aldehyde moiety condenses with malonic acid to form an acrylic acid substituent. In the case of DFF **6**, both of the aldehyde groups react with malonic acid, forming a C-10 product. The acrylic acid product can be hydrogenated to the saturated acid (Scheme 2.9).



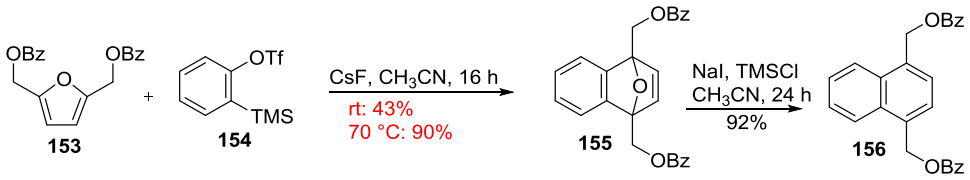
Scheme 2.9. Alternative method for C-10 diacids

Other substrates that contained an aldehyde moiety were investigated with the Perkin condensation including HMF. These substrates gave lower yields than DFF (Scheme 2.10).



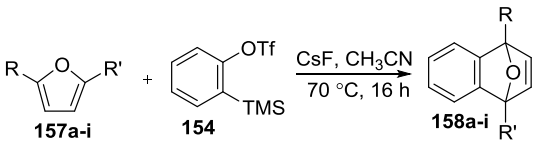
Scheme 2.10. Perkin condensation

The next area of focus was on the development of naphthalene analogs of terephthalic acid for the formation of bio-based polyethylene terephthalate (PET) analogs by reacting the HMF derivatives with benzyne. We first explored the *in situ* generation of benzyne with 2-(trimethylsilyl) phenyl triflate **154;** however, due to its high cost, it is not an attractive benzyne source. Upon optimizing the conditions, it was found that heating to 70 °C was more efficient than at room temperature (Scheme 2.11).



Scheme 2.11. Diels-Alder reaction with benzyne

A substrate scope was performed at 70 °C (Table 2.9). FDCA **2** did not react with benzyne. Two possible reasons why FDCA **2** did not react with benzyne are 1) solubility issues and 2) acids are known to be trapped once benzyne is generated.[114] This could also explain why **148**, which has the acid moiety, did not react as well. It is interesting to note that **153**, the protected diol, reacts whereas the diol **11** does not react with benzyne. It is still unclear why the dialdehyde substrate **6** does not react under these conditions.



Entry[a]	R	R'	Yield (%)[b]
a	CH_2OBz	CH_2OBz	90
b	Me	Me	97
c	COOMe	COOMe	82
d	CN	CN	85
e	COOH	COOH	NR
f	CH_2OH	CH_2OH	NR
g	CHO	CHO	NR
h	CHO	CH_2OBz	NR
i	$(CH_2)_2COOH$	$(CH_2)_2COOH$	NR

[a] Reactions performed under argon, monitored by TLC [b] isolated yields

Table 2.9. Substrate scope

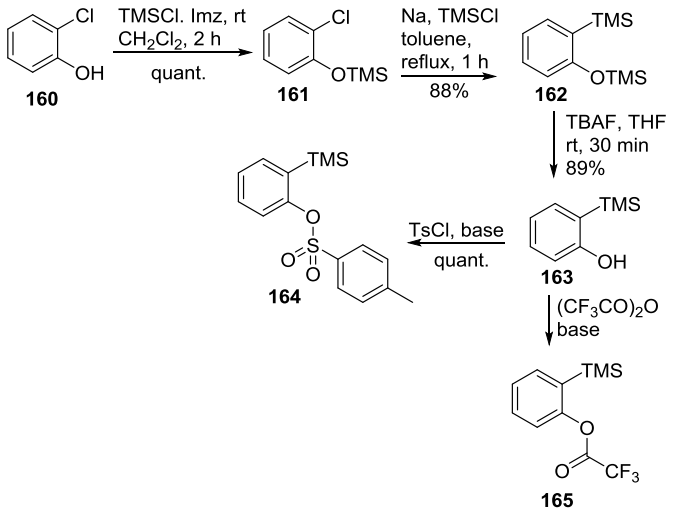
Based on the substrates that reacted with benzyne **158a-d**, they were aromatized to naphthalene analogs of terephthalic acid **159** (Table 2.10). These naphthalene analogs could be used for the formation of bio-based polyethylene terephthalate (PET). It is interesting to point out that the reaction works excellently when the substituents are electron donating. The reaction does not work or does not work well when the substituents are electron withdrawing as in the case of methyl ester and cyano substituents. Other conditions for the deoxygenation followed by aromatization may work better for the EWG containing substrates.

Entry	R	Yield (%)
1	CH_2OBz	92
2	Me	91
3	COOMe	20
4	CN	NR

[a] Reactions performed under argon, monitored by TLC [b] isolated yields

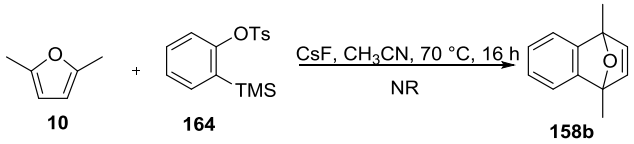
Table 2.10. Naphthalene analogs of terephthalic acid

An alternative approach was followed to avoid the expensive benzyne precursor **154**. A tosyl analog **164** was synthesized through a nucleophilic substitution/protection of 2-chlorophenol **160** (Scheme 2.12).



Scheme 2.12. Synthesis of benzyne precursor

A Diels-Alder reaction with the recently synthesized tosylate benzyne precursor **164** and DMF was attempted. DMF was chosen as the diene since the reaction worked great (97% yield) with the triflate benzyne precursor **154**. However, the Diels-Alder reaction with DMF did not proceed (Scheme 2.13). A possible explanation for why DMF did not react with the tosylate benzyne precursor **164** is that the triflate is a better leaving group than the tosylate.



Scheme 2.13. Diels-Alder reaction with tosylate benzyne precuror

2.3. Conclusions and future work

In conclusion, HMF serves as a versatile platform chemical made from biomass. The HMF derivatives can serve as starting materials for polymeric materials. Diels-Alder reactions are an important method in synthetic organic chemistry. In our work, the Diels-Alder reaction of HMF and FDCA derivatives did not work with ethyl vinyl ether, phenyl acetylene, trimethylsilyl acetylene, ethoxy ethyne or potassium ethynyltrifluoroborate. To our surprise, no combination of Lewis acids or molecular sieves generated any product.

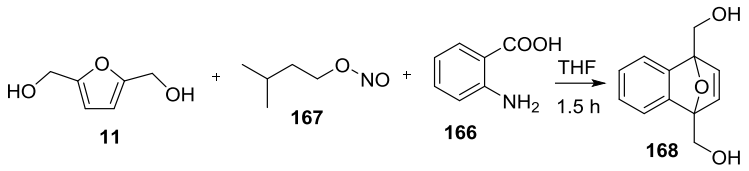
It was found that having two EWGs on the dienophile was required to react with the diol **11**. The two EWGs made the triple bond more electron poor, which was needed for the electronics to match up.

An alternative method for the generation of C-10 products was achieved through the Perkin condensation of **1**, **6**, and **150** with malonic acid. The aldehyde moiety condenses with malonic acid to form an acrylic acid substituent. In the case of DFF **6**, both of the aldehyde groups react with malonic acid, forming a C-10 product. The acrylic acid product can be hydrogenated to the saturated acid. This alternative method generated the saturated product in good yields 80-90%.

The development of naphthalene analogs of terephthalic acid for the formation of bio-based polyethylene terephthalate (PET) analogs was achieved using 2-(trimethylsilyl) phenyl triflate. The yields were good to excellent depending on which HMF derivative was used. FDCA did not react due to solubility reasons or the trapping of the acid when benzyne was generated.

Due to the expensive benzyne precursor, another method for benzyne generation needs to be investigated. Anthranilic acid **166** was investigated based on a reported procedure reacting

BHMF **11** with anthranilic acid (Scheme 2.14).[115] This is a promising precursor as **11** did not react with **154**, hopefully, this new method can be suitable for other substrates that did not react with **154.** Another benefit for this method of benzyne generation is the low cost of anthranilic acid **166** compared to 2-(trimethylsilyl) phenyl triflate **154**.



Scheme 2.14. Generation of benzyne from anthranilic acid

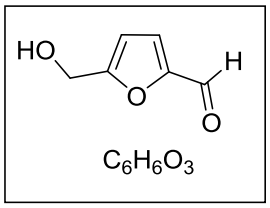
2.4. Experimental

2.4.1. General experimental information

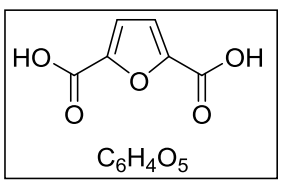
Methylene chloride was distilled from calcium hydride prior to use. Powdered molecular sieves 4 Å (MS 4Å) was purchased from Aldrich Chemical and dried at 250-300 ºC under vacuum before use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCO CombiFlash Companion with Analogix RS-4 columns. Thin layer chromatographic analyses were performed on silica gel Whatmann-60F glass plates and components were visualized by illumination with UV light. All glassware was oven dried, assembled hot and cooled under a stream of dry nitrogen before used. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR was recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz) spectrometer. Chemical

shifts are reported in parts per million (ppm) downfield from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublets of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad, AB sys = AB system), coupling constant(s) and integration. ^{13}C NMR was recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian/Inova-400 (100 MHz) spectrometers using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.23) as an internal standard. FT-IR spectra were recorded on a Mettler-Toledo ReactIR-4000. High-resolution mass spectra (HRMS) [ESI+] were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

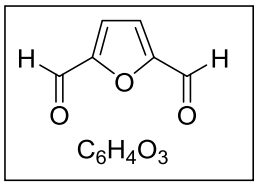


5-(Hydroxymethyl)-2-furaldehyde (1): Fructose (10 g, 55.5 mmol, 1 equiv.), lithium bromide (10.6 g, 122.04 mmols, 2.2 equiv.) and DMA (100 mL) were added to a 250 mL round bottom flask. Sulfuric acid (0.32 mL, 0.0055 mmol, 0.0001 equiv.) was then added. Reaction was allowed to stir at 100 °C for six hours. Reaction was filtered with celite to remove any fructose, distilled to remove DMA and filtered again over celite to remove LiBr. Crude was purified by flash column chromatography (hexane/ethyl acetate 1:1). Yellow oil; yield: 4.71 g, 65%; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.71 (s, 2H), 6.50 (d, *J* = 3.6 Hz, 1H), 7.18 (d, J = 3.6 Hz, 1H), 9.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 57.9, 110.2, 122.8, 152.6, 160.6, 177.9. Spectroscopic and analytical data for the product corresponded to those described in the literature.[116]

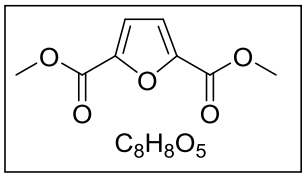


Furan-2,5-dicarboxylic acid (2): To a solution of hydroxyl methyl furfural **1** (2 g, 16.13 mmol, 1 equiv.) in a sodium hydroxide solution

(14.81 g in 161 mL H_2O, 371 mmol, 23 equiv.) crystals of potassium permanganate (5.85 g, 37.1 mmol, 2.3 equiv.) were added at room temperature. The reaction was stirred for three hours. Solution was filtered and poured into a flask containing 20 mL of ice and placed in an ice bath. Hydrochloric acid was added to the filtrate to bring the pH to 1 or less thereby precipitating FDCA. The precipitate was filtered and washed with ice water and dried over $MgSO_4$. Residue was used for the next step without purification. White solid; yield: 1.5 g, 60%; mp = >200 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.24 (s, 1H), 13.61 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 119.1, 147.7, 159.6. Spectroscopic and analytical data for the product corresponded to those described in the literature.[92]

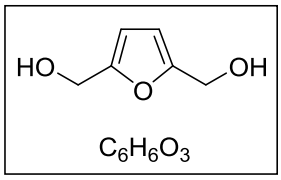


2,5-Furandicarboxaldehyde (6): Manganese oxide (7.06 g, 81.2 mmol, 4.3 equiv.) was added to a solution of HMF **1** (2.0 g, 15.8 mmol, 1 equiv.) in dichloromethane (50 mL). Reaction was allowed to stir for eight hours at 40 °C. Reaction was filtered through celite and solution was concentrated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate 1:1). Yellow solid; yield: 1.5 g, 65%; mp = 108-110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (s, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 119.5, 154.4, 179.4. Spectroscopic and analytical data for the product corresponded to those described in the literature.[75]

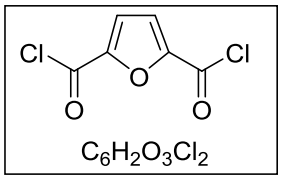


Dimethyl-2,5-furandicarboxylate (7): To a solution of FDCA **2** (2.0 g, 12.82 mmol, 1 equiv.) in methanol (30 mL), thionyl chloride (3.44 mL, 47.7 mmol, 3.72 equiv.) was added at 0 °C, then the reaction was heated to reflux and stirred overnight. The solvent was removed under vacuum, washed with sodium bicarbonate solution, rinsed three times with dichloromethane then dried with sodium

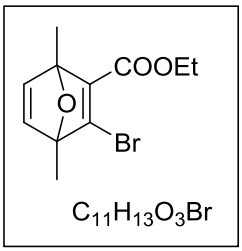
sulfate. The solid was used for the next step without purification. White solid; yield: 2.16 g, 92%; mp = 109-111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (s, 3H), 7.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.6, 118.7, 146.8, 158.6. Spectroscopic and analytical data for the product corresponded to those described in the literature.[113]



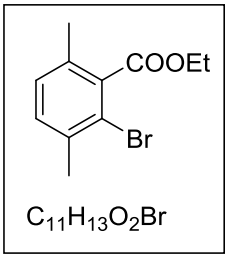
2,5-Bis(hydroxymethyl)furan (11): HMF **1** (5.0 g, 39.6 mmol, 1 equiv.) was added to a 100 mL round bottom flask containing absolute ethanol (20 mL). Sodium borohydride (1.63 g, 43.1 mmol, 1.1 equiv.) was slowly added while flask was in an ice bath. The reaction stirred at room temperature overnight. Reaction was concentrated and crude was purified by column chromatography DCM/Methanol (95:5). White solid; yield: 4.1 g, 89%; mp = 75-77 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.28 (s, 2H), 6.11 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 56.3, 108.0, 155.2. Spectroscopic and analytical data for the product corresponded to those described in the literature.[113]



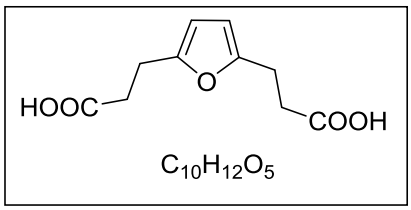
2,5-Furandicarbonyl chloride (53): A mixture of FDCA **2** (1.0 g, 6.4 mmol, 1 equiv.), thionyl chloride (1.73 mL, 23.8 mmol, 3.72 equiv.) and benzene (20 mL) was heated at 70 °C for 24 hours. Excess thionyl chloride was removed under vacuum and residue was used for the next step without purification. White solid; yield: 1.21 g, 99%; mp = 77-79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 123.2, 149.3, 155.9. Spectroscopic and analytical data for the product corresponded to those described in the literature.[89]



2-Bromo-3,6-dimethyl-3,6- epoxy ethylbenzoate (143): Dimethylfuran **10** (160 mg, 1.66 mmol, 1 equiv.) and ethyl bromopropiolate (100 mg, 0.56 mmol, 0.34 equiv.) were added to a 10 mL round bottom flask containing toluene (5 mL). Reaction stirred at 90 °C for 12 hours. Residue was used for the next step without purification. Yellow oil; yield: 316 mg, 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J* = 1.2 Hz, 3H), 1.51 (s, 3H), 1.83 (s, 3H), 4.21 (d, *J* = 1.2 Hz, 2H), 6.83 (d, *J* = 4.8 Hz, 1H). 6.94 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 15.8, 16.7, 60.8, 92.9, 93.4, 145.5, 145.8, 148.1, 153.4, 163.3; IR (Film) 3429, 1715, 1652, 1615, 1588, 1436, 1253 cm^{-1}; HRMS calcd. for $C_{11}H_{13}O_3BrNa^+$ 294.9940; found 299.9945.

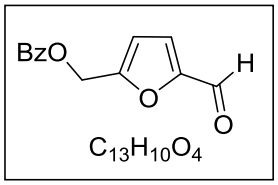


2-Bromo-3,6-dimethyl ethylbenzoate (144) To the starting material **143** (27 mg, 0.1 mmol, 1 equiv.) in acetonitrile (2 mL) was added sodium iodide (45 mg, 0.3 mmol, 3 equiv.) at room temperature to a 5 ml round bottom flask. The reaction was cooled to 0 °C, placed under argon, and trimethylsilyl chloride (40 µL, 0.3 mmol, 3 equiv.) was added slowly and the mixture was stirred at room temperature for 24 hours. Yellow oil; yield: 18 mg, 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (d, *J* = 1.2 Hz, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 4.40 (q, *J* = 1.2 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 19.3, 23.0, 61.8, 121.5, 129.0, 130.2, 131.2, 134.3, 135.8, 137.8; IR (Film) 3048, 2961, 1734, 1588, 1474, 1402, 1162, 1134 cm^{-1}. HRMS calcd. for $C_{11}H_{13}O_2BrNa^+$ 278.9950; found 278.9945.

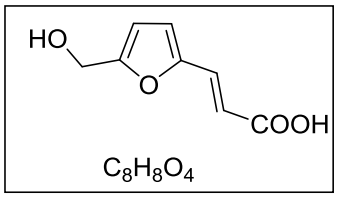


2,5-Furandipropanoic acid (148): Diacid **149** (50 mg, 0.24 mmol, 1 equiv.) was added to a 5 mL round bottom flask

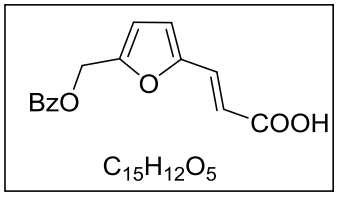
followed by the addition of methanol (1 mL). Pd/C (5 mg, 0.047 mmol, 0.2 equiv.) was then added. The flask was sealed and placed under vacuum to remove any air. A hydrogen balloon was placed into flask and vented three times. The balloon was replaced in the flask and reaction was allowed to stir for 3.5 hours. The reaction turnes balck when reaction is complete. Reaction was filtered over celite and washed with water. White solid; yield: 48.4 mg, 95%; mp = 133-137 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.44 (t, J = 7.2 Hz, 4H), 2.71 (t, J = 7.2 Hz, 4H), 5.88 (s, 2H), 12.90 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 31.3, 56.4, 58.2, 152.7, 167.8.



5-Benzoyloxymethylfurfural (150): DMAP (0.1 g, 0.793 mmol, 0.1 equiv.) was dissolved in dichloromethane (35 mL) in a 100 mL 2-neck flask. HMF **1** (1.0 g, 7.93 mmol, 1 equiv.) and triethyl amine (2.2 mL, 15.86 mmol, 2 equiv.) were added at 0 °C, followed by a slow addition of benzoyl chloride (1.4 mL, 11.90 mmol, 1.5 equiv.). Reaction was stirred for 14 hours at room temperature. Reaction was quenched with NH_4Cl aqueous solution and extracted with DCM. Organic layer was dried over sodium sulfate and concentrated under vacuum. Crude was purified by flash column chromatography (hexane/ethyl acetate 85:15). Yellow solid; yield: 1.46 g, 81%; mp = 49-52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.36 (s, 2H), 6.65 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.55 (dd, J = 8.2, 8.4 Hz, 1H), 8.02 (d, J = 8.2 Hz, 2H), 9.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.4, 112.9, 121.9, 128.7, 129.5, 130.0, 133.6, 153.1, 155.7, 166.1, 178.0. Spectroscopic and analytical data for the product corresponded to those described in the literature.[117]

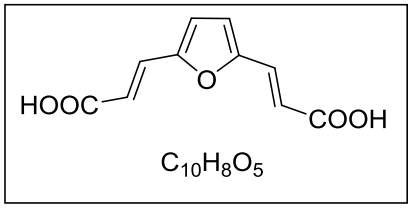


5-Hydroxymethyl-2-furanacrylic acid (151a): Malonic acid (340 mg, 3.35 mmol, 1 equiv.) was dissolved in pyridine (800 µL) and HMF **1** (422 mg, 3.35 mmol, 1 equiv.) and piperidine (330 µL, 6.7 mmol, 2 equiv.) were added to 5 mL round bottom flask. Reaction was stirred at reflux for 14 hours. After the 14 hours, the reaction was transferred to an Erlenmeyer flask and placed in an ice bath, and 2N HCl (25 mL) was added. A precipitate formed and was collected by filtration and was washed with water. Solid was used for the next step without purification. Brown solid; yield: 342 mg, 60%; mp = 109-112 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.44 (s, 2H), 6.04 (d, J = 14.6 Hz, 1H), 6.37 (d, J = 14.6 Hz, 1H), 6.79 (d, J = 7.2 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 13.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 56.4, 110.3, 115.9, 117.1, 131.5, 150.2, 159.0, 168.1.

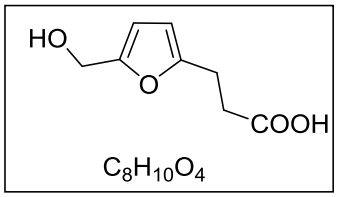


5-[(Benzoyloxy)methyl]-2-furanpropenoic acid (151b): Malonic acid (170 mg, 0.87 mmol, 1 equiv.) was dissolved in pyridine (200 µL) and furan **150** (200 mg, 0.87 mmol, 1 equiv.) and piperidine (165 µL, 1.74 mmol, 2 equiv.) were added. Reaction was stirred at reflux for 14 hours. After the 14 hours, the reaction was transferred to an Erlenmeyer flask and placed in an ice bath, and 2N HCl (25 mL) was added. A precipitate formed and was collected by filtration and was washed with water. Solid was used for the next step without purification. Brown solid; yield: 158 mg, 67%; mp = 96-101 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.31 (s, 2H), 6.34 (d, J = 15.6 Hz, 1H), 6.54 (d, J = 3.6 Hz, 1H), 6.63 (d, J = 3.6 Hz, 1H), 7.40 (d, J = 10.8 Hz, 2H), 8.03 (d, J = 13.6 Hz, 1H), 8.05 (dd, J = 1.2, 5.6 Hz, 1H), 8.09 (d, J = 5.6 Hz, 2H), 12.98 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 58.9, 114.1, 116.8, 117.4, 129.2, 129.5, 129.9, 131.2, 133.5, 134.3, 151.5, 152.5,

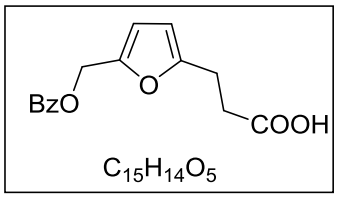
167.8. IR (Film) 3760, 3006, 1712, 1638, 1451, 1268, 1069, 711 cm^{-1}; HRMS calcd. for $C_{15}H_{12}O_5Na^+$ 295.0577; found 295.0579.



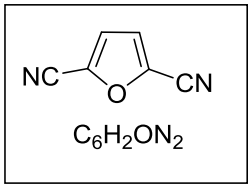
3,3'-(2,5-Furandiyl)bis-2-propenoic acid (149): Malonic acid (680 mg, 6.6 mmol, 2 equiv.) was dissolved in pyridine (800 µL) and furan **6** (422 mg, 3.3 mmol, 1 equiv.) and piperidine (660 µL, 6.6 mmol, 2 equiv.) were added. Reaction was stirred at reflux for 14 hours. After the 14 hours, the reaction was transferred to an Erlenmeyer flask and placed in an ice bath, and 2N HCl (25 mL) was added. A precipitate formed and was collected by filtration and was washed with water. Solid was used for the next step without purification. Brown solid; yield: 642 mg, 90%; mp = 102-105 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.33 (d, J = 15.6 Hz, 1H), 6.97 (s, 1H), 7.34 (d, J = 16.0 Hz, 1H), 13.04 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 118.2, 119.0, 130.6, 152.7, 167.8.



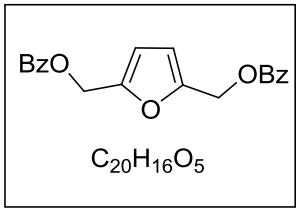
5-Hydroxymethyl-2-furan propanoic acid (152a): **151a** (200 mg, 1.17 mmol, 1 equiv.) was added to a 5 mL round bottom flask followed by the addition of methanol (1 mL). Pd/C (20 mg, 0.234 mmol, 0.2 equiv.) was then added. The flask was sealed and placed under vacuum to remove any air. A hydrogen balloon was placed into flask and vented three times. Then balloon was placed in the flask and reaction was allowed to stir for 3.5 hours. Reaction was filtered over celite and washed with water. Brown solid; yield: 170 mg, 84%; mp = 127-129 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.44 (s, 2H), 2.48 (t, J = 8.4 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 5.95 (d, J = 3.2 Hz, 1H), 6.09 (d, J = 3.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 31.4, 56.4, 62.1, 89.9, 117.1, 131.1, 150.4, 159.3.



5-[(Benzoyloxy)methyl]-2-furanpropanoic acid (152b): **151b** (200 mg, 0.73 mmol, 1 equiv.) was added to a 5 mL round bottom flask followed by the addition of methanol (1 mL). Pd/C (20 mg, 0.146 mmol, 0.2 equiv.) was then added. The flask was sealed and placed under vacuum to remove any air. A hydrogen balloon was placed into flask and vented three times. Then balloon was placed in the flask and reaction was allowed to stir for 3.5 hours. Reaction was filtered over celite and washed with water. White solid; yield: 208 mg, 80%; mp = 126-128 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.56 (t, J = 8.4 Hz, 2H), 1.31 (s, 2H), 2.01 (t, J = 8.4 Hz, 2H), 6.31 (d, J = 3.2 Hz, 1H), 6.78 (d, J = 3.2 Hz, 1H), 7.05 (s, 2H), 7.38 (d, J = 5.6 Hz, 2H), 7.56 (d, J = 5.6 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 31.2, 56.4, 58.7, 62.1, 89.9, 111.9, 117.1, 128.5, 129.9, 133.3, 150.5, 159.3. 166.3.

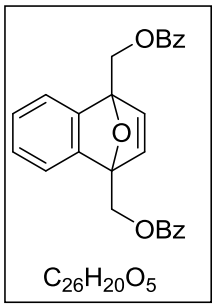


2,5-Furandicarbonitrile (157): 2,5-Furandicarboxamide **(169)**: (200 mg, 1.3 mmol, 1 equiv.) was added to flask. Then dioxane (12 mL), pyridine (0.90 mL, 11.18 mmol, 8.6 equiv.) and trifluoroacetic anhydride (0.78 mL, 5.59 mmol, 4.3 equiv.) were added at 0 °C. The reaction was stirred at room temperature overnight. Solvent was removed under vacuum. White solid; 85 mg, yield: 55%; mp = 61-63°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.0, 109.5, 122.3. Spectroscopic and analytical data for the product corresponded to those described in the literature.[118]

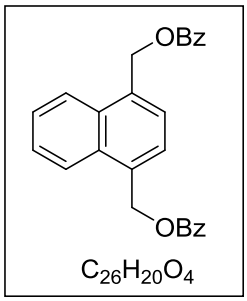


2,5-Furandimethanol dibenzoate (153): DMAP (0.2 g, 0.78 mmol 0.1 equiv.) was dissolved in dichloromethane (35 mL). Diol **11** (1.0 g, 7.8

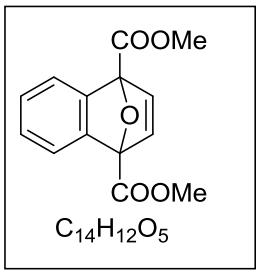
mmol, 1 equiv.) and triethyl amine (4.4 mL, 15.6 mmol, 2 equiv.) were added at 0 °C, followed by a slow addition of benzoyl chloride (2.8 mL, 11.7 mmol, 1.5 equiv.). Reaction was stirred for 14 hours at room termperature. Reaction was quenched with NH_4Cl aqueous solution and extracted with DCM. Organic layer was dried over sodium sulfate and concentrated under vacuum. Crude was purified by flash column chromatography (hexane/ethyl acetate 50:50). Yellow solid; yield: 2.46 g, 95%; mp = 71-72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.29 (s, 4H), 6.46 (s, 2H), 7.42 (d, *J* = 7.6 Hz, 4H), 7.54 (d, *J* = 7.6 Hz, 2H), 8.04 (d, *J* = 7.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.0, 58.7, 111.9, 128.5, 129.9, 133.3, 150.5, 166.3.



1,4-Dihydro-1,4-dibenzoate-1,4-epoxynaphthalene (155): To a stirred solution of furan (318 mg, 0.94 mol, 1 equiv.) and cesium fluoride (318 mg, 2.07 mol, 2.2 equiv.) in acetonitrile (12 mL) was added a solution of 2-(trimethylsilyl) phenyl triflate (300 µL, 1.22 mol, 1.3 equiv.) in acetonitrile (12 mL) drop wise by a syringe pump over 16 hours at 70 ° C. Reaction was concentrated under vacuum and crude was purified by flash column chromatography (hexane/ethyl acetate 50:50). White solid; yield: 350 mg, 92%; %; mp = 119-123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 4H), 5.06 (d, *J* = 12.8 Hz, 2H), 5.26 (d, *J* = 12.4 Hz, 2H), 7.25 (m, *J* = 2 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 4H), 7.55 (t, *J* = 7.2 Hz, 2H). 8.06 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 62.1, 91.3, 119.8, 125.7, 128.7, 129.9, 130.1, 133.5, 144.2, 149.4, 166.6; IR (Film) 3112, 326, 1715, 1267, 1107 cm^{-1}; HRMS calcd. for $C_{26}H_{20}O_5Na^+$ 435.1203; found 435.1205.

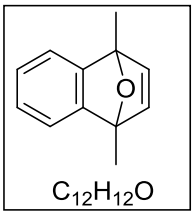


1,4-Naphthalenedimethanol-1,4-dibenzoate (156): To the starting material **155** (130 mg, 0.315 mmol, 1 equiv.) in acetonitrile (6 mL) was added sodium iodide (141 mg, 0.945 mmol, 3 equiv.) at room temperature. The reaction was cooled to 0 °C, placed under argon, and trimethylsilyl chloride (120 µL, 0.945 mmol, 3 equiv.) was added slowly and the mixture was stirred at room temperature for 24 hours. Reaction was quenched with $NaHCO_3$ aqueous solution and extracted with DCM. Organic layer was dried over sodium sulfate and concentrated under vacuum. Crude was purified by flash column chromatography (hexane/ethyl acetate 80:20). White solid; yield: 117 mg, 92%; mp = 122-126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (s, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.62 (m, *J* = 3.2, 5.6 Hz, 2H), 8.03 (d, *J* = 1.6 Hz, 2H), 8.05 (d, *J* = 8.0 Hz, 2H), 8.16 (dd, *J* = 3.2, 3.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 65.2, 124.5, 126.9, 127.1, 128.6, 129.9, 130.2, 132.2, 133.0, 133.3, 166.6; IR (Film) 3123, 3062, 2965, 1716, 1266 cm^{-1}; HRMS calcd. for $C_{26}H_{20}O_4Na^+$ 419.1257; found 419.1254.

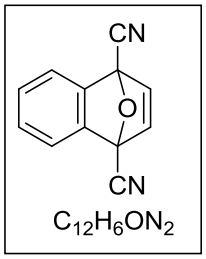


1,4-Naphthalenedicarboxylic acid, 1,4-dimethyl ester (158b): To a stirred solution of furan **7** (175 mg, 0.951 mmol, 1 equiv.) and cesium fluoride (318 mg, 2.09 mmol, 2.2 equiv.) in acetonitrile (12 mL) was added a solution of 2-(trimethylsilyl) phenyl triflate (300 µL, 1.24 mmol, 1.3 equiv.) in acetonitrile (12 mL) drop wise by a syringe pump over 16 hours at 70 ° C. Reaction was concentrated under vacuum and crude was purified by flash column chromatography (hexane/ethyl acetate 70:30). White solid; yield: 128 mg, 82%; mp = 84-86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97 (s, 3H), 7.05 (d, *J* = 2.8 Hz, 2H), 7.12 (d, *J* = 1.6 Hz, 2H),

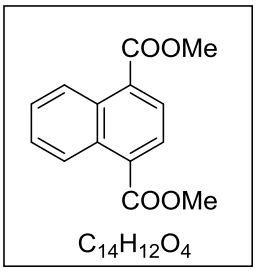
7.36 (d, *J* = 3.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.1, 90.4, 120.4, 126.2, 143.2, 146.3, 167.4; HRMS calcd. for $C_{14}H_{12}O_5Na^+$ 283.0577; found 283.0572.



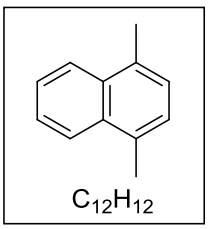
1,4-Dihydro-1,4-dimethyl-1,4-epoxynaphthalene (158c): To a stirred solution of furan **10** (100 µL, 0.95 mmol, 1 equiv.) and cesium fluoride (318 mg, 2.09 mmol, 2.2 equiv.) in acetonitrile (12 mL) was added a solution of 2-(trimethylsilyl) phenyl triflate (300 µL, 1.24 mmol, 1.3 equiv.) in acetonitrile (12 mL) drop wise by a syringe pump over 16 hours at 70 °C. Reaction was concentrated under vacuum and crude was purified by flash column chromatography (hexane/ethyl acetate 50:50). White solid; yield: 159 mg, 97%; mp = 33-35 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (s, 3H), 6.72 (s, 2H), 6.95 (d, *J* = 7.2Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5, 88.8, 118.6, 124.9, 147.1, 153.1. Spectroscopic and analytical data for the product corresponded to those described in the literature.[119]



1,4-Dihydro-1,4-dicarbonitrile-1,4-epoxynaphthalene (158d): To a stirred solution of furan **157** (110 mg, 0.93 mmol, 1 equiv.) and cesium fluoride (220 mg, 2.05 mmol, 2.2 equiv.) in acetonitrile (12 mL) was added a solution of 2-(trimethylsilyl) phenyl triflate (210 µL, 1.21 mmol, 1.3 equiv.) in acetonitrile (12 mL) drop wise by a syringe pump over 16 hours at 70 ° C. Reaction was concentrated under vacuum and crude was purified by flash column chromatography (hexane/ethyl acetate 50:50). Yellow solid; yield: 144 mg, 80%; mp = 156-159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (s, 1H), 7.21 (d, *J* = 2.8 Hz, 1H), 7.48 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 79.9, 113.4, 120.8, 127.8, 142.6, 143.7; IR (Film) 3390, 3112, 2391, 2248, 1674, 1521, 1456, 1266, 1197, 976 cm^{-1}; HRMS calcd. for $C_{12}H_6N_2ONa^+$ 217.0372; found 217.01370.

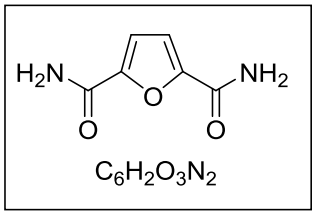


1,4-Dimethyl ester 1,4-naphthalenedicarboxylic acid (159b): To the starting material **158b** (93 mg, 0.36 mmol, 1 equiv.) in acetonitrile (6 mL) was added sodium iodide (161 mg, 1.08 mmol, 3 equiv.) at room temperature. The reaction was cooled to 0 °C, placed under argon, and trimethylsilyl chloride (137 µL, 1.08 mmol, 3 equiv.) was added slowly and the mixture was stirred at room temperature for 24 hours. Reaction was quenched with $NaHCO_3$ aqueous solution and extracted with DCM. Organic layer was dried over sodium sulfate and concentrated under vacuum. Crude was purified by flash column chromatography (hexane/ethyl acetate 80:20). White solid; yield: 17.7 mg, 20%; mp = 65-67 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97 (s, 3H), 7.07 (s, 1H), 7.22 (d, *J* = 5.6 Hz, 1H), 7.34 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.7, 128.4, 128.6, 128.9, 130.2, 135.6, 168.4. Spectroscopic and analytical data for the product corresponded to those described in the literature. [120]

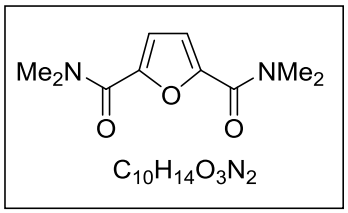


1,4-Dimethylnaphthalene (159c): To the starting material **158c** (150 mg, 0.87 mmol, 1 equiv.) in acetonitrile (6 mL) was added sodium iodide (388 mg, 2.6 mmol, 3 equiv.) at room temperature. The reaction was cooled to 0 °C, placed under argon, and trimethylsilyl chloride (331 µL, 2.6 mmol, 3 equiv.) was added slowly and the mixture was stirred at room temperature for 24 hours. Reaction was quenched with $NaHCO_3$ aqueous solution and extracted with DCM. Organic layer was dried over sodium sulfate and concentrated under vacuum. Crude was purified by flash column chromatography (hexane/ethyl acetate 95:5). Yellow oil; yield: 122 mg, 91%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (s, 3H), 7.21 (s, 2H), 7.53 (m, *J* = 3.2, 3.6 Hz, 2H), 8.02 (m, *J* = 3.2, 3.6 Hz,

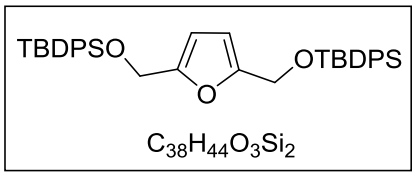
2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7, 125.0, 125.7, 126.6, 132.7, 133.1. Spectroscopic and analytical data for the product corresponded to those described in the literature.[121]



2,5-Furandicarboxamide (169): Ester **7** (500 mg, 2.72 mmol, 1 equiv.), methanol (8.7 mL) and ammonia (6.2 mL) were added to a flask under nitrogen and stirred overnight at room temperature. Reaction was filtered and washed with water. White solid; yield: 205 mg, 55%; mp = >230 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.55 (s, 2H), 7.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 119.5, 156.2, 162.4.

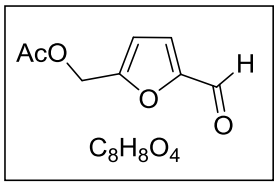


N, N, N', N'-Tetramethyl-2,5-furandicarboxamide (170): Dicarbonyl dichloride **53** (617 mg, 3.2 mmol, 1 equiv.) and dimethylamine (538 mg, 6.6 mmol, 2 equiv.) were dissolved in dichloromethane under argon. Triethylamine (1.05 mL, 7.48 mmol, 2.3 equiv.) was added slowly at 0 °C. The reaction stirred at room temperature for three hours. The reaction was quenched with water and extracted with DCM. White solid; yield: 504 mg, 75%; mp = 182-185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.09, (s, 3H), 6.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.6, 38.5, 116.7, 148.7, 159.9.



2,5-tert-Butyldiphenylsilyl ether furan (171): TBDPSCl (1.65 g, 6 mmol, 1.1 equiv.) was added slowly to imidazole (820 mg, 12 mmol, 2.2 equiv.) and diol (700 mg, 5.45 mmol, 1 equiv.) in dimethylformamide (20 mL) at 0 °C. The reaction stirred at room temperature for 14 hours. The solution was quenched with NH_4Cl aqueous solution and extracted with dichloromethane, dried over $MgSO_4$. Crude was purified by flash column chromatography

hexane/ethyl acetate (98:2). White solid; yield: 2.27 g, 66%; mp = 79-82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02, (s, 2H), 4.56 (s, 3H), 6.00 (s, 1H), 7.33 (m, *J* = 5.4 Hz, 2H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 26.9, 31.3, 59.2, 108.1, 127.8, 129.8, 133.6, 135.8, 153.7. IR (Film) 3070, 2957, 2930, 2857, 1427, 1111, 1067, 822, 700 cm^{-1}; HRMS calcd. for $C_{38}H_{44}O_3Si_2Na^+$ 627.2721; found 627.2724.



5-Acetoxymethyl furfuraldehyde (172): To a stirred solution of HMF **1** (500 mg, 3.96 mmol, 1 equiv.) and sodium acetate (680 mg, 8.24 mmol, 2.08 equiv.) at 80 °C was added acetic anhydride (935 µL, 9.9 mmol, 2.5 equiv.) drop wise. The mixture was stirred for 2.5 hours, then cooled to room temperature and hydrolyzed with water (2.5 mL). The solution was evaporated, filtered and extracted with diethyl ether, then dried with sodium sulfate anhydrous. Residue was used for the next step without purification. Yellow liquid; yield: 395 mg, 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15, (s, 3H), 5.17 (s, 2H), 6.60 (d, *J* = 3.6 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 58.2, 113.4, 122.5, 154.6, 156.0, 170.1, 178.2. Spectroscopic and analytical data for the product corresponded to those described in the literature.[122]

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