EXPLOITATION OF BIOMASS FOR APPLICATIONS IN SUSTAINABLE MATERIALS SCIENCE

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Exploitation of Biomass for Applications in Sustainable Materials Science

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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

DOCTOR OF PHILOSOPHY

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ABSTRACT

Biorefinery may be defined as the process of accessing chemical commodities from living systems; consequently, biomass becomes the antecedent for renewable resources through biorefinery. Advantages to this process over petroleum refinery include: (1) increased potential for sustainable products, (2) increased diversity in chemical structure including heterocycles, and (3) potential for regional resource independence. Despite these clear advantages, adoption of biorefined commodities can be limited by the risk associated with small initial application portfolios and concomitant uncertainties. The strategies adopted by our dynamic and collaborative research team entail continuous engagement of those issues by: (1) preparing renewable polymers, (2) chemical diversification of biomass-derived platform chemicals, (3) direct modification of biopolymers, and (4) development of petroleum replacements.

Battling the inveterate proclivity towards portents of gloom need not solely justify investigations into biorenewable feedstock chemicals; the ramifications of bioinspired molecular inquiry create opportunities to go beyond mere sustainability through innovation. This dissertation includes specific examples which illustrate utilization of three types of biomass: (1) oil seeds, (2) lignin, and (3) carbohydrates. Each class of biomass-derived materials offered unique advantages as well as challenges associated with their varied structures. The presentation has been divided into five sections: (1) biomass, sustainable chemistry and design thinking; (2) styrene replacements and their application in renewable vinyl ester thermosets; (3) catalyst-free lignin valorization by acetoacetylation; (4) chemical diversification of HMF; (5) valorization of cellulose-derivable platform chemicals by cycloaddition with a potentially bioderivable reactive intermediate: benzyne.

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Thanks are due to my graduate advisory committee and especially to Prof. Mukund P. Sibi. To quote him when awarded distinguished professorship at North Dakota State University in 2007: *"Curiosity and a strong desire to solve important scientific problems, and teaching and training students in the art of critical thinking are the driving force behind my research efforts."* I have benefited enormously from exposure to this attitude and strive to emulate.

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I want the many students and fellow researchers with whom I have shared experiences during my graduate studies to be recognized. Thank you for the intelligent conversation, criticisms, patience and humor.

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AA type monomer.....difunctional molecule with two indistinguishable electrophilic reactive centers such as a symmetrical dicarboxylic acid

AB type monomer.....difunctional molecule with two reactive centers making it capable of homopolymerization such as a hydroxyacid

AMF.....5-(acetoxymethyl)furfural

AMF.....5-(acetoxymethyl)-2-furoic acid

ATR.....attenuated total reflectance

AVV.....3-allyl-5-vinylveratrole

BAMF.....2,5-bis(acetoxymethyl)furfural

BB type monomer.....difunctional molecule with two indistinguishable nucleophilic reactive centers such as a symmetrical diol or diamine

BBB type monomer.....trifunctional molecule with three indistinguishable nucleophilic reactive centers

BHT.....butylated hydroxytoluene, a peroxide inhibitor for ethereal solvents

BHMF.....2,5-bis(hydroxymethyl)furfural

Calcd.....calculated

CDF.....cellulose-derived furan

CDN.....cellulose-derived naphthalene

CMF.....5-(chloromethyl)furfural

CPME.....cyclopentylmethyl ether

$CDCl_3$.....deuterated chloroform

DAR.....Diels-Alder reaction

DAA.....Diels-Alder adduct

DCC.....*N*,*N*'-dicyclohexylcarbodiimide

DCM .....dichloromethane

DFF 2,5-diformylfuran

DI .....deionized as is “deionized water”

DMAP .....4-(*N*,*N*-dimethylamino)pyridine

DME.....1,2-dimethoxyethane

DMESS .....dimethacrylated epoxidized sucrose soyate

DMF .....*N*,*N*-dimethylformamide

DMFBA .....dimethyl 2,5-furanbis(acrylate) or dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate

DMFBP .....dimethyl 2,5-furanbis(propanoate) or dimethyl 3,3'-(furan-2,5-diyl)dipropionate

DMSO .....dimethyl sulfoxide

DV.....3,5-diallylveratrole

EtOH .....ethanol

EtOAc .....ethyl acetate

eq.....molar equivalent.

ESS.....epoxidized sucrose soyate

FBAA.....2,5-furanbis(acrylic acid) or (2*E*,2'*E*)-3,3'-(furan-2,5-diyl)diacrylic acid

FDCA.....2,5-furandicarboxylic acid

FTIR.....Fourier transform infrared spectroscopy

H_2O .....water

Hex.....hexanes

HMF .....5-(hydroxymethyl)furfural

HMFA.....5-(hydroxymethyl)furoic acid

HOMO .....highest unoccupied molecular orbital

HPLC .....high performance liquid chromatography

HRMS .....high resolution mass spectrometry

IR.....infrared

IPA .....isopropyl alcohol also 2-propanol

$KMnO_4$.....potassium permanganate

LUMO.....lowest unoccupied molecular orbital

*m*CPBA .....*meta*-chloroperoxybenzoic acid

MF.....5-methylfurfural

MFA.....5-methyl-2-furoic acid

MMF .....methyl 5-formyl-2-furoate

min. .....minute(s)

mL.....milliliter; unit of volume

MCF .....5-(methoxycarbonyl)furfural

MCFA .....5-(methoxycarbonyl)furan-2-carboxylic acid

MHMF .....methyl 5-(hydroxymethyl)-2-furoate

MnO_2.....manganese dioxide

MeOH .....methanol

MOF.....metal organic framework

MPa.....mega pascals

nm .....nanometers; unit of wavelength

NMR .....nuclear magnetic resonance spectroscopy

NIPU .....non isocyanate polyurethane

NADPH.....nicotinamide adenine dinucleotide phosphate

OBMF .....5,5'-[oxybis(methylene)]di(2-furaldehyde)

PEF.....poly[ethylene-2,5-furanoate]

PTFE .....poly[tetrafluoroethylene]

1,4-PEN.....poly[ethylene-1,4-napthalate]

2,6-PEN.....poly[ethylene-2,6-napthalate]

PET .....poly[ethyleneterephthalate]

ppm .....parts per million

PTFE .....polytetrafluoroethylene

PPTS .....pyridinium *p*-toluenesulfonate

rpm .....rotations per minute

tert-.....truncation of *tertiary*

TBAA.....*tert*-butyl acetoacetate

THF .....tetrahydrofuran

TPA .....terephthalic acid

TLC .....thin layer chromatography

V.....vanillin

VA.....vanillic acid

VOC .....volatile organic compound

VV.....4-vinylveratrole

UV.....ultraviolet

LIST OF SYMBOLS

° .....degree

% .....percent

α .....alpha

β .....beta

^{1}H .....proton

^{13}C .....Carbon isotope 13

^{31}P.....phosphorous isotope 31

C.....Celsius; unit of temperature

cm^{-1} .....wavenumber, inverse centimeters

g.....gram; unit of mass

h.....hour(s)

J .....joule(s)

M .....molarity; mole/liter; unit of concentration

m.....molality; mole/kilogram; unit of concentration

m/z.....Mass of molecular species divided by the charge of the species

R.....'*Radikal'* Deutsche for any pendant group in which a carbon or hydrogen atom is attached to the interesting portion the molecular illustration

R^{1}.....Additional *radikal* distinct group

R_f .....retention factor

$wt_{\%}$ .....weight by weight percent

X.....typical leaving group such as chlorine, bromine, iodine, acetate, tosylate, mesylate, triflate…etc.

1. PARADIGMS OF BIOMASS UTILIZATION AND SUSTAINABILITY

The minds of early hominids were likely transformed by studying the materials and phenomena of the natural world: chemistry. As they sought tools for survival, they experimented with naturally occurring resources for novel applications. Modern synthetic chemistry was dominated by naturally abundant feedstocks until the petroleum revolution paved the way for economically lucrative liquid and gaseous feedstocks. Biorefinery, the procurement of value-added products from biological detritus, is once again growing in market share as the 21st century gains momentum despite the continued expansion of chemical industries; let this century be one of sustainable practices.

The story of sustainable materials science at North Dakota State University began early in the 20th century with NDSU's first professor of chemistry: Prof. Edwin Fremont Ladd. Prof. Ladd's interest in applying chemistry and sustainable agriculture was reflected in his published works. These include chemical investigation into maturing corn (prior to appointment at NDSU),[1] determination of minerals bound in organic components of soil (humates) and their relation to soil productivity,[2] along with analyses of paint formulations.[3, 4] In those times, all commercially available paints were at least partially bioderived from drying oils such as linseed oil (diluted with benzene and H_2O).

The strong tradition of NDSU's chemical research programs has colloquially been attributed to Prof. Ladd's influence. As evinced by a 1952 rededication of the chemistry building or Ladd Hall as it is known today, studying sustainable materials science can make a lasting impact. This tradition of excellence with a persuasion towards renewable resources is currently illustrated prominently by the success of NDSU's participation in the collaborative Center for Sustainable

Materials Science. The subject of this dissertation, The Exploitation of Biomass for Applications in Sustainable Materials Science, is a product of NDSU's ongoing tradition of informative inquiry.

An overwhelming amount of chemicals consumed by polymer industries are currently derived from petroleum resources. The fossil precursors of these materials are nonrenewable and thereby lack long-term sustainability since society cannot rely on their continued supply in perpetuity. The types of structures available from petroleum feedstocks are generally limited to non-oxidized electron rich aromatics, olefins, alkanes and derivatives thereof. The development of efficient synthetic methods for polymer applications using renewable feedstocks has received intense scrutiny.[5-8] This increased activity addresses issues related to long-term sustainability and also opportunistic utilization of the chemical-structural-diversity inherent in biomass-derived materials. There are at least three major classes of biomass that provide excellent feedstocks for the synthesis of useful monomers. They are lignin,[9] oil seeds,[10] and carbohydrates.[11]

1.1. Biorefinery

The drive to develop renewable fuels and chemical building blocks is motivated by both political and technical aspects. These motivators are contributing to a growth of sustainable chemical industries. While it has been estimated that less than 15% of petroleum is consumed for non-fuel applications, achieving access to alternative polymeric materials from renewable building blocks is not only a worthy task but actually has economically relevant historical precedence.

Fluctuations in the oil market play havoc with sustainable supply streams. Oil gluts have killed such ventures in the past while oil-supply shortages have resulted in reanimation.[12] Advancing the field of biorefinery must be opportunistic. For example, the shale-gas revolution can supply cheap energy (with adverse environmental impact) but has a low content of butadiene

and aromatics. This rupture in the supply chain of those petroleum derived commodity chemicals can be harnessed to motivate development of sustainable butadiene and aromatics.[13]

While there are many conceptual similarities between fossil- and bio- refinement, delineation of the differences is more useful in understanding the predominance of petroleum and the pregnant potential of biorefinery. Crude oil is extracted from the earth in liquid form and built up in chemical complexity along the supply stream. Conversely, biomass feedstocks exist as complex mixtures of small and macromolecular assemblies containing a staggering degree of complexity. Exacerbated by such minor factors as disparate regional rainfall or wind patterns, the differential heterogeneity of biomass confounds performance reproducibility and product uniformity. These crude mixtures often reach the site of biorefinery as solid mixtures containing inorganic impurities. Biomass must be homogenized, analyzed, and separated. Processing these feedstocks relies on breaking down the complex biomolecules into chemical platform chemicals or into biofuels. Biofuel technologies could also serve as a great homogenizer by providing uniform petroleum alternatives; but they may not be fully exploitive of the chemical potential latent in biomass.

The relative uniformity of petroleum feedstocks is starkly different from biomass due to the homogenizing influence of fossilization. In this vein, there is a real need to diversify the product portfolio from renewable platform chemicals to stabilize their markets and to address changing needs in a dynamic industry. At the same time, there is a need to improve analytical techniques which deal with the extensive diversity found in feedstocks from different areas.

A further motivation for investing in renewable chemicals can be found in the concept of energy and materials independence. The suitable place to locate a petroleum refinery is on the coast, near the source of petroleum (either barges or drilling rigs). Ironically, this is very far from

a major consumer of petroleum: industrial agriculture. Also, this tends to consolidate wealth in the hands of easily controlled refineries and not in the hands of producers of crude oil. In contrast, a good place to locate a biorefinery is near a field and a road. This concept will be one of the greatest benefits offered by sustainable chemistry and engineering in the 21st century as more people attempt ascension to higher standards of living.

The broadly defined term, biorefinery, may include production of fuel and/or synthetic feedstocks. Biorefineries may employ bioreactors in the process of fermentation. Esposito and Antonietti (2015) redefined biorefinery accentuating unconventional scaffolds and the new possibilities afforded to the chemical sciences derived therefrom.[14] Their key points included: (1) sustainable investigation of monomer space, (2) degradative and non-degradative deconstruction strategies for lignocellulosic biomass, (3) hydrothermal and solvothermal processing combined with robust catalysis, (4) the often complementary novel properties of materials prepared from bio *versus* petroleum refineries, and (5) enhanced sustainability of many current (nano)technologies.

The proliferation of articles describing biorefined products and sustainable materials science was attributed to a refocusing on molecular structure contrasted with a previous fixation upon energy content: a drastic paradigm shift. A common argument which should not be ignored has been dubbed the "food *versus* fuel" debate. This argument typically contains allusions to starving peoples of the world and the injustice of wealthy nations' burning edibles to power cellular phones and extravagant vehicles while everyone everywhere starves.

An argument less dependent on *pathos* can be made from the broad perspective of agricultural producers such as the United states and specifically North Dakota where the local economy is directly tied to agricultural expenditure; biorefineries are good for farmers since they increase demands for agricultural products. A large benefit to the farmers around the world

(especially in marginal territories) is potential liberation of agricultural development from traditional products such as corn, soybeans, and wheat, by allowing diversification into nonedible crops such as switchgrass.

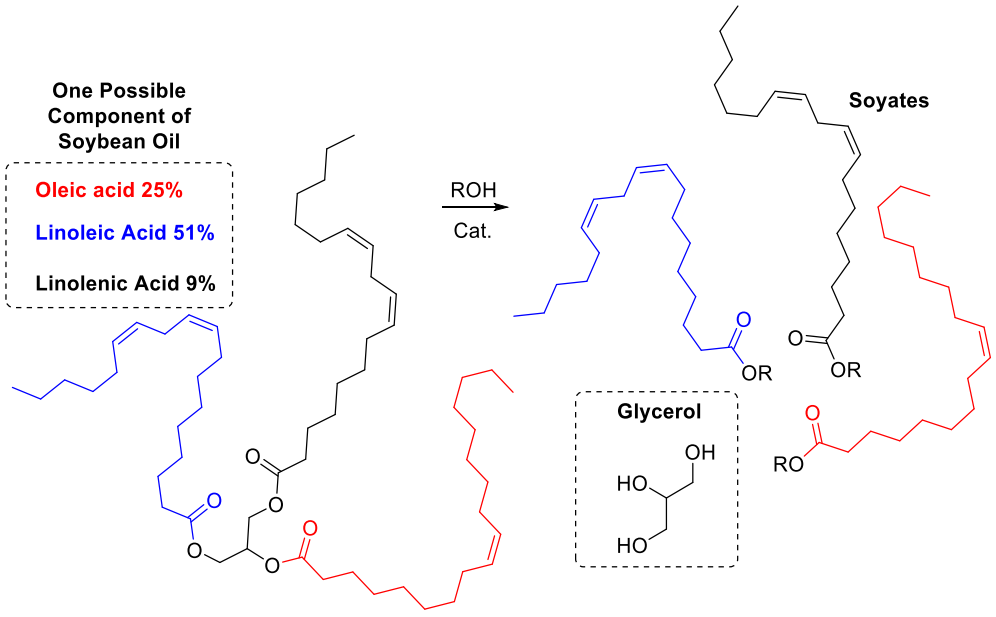
While the energy content of these nonedible crops in some cases may not be suitable for conversion to biofuels, they can provide feedstocks to biorefineries. Investment in biorefinery can therefore act as a powerful mechanism for wealth generation in developing nations and domestically by creating new avenues for production of value added products. A biorefinery strategy will contribute to alleviating many of the logistical barriers which currently lead to widespread malnourishment in some countries while combating domestic devaluation of locally produced commodities. In this context, more diversification is better. More diversified uses of agricultural products will lead to more diversity in profitable crops which will cycle forth to create even more biorefined products. In combination with advancements in renewable energy, biorefinery will lead to a sustainable future which is more equable and less dependent on inherited land or fossil wealth.

The superseding intellectual drive towards exploitation of biomass is the investigation and development of novel structures and properties. The ethical drive is derived from considerations of sustainability. The mechanism by which these drives are expressed is collectively known as biorefinery.

1.1.1. Oil Seeds

Triglycerides, prepared in nature from glycerol and fatty acids, are the major components of the oil pressed from oil seeds such as soy but also including nonedibles such as crambe. The composition (degree of unsaturation or olefin functionalization) of the fatty acid depends on the species of plant from which the oil is derived. Researchers have employed fatty acids, their esters,

and compounds derived from the fatty acids as monomers or building blocks in polymer chemistry.[15-20] Two features describe typical monomers derived from oil seeds (Scheme 1.1): (1) flexible aliphatic chains spacing functionalization sites from polar attachment points (ester linkage) and (2) diversity in structure modulated by altering the polyol core or secondary olefin functionalization.



Scheme 1.1. One possible component of soybean oil and its conversion to soyates and glycerol

1.1.1.1. Structure and Biorefinery Processing of Oil Seeds

Oil seed crops include edibles such as peanuts, oil palms, olives, coconuts, soybeans, canola, sunflowers *etc*. They also include inedible crops such as tung nuts, crambe, and castor beans among others which could provide biorefinery feedstocks while avoiding the "food *versus* fuel" dilemma.[21] As connoted by their name, oil seeds are typically classified as crops which are grown primarily for their oil.

That oil is a liquid chemically composed of triglycerides (carboxylic esters of glycerol with long lipophilic tails containing olefinic functionality).[22] In this regard, oil seeds in biorefinery share the most similarities with petroleum feedstocks. Many seed oils have found use as ingredients in

surfactants and as biodiesel precursors. The degree of unsaturation in plant derived fatty acids is controlled by fairly well-understood genes which can be modulated with standard techniques to manipulate the chemical content—*and consequently the olefin content*—of triglycerides.[22] The combination of structural components—*existence as liquids, relatively low oxygen content, multiple unsaturations in the fatty acid tail*—provide a unique platform for biorefinery. The primary mechanism for crosslinking reactions between plant derived fatty esters is known as autooxidation and can be accelerated by the addition of catalysts colloquially known as dryers (since they make paint *dry* faster).[23, 24]

Oil seeds provide the most stable, well established, and economically feasible platform for biorefinery to date. The major method of isolating oil from meal and hulls can be illustrated by soybean processing. Soybeans are the dominant oil seed in terms of world trade and account for over 50% of world production.[25] They are grown worldwide and are especially prevalent in the Midwest and Prairie states of the USA. They are valued for their nodules' ability to fix nitrogen in the soil from the atmosphere in a symbiotic relationship with bacteria. Risk of production variances associated with dry spells is less pronounced in soybean crops than in corn crops. Efforts are currently underway to increase the robustness of soy and other oil seed crops to harsh environmental conditions in marginalized territories through the implementation of selective breeding.[26] Yields continue to increase by strengthening the germ plasm and the oil content of seeds has been modified by induced mutation.[27] A dependence on biorefinery thereby creates an adaptive economy which can grow and develop over time to meet new needs.

Soybeans typically grown in North America afford bright yellow beans which dry in their husk prior to harvest. The beans are crushed to isolate soy meal which is a preferred animal feed to swine and poultry farmers around the world due to its high protein content.[28] During crushing,

soy bean oil is extracted from the meal. Soy bean oil is the world's second most popular cooking oil (after palm) and it was used as lamp oil in ancient China where a report from 980 CE also describes mixing soy oil with tung oil for ship caulking.[29]

Many applications require liberation of glycerol from triglycerides by transesterification reactions with MeOH. This is the source of all biobased glycerol. The liberated fatty esters may be used in biodiesel applications, purified as commodity chemicals, or undergo further transformation. Methyl fatty esters derived from waste cooking oils were utilized as petroleum replacements in the preparation of renewable light olefins by hydroprocessing and sequential steam cracking.[30] The key to this innovation was presaturation of olefins in the fatty tails to avoid undesirable guard bed fouling.

1.1.1.2. Oil Seed Products in Sustainable Materials Science Applications

In the field of renewable polymers, soybean oil has been converted into the well-defined dual functional monomer: (acryloylamino)ethyl soyate. The reported process involves a one-step transesterification with a prepared *N*-(hydroxyethyl)acrylamide. Reactivity ratios were determined and there was distinct chemoselection observed between the α,β-unsaturated olefins (which were amenable to free radical polymerization) and olefins contained in the fatty ester tails (practically inert in presence of free radical initiators). This novel vinyl monomer is a hydrophobic liquid at room temperature from which macromonomers can be prepared by free radical reactions. Those macromonomers contain fatty esters with remaining vinyl moieties derived from soy bean oil which are cross-linkable by oxidative curing and suitable for preparation of organic coatings.[31]

The development of acrylic monomers from *N*-(hydroxyethyl)acrylamide transesterification with seed oil has been extended to include olive, linseed and partially hydrogenated soybean oils to create a versatile platform for controlling the properties of latex

polymer networks. The molecular weights and glass transitions determined for products of miniemulsion copolymerization with styrene was dependent primarily upon the number of unsaturates contributed by the oil-derived fatty ester tails. The mechanical properties were correlated to cross-link density and therefore could be modulated by controlling the olefin content of the fatty ester feed during copolymerization.[32]

Transesterification of soy oil with 2-(vinyloxy)ethanol led to the preparation of (2-vinyloxy)ethyl soyate which is amenable to cationic polymerization exclusively at the vinyl ether moiety. The unsaturates contained in the fatty ester further modified by epoxidation and subsequent cyclocarbonation. Thus, three new macromolecular resins were produced efficiently from soybean derived triglycerides. Coatings could be prepared with cross-links formed from autooxidation, ring-opening of oxiranes, and ring-opening of cyclocarbonates. The last functionality was especially interesting since the derived materials would fit into a laudable category of safer materials known as renewable non-isocyanate polyurethanes (NIPUs) upon reaction with bioderived diamines.[33]

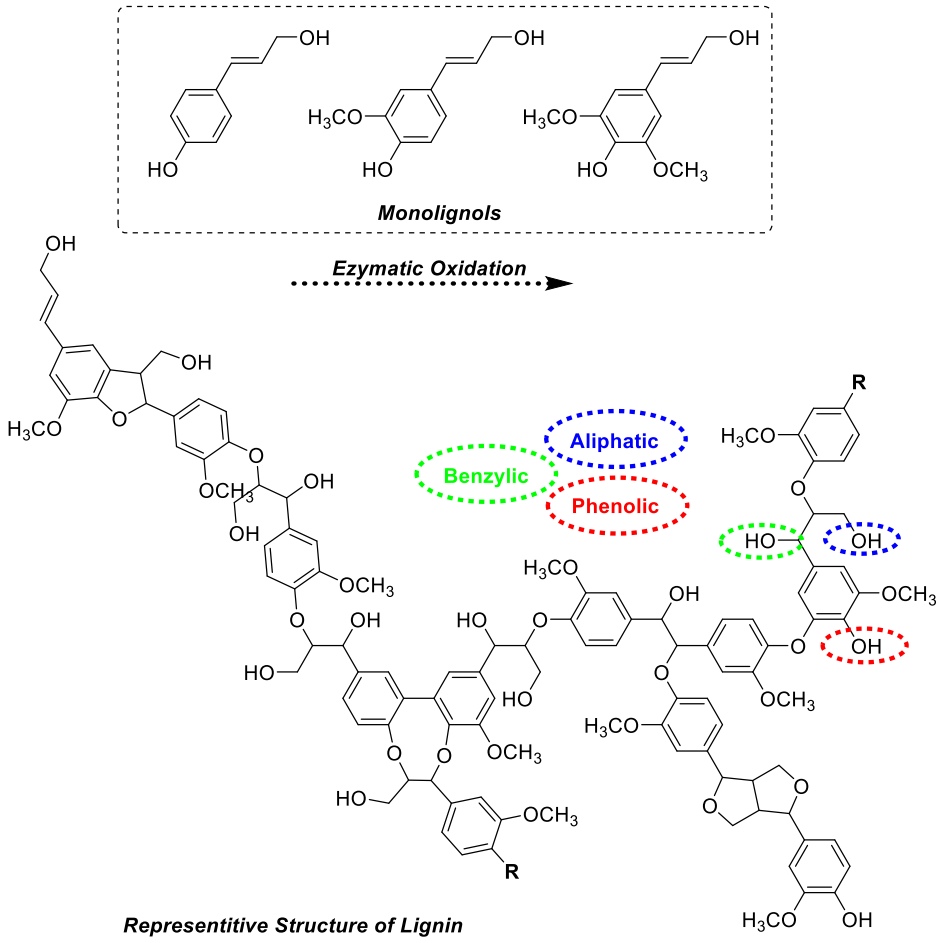
Recently, NIPU precursors from oil seeds were prepared from sebacic biscyclocarbonates. Sebacic acid derived from castor oil and glycerol carbonate were amalgamated in a solvent-free synthesis which utilized a lipase enzyme for the key coupling in greater than 95% yield. The lipase mediated esterification was optimized to reduce formation of oligomers from premature opening of glycerin cyclocarbonates.[34]

1.1.2. Lignin

Lignin is a heterogeneous polymer and is derived mainly from three phenolic building blocks.[35] Depolymerization[36] and/or modification[37] of lignin provides access to monomers which contain an aromatic core structure. Multiple sites of oxygenated functionality provide the major

structural differences between petroleum derived (non-oxidized) aromatic monomers and those from lignin. The presence of phenolic hydroxyl groups and other oxidized moieties combined with the aromatic ring provide the incentives, opportunities, and challenges for successful lignin biorefinery.

1.1.2.1. Structure and Biorefinery Processing of Lignin



Scheme 1.2. Generalized biological polymerization reaction from monolignols to lignin

While most have considered lignin as a waste product from lignocellulosic biorefineries which targeted commodities derived from polysaccharide components, there is a growing trend fertilized by the recent advancements in lignin utilization: a lignin-first approach. The lignin-first approaches harness lignin solvation and hydrogenolysis during paper pulp processing. An

optimized procedure affords small molecular lignin derivatives (contrariwise to technical lignins) and paper pulp both in high quality. A chemocatalytic lignin-first approach in *n*-butanol has been proposed for the preparation of: (1) lignin derived monophenolics, (2) hemicellulose derived polyols, and (3) cellulose pulp.[38]

Supply streams produced by a lignin-first strategy generally have a narrow distribution of structures and molecular weights. One of the greatest challenges facing lignin-first initiatives is the hydrolysis of hemicellulosic esters which leads to acidification of the liquor and contributes to side reactions. The formation and fate of sugar derived acids and their role in lignin biorefinery is under study and has already born some fruit.[39] A mitigation strategy has been developed which leads to hydrogenation of sugar acids and the isolation of sugar alcohols without the concomitant degradation of lignin or paper pulp.

1.1.2.2. Lignin Derived Products in Sustainable Materials Science Applications

Lignin-derived epoxy resins can replace formaldehyde-based wood adhesives. These novel adhesives combine lignin and glycerol (from oil seed biorefinery) which are H_2O-tolerant, fast curing, and display comparable adhesion performance to classical formaldehyde formulations. Use of formaldehyde is driven by its stellar reactivity but repulsive owing to its acute toxicity and classification as a known human carcinogen. Kraft lignin was utilized since it provides the largest supply stream and limits batch inconsistences to actual wood utilized in the Kraft process.[40]

Related technology includes the preparation of vitrimers for potential application in recoverable adhesives from lignin and sebacic acid (castor oil derived) diglycidyl esters. A key difference in this preparation was in the treatment of Kraft lignin with ozone to prepare multiple carboxylic acid moieties with the added benefit of improving the coloration of the lignin from dark

brown to light tan. These materials showed excellent shape memory and self-repairing properties at elevated temperatures.[41]

Industrial pine Kraft lignin has been modified at up to 30% of its hydroxyls with a silicon containing vinyl capping group (divinyl tetramethyldisilazane) to prepare thermally stable and tough coatings. The reaction was performed in the melt state as a neat mixture of washed substrate and disilazane reagent to combat the challenges associated with dissolving many types of lignin. The reaction was exothermic which has been attributed to the negative enthalpy associated with exchanging N–Si bonds for O–Si bonds. Hydroxyl content was determined by quantitative ^{31}P NMR following modification. Modified Kraft lignin was copolymerized with poly(acrylonitrile) and compared with unmodified Kraft lignin poly(acrylonitrile) composites. The (vinylsilyl)ether modified lignin resulted in tougher solution cast coatings. Importantly, this modification was noted for the remarkable improvement to processability of the modified lignin. This desirable trait was ascribed to decreases in viscosity consequent of masking hydroxyl functionality which also increased the lignin macromolecular mobility.[42]

When the complex heterogeneous composition of technical lignins sufficiently aggravates researchers, they employ lignin model compounds.[43] The use of abbreviated model systems representing moieties and linkages common to targeted feedstocks is akin to studying an atlas before embarking on a road trip. The results of model compound studies combined with contextual reference can be illuminating and can save on the cost of screening nascent technologies.

Lignin model compounds have been used to examine the interplay between time and temperature as they impact MeOH reformation and hydrogenative transformation of simple lignin model compounds over a copper-doped porous metal oxide in the presence of supercritical MeOH. Results of this study were conspicuous but perhaps would have been difficult to pin down utilizing

bulk lignin by analyzing its complex products. The conclusion of the article was that hydrogen production was not the limiting step in batch reactors and in fact overproduction of hydrogen could lead to loss of chemoselectivity.[44]

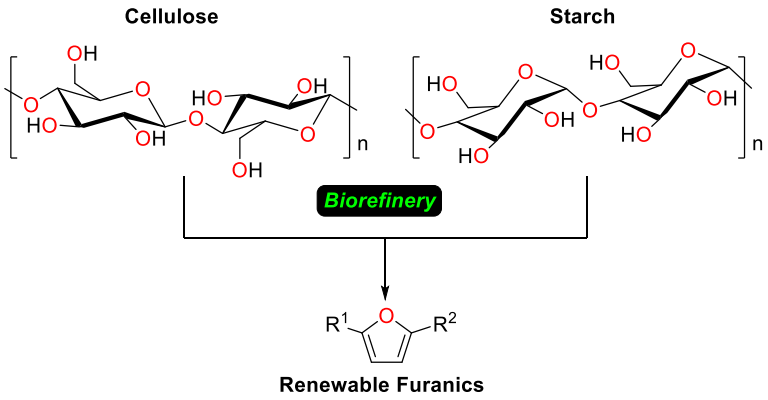
Optimization of economic phenolic monomer production from lignin would be the ideal outcome of model compound studies as described above. One group has employed such a model compound-free approach which was facilitated by a sophisticated analysis. A central composite response surface statistical model was used to analyze solvent liquefaction of technical lignin in mixtures of *o*-cresol and tetralin. The express goal of their project was development of an economic and robust solvent liquification process which could valorize lignin isolated as byproduct of cellulosic EtOH biorefineries by producing renewable small molecules. The roles of solvent mixture, reaction temperature, solids loading, and residence time were evaluated by monitoring multiple response variables: (1) mass balance of liquid and solid products, (2) yield of distillable products, and (3) yields of identifiable small molecule products. The overall process for lignin depolymerization was hydrogenative with tetralin acting as the hydrogen-source at temperatures around 280 °C under the optimized conditions. In order to solvate the lignin, *o*-cresol was required which also stabilized the small molecule products. Importantly, the *o*-cresol could likely be replaced with the small molecule products and thus create a solvent recycle in a continuous lignin reactor. That reactor would require only modest reinput of tetralin depending on the desired products distribution.[45]

1.1.3. Cellulose

1.1.3.1. Structure and Biorefinery Processing of Cellulose

Cellulosic biomass provides access to compounds with a furan skeleton (Scheme 1.3):[46] a structural feature not accessible from fossil sources. Two compounds derived from cellulose,

HMF,[47] and FDCA,[48-51] have been identified as top value added feedstocks for monomer synthesis.[52] HMF has two functional groups at different oxidation states that can be selectively manipulated to provide access to other furan-based monomers (AA, BB, and AB types).



Scheme 1.3. Renewable furanics from polysaccharide biorefinery

In the original context of nylon synthesis, Wallace Carothers referred to diamines as AA type monomers which could be condensed with diacids (BB type monomers) to form polyamides. By utilizing AB type monomers such as 11-aminoundecanoic acid, junior level undergraduates may readily prepare high molecular weight nylon 11 (used industrially in fishing lines). Some researchers have taken to describing the diacid component as an AA type monomer and relegating diamines and diols to the status of BB type monomers. This shift may have been motivated by the conservation of the dicarboxylate moiety across multiple developing condensation polymer platforms. Throughout this work, diacids such as FDCA have been referred to as AA type monomers.

The HMF core structure offers opportunity for modification into symmetrically substituted products such as FDCA or for chemoselective modification to HMFA (an AB type monomer).[53] Literature contains examples wherein attention was paid to AA type (diesters,[54-57] diacids,[58] dicyanos,[59] dialdehydes[60]) and BB type (diamines[61] and diols [62, 63]) monomers for copolymerization. Additionally, six carbon BBB or triol monomers have recently been reported

from the selective hydrogenative ring-opening of HMF.[64] Particularly of note, the toxicity of HMF and some of its derivatives has been established and is considered low.[65]

HMF is an aromatic dehydration derivative of ketohexoses or their polymers such as the cellulose contained in agricultural wastes.[66] Controlling the acidic hydrothermal dehydration to afford platform chemicals such as HMF remains an impediment to cellulosic biorefinery which is often contaminated with polymeric impurities known as humins as well as H_2O soluble D-glucose polymers.[67] Toward that goal, heteropolyacid catalysts in ionic liquids have been investigated in the preparation of HMF from glucose due to their unique tunable structures.[68] Condensation of acetone with furanic platform chemicals such as HMF has afforded feedstocks for the fine chemical industry in high yield.[69]

1.1.3.2. Cellulose Derived Products in Sustainable Materials Science Applications

Cellulosic biorefinery provides access to non-phenyl aromatic structures embodied by furanic derivatives of saccharide dehydration. These furans may engage in cycloaddition chemistries energetically forbidden to benzene rings. Following cycloaddition, but often without isolation, the bicyclic adducts from Diels-Alder reaction may undergo extrusion of the bridgehead molecule with concomitant aromatization. This process is colloquially known as aromatic upgrading and may create a renewable supply of traditionally petroleum derived commodities such as terephthalic acid.

These reactions are challenging to control. They force chemists and engineers to the precipice of technology. Simple molecules undergoing complex transformation can be addressed with *in silico* chemistry. Application of density functional theory combined with experimental results has been employed to quantify the importance of electronic contribution of alkyl groups (at the C2 and C5 positions) in a cycloaddition reaction targeting aromatic upgrading. Biorenewable

2,5-dimethyl furan undergoes adduction with biorenewable acrylic acid in acidic ionic liquids for the production of *para*xylene or 1,4-dimethylbenzene (precursor of terephthalic acid). With knowledgeable practitioners, *in silico* methodologies have the power greatly reducing the costs associated with experimental reaction optimization.[70]

Another intriguing approach to renewable aromatics serves to vividly illustrate the diversity of chemical products and avenues for scientific discovery inherent in working with biorefinery products. Coumalic acid can be prepared from acid catalyzed dimerization and decarboxylation of malic acid. Malic acid is ubiquitously produced in living systems, is well known as a contributor to the sour taste of fruits and can be prepared from glucose by a fermentation process.

Optimized conditions afforded mixtures of toluic acid following Diels-Alder cycloaddition/decarboxylation/dehydrogenation domino sequence assisted by a heterogeneous Lewis acid catalyst. The use of bioavailable propylene is noteworthy since it affords simple separation of residual dienophile and products. The in-depth kinetic investigation presented, could lead to enhanced process efficiency. Knowledge of the rate limiting step (decarboxylation) could provide critical insight when other aromatics are targeted in the future.

The results of dienophile screening indicate that [4+2] cycloadditions with coumalic acid or methyl coumalate display an interesting phenomenon described as inverse electron demand Diels-Alder reactions; electron rich dienophiles had lower activation barriers and afforded greater regioselectivity in the product outcome (as measured by the *para* to *meta* ratios in produced toluic acid). As a corollary, electron poor dienophiles displayed a greater activation barrier. The energy required to overcome those barriers also overcame the selective pressure of secondary orbital interactions and led to lower regioselectivity.[71] By utilization of trifluoromethylated dienophiles,

the coumalate cycloaddition strategy also affords semi-renewable trifluoromethylated aromatics which could significantly impact agrochemical and pharmaceutical industries.[72]

Glucose is the monosaccharide precursor to cellulose: a polysaccharide. In actuality, glucose is currently prepared cheaply and in high purity from an alternative polysaccharide: starch. Since the only effective non-degradative depolymerizations of cellulose to glucose currently known are enzymatic, the potential remains to one day access renewable coumalic acid from an engineered fermentation process. Further examples of glucose in enzymatic biorefineries include recent preparations of renewable 1,5-pentandioic acid (glutaric acid).[73]

1.2. Renewability and Sustainability

Coal is an example of fossil carbon which—*along with petroleum*—has dominated chemical industry since the mauve decade and development of industrialization.[74] Coal is considered a compression fossil and the lower ranked coal known as lignite still bears recognizable resemblance to its source *e.g.* lignin from the Carboniferous Period such as *Lepidodendron* (scale trees).[75] The carbon (atoms) derived from coal and petroleum should be delineated from renewable carbon sources such as corn stover and wood by the timescale of renewal. Since the natural process of fossilization is not relevant on the timescale of human civilization—*much less an individual's subjective experience*—those sources are considered nonrenewable or finite. Recapture, utilization, and storage of escaping carbon from combusting fossil fuels is one of the largest challenges facing humanity during the 21st century;[76] sustainable practices may be achieved by the creation and maintenance of a carbon balance under human control.

A critical distinction must be made between the usage of two terms and their relationship to each other: renewability and sustainability. While often considered colloquially synonymous, these terms denote two related, often overlapping, but in no way inclusive concepts. For example,

it would be wrong to assume that a polymer derived from a renewable resource is automatically going to be more sustainable than the same polymer from fossil sources without considering energy sources and inputs. It is equally incorrect to assume that all usage of fossil resources is inherently unsustainable without considering factors such as recyclability of the material and rate of feedstock depletion. Sustainability and renewability are more than nebulous poetic fluff; they are both quantifiable. The insistence upon their discrete semantic difference lies within the manner of their quantification or evaluation.

1.2.1. Green Chemistry

Green chemistry has been broadly defined by the United States Environmental Protection Agency as "*the design of chemical products and processes that reduce or eliminate the generation of hazardous substances*" and has been thoroughly explored in a textbook made available to the public focused on green engineering.[77]

1.2.1.1. Twelve principles

Green chemistry has been specifically defined by twelve guiding principles for almost 20 years.[78] One drawback to establishing a working definition of green chemistry was the unavoidable advent of band-wagon jumpers who have used the current trends in sustainability to rebrand their science without ever considering what it means to be green. Often, such pretenders will add a sentence to their conclusion invoking one of the principles as if it were a commandment from on high. However, the research field is slowly maturing, and everyone is a potential convert. If you find that multiple selections from the twelve principles could apply to your research, then you are probably justified in describing yourself as a green chemist if and when you embrace complexity to increase your level of sophistication; figure out how to apply more of the principles, measure your improvement, and be green while solving scientific problems. The paradigm of chemistry

self-identification should shift such that people no longer describe themselves as being green chemists or otherwise. Instead they could describe their level of green achievement, perhaps their green velocity, and even their green acceleration.

Loosely, the twelve principles are:[79] (1) prevention of chemical waste, (2) atom economy, (3) devise less hazardous chemical syntheses, (4) design less-toxic chemicals, (5) employ safer solvents and auxiliaries, (6) optimize for energy efficiency, (7) exploit renewable feedstocks, (8) reduce derivatives, (9) innovate catalytic methods, (10) design for degradation, (11) engage in real-time analysis for pollution prevention, and (12) choose safer chemistry to decrease risk by accident prevention. While focusing on some facets of green chemistry is to be expected, translating those efforts to sustainable chemistry involves consideration of broader impact upon interconnected interpenetrating networks of systems. Therefore, the mindset should never involve exclusion of some principles to the advantageous development of others. A green chemist must be aware, must prioritize, and must always be improving. Challenge yourself, too many times humans act on outdated or misapplied heuristics. Think about what you are doing, and you could be a green chemist!

1.2.1.2. Targeting the twelve principles

Research which targeted two green chemistry principles simultaneously—*renewable precursors and usage of benign solvents or auxiliaries*—resulted in a new methodology for the production of a biobased benzoxazine from sesamol, furfurylamine and formaldehyde. Sesamol is derived from sesame oil and furfurylamine is derived from furfural which in turn is derived from hemicellulosic biorefinery of corncobs. The title benzoxazine, 7-(furan-2-ylmethyl)-7,8-dihydro-6*H*-[1,3]-dioxolo[4',5':4,5]benzo[1,2-e][1,3]oxazine, was prepared with extreme regioselectivity.

The reaction afforded only one product during the EtOH or EtOAc solvated pseudo-Mannich reaction and domino formation of a phenolic aminal.

Benzoxazines have been touted as green monomers since their development in the mid 1990's, however the authors review reported methodologies and cite the often monocriteric conclusions of green syntheses to be premature. So, the investigators focused on using renewables readily derived from natural sources and conspicuously only considered solvents with preferred status in the green chemistry community including during their purification process—*recrystallization with mixtures of EtOH and EtOAc*. Their benzoxazine thusly prepared was employed as a novel monomer from biomass to afford homopolymerized thermosetting materials with high thermal stability. The thermosets had a high char yield (64%) making them suitable candidates for fire retardant materials applications.[80]

1.2.1.3. Systems thinking

The twelve principles are intended to engage and expand the mental faculties of both researchers and consumers. They are actually superfluous if you can follow one golden rule. The golden rule of green chemistry could be described as systems thinking. That is to imply a need to think about interconnected systems far outside one's ken. This has also been called "one-world chemistry".[81] Chemistry needs to change, we need life cycle thinking.[82]

Currently it should be considered undesirable to continue chemical endeavors under the false premise of limitless possibility, because optimization without challenging real-world bounds significantly stifles exploration of novel solutions. This results in a dramatic underutilization of innovative potential. Chemistry has been and will always continue to be one of the major actuators of societal change; for better or worse.[83] It should be the task of all modern chemists to consider as many aspects of the interrelated systems in which their chemistry confers societal impacts—

whether in positive or negative fashion. If we had always been trained in application of systems thinking, it would not have taken government regulations to control textile factory waste H_2O effluence to name one example.[84] Another horrific example of avoidable tragedy can be found in the great pacific garbage patch. Current systems thinking continually drives development of biodegradable and biobased polymers with potential for carbon neutrality.[85]

Given the current trends of globalization and facile access to information, there are few remaining excuses for a chemist's abject ignorance of topics such as regional economics, toxicology, or environmental remediation. If ignorance is to be combated, the modern chemist must pursue sustainability and also has a duty to inform the public of that pursuit. To increase the fidelity of those communications, it is critically important to emphatically seek understanding of the interconnected consequences derived from chemical sciences.

Sustainable chemistry drives innovation towards a sustainable future.[86] Systems thinking has led to reevaluation of human labor and another industrial revolution within chemical laboratories.[87] The United Nations has set sustainability goals which can be met by widespread adoption of green practices.[88] The modern chemist is a green chemist, ignorance is tantamount to atavism in its worst form.

1.2.1.4. Systems thinking in the recent literature

An example of systems thinking in action was motivated by competitive development of novel FDCA technologies while loosening the stranglehold of cellulose derived and H_2O soluble HMF. Difficulties in HMF processing have limited its commercialization. The avenues opened by investigation of sustainable alternatives led one group to approach synthesis of the famous terephthalic acid analog and renewable replacement (FDCA) in a nontraditional fashion. This

advancement was achieved by preparing FDCA in 92% on the gram scale *via* palladium mediated, aqueous, carbonylation of 5-bromofuran-2-carboxylic acid (5-bromo-2-furoic acid).[89]

Hemicellulose may be obtained as a side component of lignocellulosic biorefinery and is conveniently isolated from corncobs[90] especially following delignification.[91] Furfural—*furan-2-carbaldehyde or 2-formylfuran*—is economically prepared on the industrial scale by a biorefinery approach and serves as the feedstock for commercial furan and maleic anhydride.[92] It can be oxidized by silver/copper oxides and oxygen in alkaline aqueous medium to afford furan-2-carboxylic acid (furoic acid).[93] Furoic acid can be selectively brominated utilizing bromine to afford the substrate for carbonylation.[89]

A clever study exploited diverse structures afforded by renewable platform chemicals to make improvement to the sustainability of common poly(acrylonitrile-butadiene-styrene) (ABS) rubber.[94] Proliferation of radicals throughout the matrix of the rubber has been attributed to oxidation especially during melt processing and is a leading cause of product inconsistencies and degradation. To combat the negative effects of oxygen, rubber formulators add phenolic compounds before melt extrusion. The choice of phenolic antioxidants was fairly limited prior to the biorefinery revolution and access to many new hydroxybenzenes became feasible.

A careful study of biophenols' antioxidant properties determined the changes in oxidation enthalpy of ABS polymers by investigating a series of eight renewable phenols derived from various biorefinery platforms. They compared and contrasted structures and results to deduce the roles of phenol *versus* cinnamic acid, hydroxybenzoic acid *versus* hydroxycinnamic acid *versus* vinylphenol *versus* allylphenol, and number of free hydroxyls combined with cinnamic acid. The number of mesomeric forms or canonical structures of each biophenol could be correlated to their depressive effect upon ABS polymer oxidation enthalpies. In parallel, the biophenols which also

contained carboxylic acid moieties were found to be effective additives for increasing compatibility between ABS and renewable-biodegradable-poly(lactic acid) inversely related to quantity of resonance forms. Specifically, phenolic acids served a dual role as they created covalent cross-links between the polar and non-polar polymers and shielded against oxidation during melt processing.[94]

The use of renewables such as eugenol from clove oil and other essential oils or spice derivatives offers an exciting opportunity to design novel materials systems which are inherently safer for workers since exposure to these compounds is well understood in mammalian systems. Their production can bolster existing markets while providing targets for lignocellulosic biorefinery. Since many of these aromatic flavorants are prepared and isolated like medicinal natural products, their scale typically limits them to niche applications wherein their complex functional group portfolio can lead to high-performance applications.

The recent development of a low-dielectric polymer from eugenol and (benzocyclobutane)dimethyl silane serves as an example of hybrid fossil-bioderived novel polymer synthesis. Novel 4-allyl-1,2-phenylenebis(benzocyclobutanedimethylsilylether) was prepared in one step with minimal catalyst. Interestingly, the novel monomer underwent thermal polymerization to afford a cross-linked network which included both dibenzocyclooctane and benzocyclohexane functionalities. This was consistent with previous work and indicated the intermediacy of an *o*-quinodimethane type which are susceptible to competitive dimerization and Diels-Alder reactions. The thermoset derived thusly had in addition to a low dielectric constant, good thermal stability, high storage modulus, and low H_2O uptake; such materials may prove suitable for applications in microelectronics such as printed circuit boards.[95]

Innovation is a valued result of systems thinking. As investigators consider novel materials beyond the classical boundaries of their discipline and outside the realm of established feedstocks. The preparation of bioderived modified terpenes like farnesene-starch esters provides an example of such advancements with potential for extension to novel polyol derivatives. Sesquiterpenes—*such as farnesene*—are examples of semiochemicals used for signaling or defense in plants and are composed of three isoprene units—*the bulk monomer of natural rubber*. Trans-β-farnesene served as both the solvent and diene in ester-installation *via* [4+2] cycloadditions with acrylate esters, maleic anhydride, and dimethylacetylene dicarboxylate. The products contained three distinct olefins and ester residues which could be exploited for further modification. An organocatalytic transesterification with starch in dimethyl sulfoxide created ambiphilic graft copolymers in high yield.[96]

A promising consequence of systems thinking is entrepreneurial development of safer solutions to replace established conventions; systems thinking encourages paradigm shifts. For example, vinyl ester resins are important thermosetting materials and, in many cases, may be biomass derived. Unfortunately, their containing multiple ester functionalities typically corresponds with very high viscosities which precludes their usage without a solvent or other thinning additive. The preferred method to formulate such resins has been to employ a reactive solvent or thinner known as a reactive diluent. In these formulations, the solvent becomes covalently integrated into the thermosetting network upon curing. Styrene serves as a banal example which has become threatened by concerns over worker exposure—*due to its suspected human carcinogenicity*.

Recently, novel sobrerol was prepared from hydration of α-pinene oxide in the presence of carbon dioxide. The resulting strained olefin containing diol—*sobrerol*—could be selectively

coupled to acrylic or methacrylic acid to prepare acrylic monomers with extremely low volatility. Volatility is an important concern since most worker exposure in coatings applications is through inhalation of diluent or thinner vapors. The resulting multifunctional vinyl ester monomers were substituted for styrene in formulating three vinyl ester thermosets—*one commercially available and two bioderived resins*. Vinyl ester derivatives of sobrerol were capable of dissolving all three resins with useable viscosities, although all were an order of magnitude higher in viscosity than compared mixtures using styrene. Gel contents served as a measure of crosslink density; they were also lower for the sobrerol derived diluents as compared with styrene diluted formulations.[97]

1.2.2. Sustainability Metrics

Ability to measure the sustainability of a technology is crucial because of a directly proportional relationship to the management of sustainability constraints. Large corporations are investing in sophisticated strategies informed by process assessment to maximize their profits *via* sustainability.[98] As the sophistication of metrics improves, advancements are made in evaluating the quintessential greenness of a technology. The charlatans and green washers who seek to game the system can only be sorted by quantitation, everyone else benefits from developing a precise language of sustainability.

While traditional measurements of efficiency such as yield, or step economy retain importance in deciding between methodologies, the search for sustainability provides a great opportunity for innovation as well as education. New frontiers for exploration are developed by the dynamic and interdisciplinary scholars of sustainability for whom univariate evaluation platforms are insufficient and often misleading. Strive to embrace complexity by the adoption of multivariate assessments. Iterative data-driven improvements are a necessity in making well-informed, multicriterial judgments.

Sustainability metrics are developing into a language of sustainability which continues to grow in complexity as does the sustainable economy. Like any tool, proper knowledge of its intended use combined with a library of available tools facilitates efficient constructions. A primer on common sustainability metrics used in organic chemistry, materials science and engineering should be undertaken by every overlapping researcher to improve their understanding of selection of criteria—*what should be tracked, recorded, calculated, or assessed*. Discussion of metrics has become a central part of constructing research articles in the field of sustainable materials science.

These tools can be extremely useful in combating the oversimplification and marketing voodoo known as green washing. Green washing spans a multidimensional spectrum and includes actions: (1) as abhorrent as claiming everything under the sun as green while ignoring most of the twelve principles, (2) as objectionable as fear mongering *via* vilification of competitors' *chemicals*, and (3) as repugnant as labeling consumer products as "*chemical*-free".

1.2.2.1. Hazard assessment

The principles of green chemistry demand a reduction in the hazards associated with the chemicals themselves. This simple yet tenuous concept permeates sustainable product design and drives revolutionary changes in our perception of desirable products. Sadly, too many people exposed to commercial chemicals lack a sound system for rapidly performing a multivariate assessment of the hazards. One way to address this potential lack of proficiency in the end-users is for initial investigators to take it upon themselves to insinuate hazard assessment into the broader calculus of risk assessment which also takes into account routes of exposure. They must also communicate their assessments to peers and the general public.

A seriously underrepresented knowledge space includes the toxicological ramifications of chemical exposure. Without understanding action of a substance in living systems or its

biotransformed products, attempts to forge safer chemistry can lead to regrettable substitutions. Robust read-across methods are under development to assist investigators' identification of safer chemicals at the early screening level; these incorporate a sophisticated marriage between chemical assay databases and *in silico* calculations.[99]

One tool which has been developed to assist chemical developers of safer products in making informed substitutions is known as GreenScreen. The focus of GreenScreen and related resources is to identify which chemicals do not yet have sufficient accumulated information to justify their use in safer formulations. This use was applied in the evaluation of phthalate alternatives in polymer plasticization and has been reported in an accessible format. The outcome of the evaluation was a delineation between those phthalate alternatives which contain sufficient data to support their substitution for phthalates in consumer products and those which require further investigation.[100]

1.2.3. Chapter Conclusions

The chemical literature seems ebullient with exciting innovations. Systems thinking is being employed in tandem with sustainability metrics to make multicriterial decisions based on ethical, physical, and financial constraints. Biomass is being exploited for renewable chemicals with potential for myriad applications including those yet unimagined. These advancements are marching our society towards a sustainable future.

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2. STYRENE REPLACEMENTS FROM LIGNIN BIOREFINERY

Since lignin is the most abundant source of naturally occurring aromatic moieties, and due to the structural complexity connoted by its randomly crosslinked assemblage, a joint research program directed towards the valorization of lignin was initiated; known as Dakota Biocon, this venture provided a platform for collaborative discussion between students and faculty in multiple disciplines including chemistry, engineering, and materials science.

To add value despite the process challenges conferred by lignin's structural complexity, a major division of strategies within the Dakota Biocon consortium (also abroad) focuses on extracting biorefined platform chemicals from lignin. However, the financial burden of developing totally unproven technologies such as biorefineries has been understandably limited. Cheapness, abundance, and control throughout the refinement of petroleum during the 20th century stifled research into renewables.

2.1. Development of Sustainable Styrene Replacements

Further incentivization for the adoption of sustainable practices can be realized by stabilizing the market for renewable products. The Sibi research group approached contribution to Dakota Biocon primarily through the chemical diversification of renewable feedstocks which other researchers were deriving from lignocellulosic biomass through biorefinery. One outcome of these endeavors was a collaborative paper with the Webster research group (experts in sustainable thermosetting materials).[1] A strategic series renewable monomers from lignin derived materials were screened as styrene replacements within the context of a renewable thermosetting resin formulation. The story of renewable veratrole diluent development comprises this chapter.

2.1.1. Styrene and Reactive Diluents

2.1.1.1. Styrene

Styrene was first isolated from renewable sources; however, it is currently produced as a commodity chemical from fossil sources. Its simplicity, viscosity and diverse chemical reactivity have transitioned styrene from competition with alkylated cellulose in the late 1930's to a premier reactive monomer of the petroleum age.[2] Although styrene is a small and cheap molecule to produce, health concerns and its fossil-source have fueled the search for renewable alternatives.

Styrene is a liquid-vinyl-monomer having a significant vapor pressure (5 Torr at 20 °C), is considered a volatile organic compound (VOC) by the United States' Environmental Protection Agency (boiling point 145 °C), and is a suspected human carcinogen.[3] It is employed ubiquitously in materials science with primary usage as a thermoplastic as well as a reactive diluent for unsaturated polyester and vinyl ester resins.[4] Certain applications in confined spaces wherein VOCs must be eliminated due to customer demand combined with growing uncertainty regarding long term exposure to styrenated resins have created a new frontier for exploration into the application of biosouced alternatives with potential as sustainable and benign replacements.

2.1.1.2. Sustainable Reactive Diluents

Bio-based alternatives may provide structural analogs to styrene while imparting enhanced properties and different toxicity profiles. For example, if the vapor pressure of a styrene replacement was significantly reduced without sacrificing the physical properties of thermosets, a major route to human exposure would be mitigated. However, altering the physical properties of a material enough to affect significant change in properties—*such as vapor pressure*—without sacrificing desired traits—*such as viscosity, reactivity and strength properties*—would be extremely challenging. Also constraining the issue, a true drop-in replacement would require a

comparable weight substitution. The development of these tantalizing targets presents an opportunity to attenuate the negative aspects of styrene while improving the bio-based content in thermoset applications—*where exposure to styrene is extremely prevalent*.

Lignin is an abundant source of non-edible biomass with a complicated network structure.[5] Recent endeavors in the field of lignin biorefinery[6] have focused on degrading[7] that complex structure into small molecule fragments for use as chemical building blocks[8-11] and fuels.[12, 13] Such renewable platform chemicals include vanillin,[14, 15] guaiacol and related compounds which have been modified for use in sustainable materials science.[16, 17] Eugenol is an essential oil isolated from cloves and can be derived from guaiacol by efficient allylation followed by aromatic Claisen rearrangement.

This work focused upon the preparation of renewable styrene replacements from biomass-derivable vanillin and eugenol as well as their application in the field of sustainable-thermosetting materials (thermosets).[18] A further advantage to worker health imparted by this strategy is the relatively benign nature of the substrates; these and many related compounds are naturally occurring FDA approved food additives often containing medicinal atributes.[19] Although toxicological characterization has not been performed on the diluents disclosed herein or upon the thermosets derived thereof, it seems promising that a structural analog—*4-allylveratrole with a boiling point of 255 °C and vapor pressure of 0.027 Torr*—has been evaluated; 4-allylveratrol was cleared safely from mammalian systems faster than it accumulated under limited exposure.[20-22]

2.1.2. Description of Oil-seed Derived Thermosetting Resin

Epoxidized sucrose soyate (ESS)[23, 24] and its methacrylated derivatives, including dimethacylated epoxidized sucrose soyate (DMESS) have been explored at NDSU.[25-28] Sucrose soyate is a mixture of renewable dendritic macromolecules derived from table sugar and soybean

oil. It is prepared by transesterification of methyl soyate with sucrose—*the disaccharide derived from sugar cane and beets*. There are eight hydroxyl residues on the sucrose molecule of varying reactivity due to steric interactions. Under optimized conditions, most of those hydroxyls undergo esterification. The olefins comprising the fatty ester tails are amenable to classic autoxidative curing. The unsaturates also undergo efficient epoxidation which serves as further activation for cross-linking and creates new synthetic handles for structural modification.

Pilot scale (10 kg) preparations of ESS resins have been reported.[29] Reaction of oxirane functionality in ESS with methacrylic acid and anhydride mixtures affords a viscous vinyl ester resin. That resin contains nearly twice as many olefins as the initial sucrose soyate and has transformed them from non-polar internal *cis*-alkenes to polar α,β-unsaturated carboxylic esters! Increased viscosities of those resins required a reactive thinner for thermoset formulation.[25-28]

The high degree of functionality combined with rigid sucrose core impart high performance in terms of thermomechanical properties to DMESS-based thermosets as compared with traditional soybean oil derived resins. Vinyl ester resins in general are well known for their robust performance in a variety of applications and are generally more reactive than unsaturated polyester resins due to the substitution pattern of the cross-linkable olefin moiety.[30] Successful substitution of petroleum feedstocks with bio-sourced alternatives has been reviewed.[31] The use of bio-sourced vinyl ester diluents has become a favorite tactic for styrene-replacement in sustainable thermosets.[32, 33]

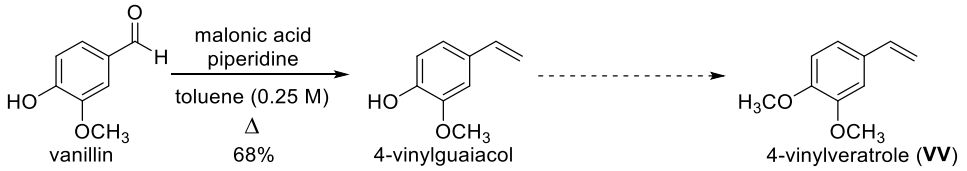
2.1.3. Design and Synthesis of Veratrole Diluents

A viable alternative to the established vinyl ester diluents was sought. Available diluents compare unfavorably with styrene in terms of viscosity reduction due to electrostatic attraction contributed by the ester moiety. We elected to investigate veratrole-diluents; these were named for

their conserved 1,2-dimethoxybenzene core structure; envisaged compounds would be composed of dimethoxybenzene-derived styrene analogs. Prominently, this family of veratrole-diluents has the potential to mitigate inhalation hazards associated with styrene due to their limited potential as VOCs; imagine construction of liquid vinyl diluents based not on benzene—*boiling point of 80 °C, vapor pressure 95 Torr at 25 °C*—but on 1,2-dimethoxybenzene—*also known as veratrole, boiling point of 206 °C, vapor pressure of only 0.7 Torr at 25 °C.*

2.1.3.1. Knoevenagel Condensation and Biostyrenes

Reactive diluent 5-vinylguaiacol has been investigated and referred to as a 'biostyrene' along with 4-vinylveratrole (VV) (Scheme 2.1) in unsaturated polyester thermosets.[34] The importance of masking the phenolic hydroxyl group—*a potential inhibitor of free radical polymerization and contributor to intermolecular attraction*—has been established.[34] Recent reports address the issue by careful protection strategies prior to polymerization followed by deprotection to reveal homopolymers of 5-vinylguaiacol.[35]

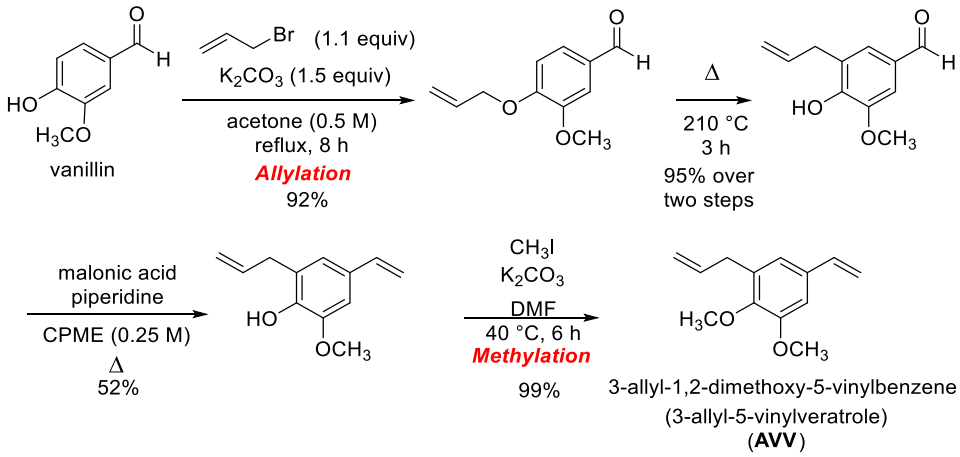


Scheme 2.1. Hypothetical preparation of 4-vinylveratrole from vanillin

Biocatalytic production of 5-vinylguaiacol from ferulic acid[36] (a potential precursor[37] and derivative of vanillin) was reported as an intermediate in the scalable-synthesis of a biobased fragrance.[38] Laboratory scale preparations of 5-vinylguaiacol have been reported from vanillin (Scheme 2.1).[39, 40] The route we employed involves piperidine-mediated addition of malonic acid to vanillin in refluxing toluene followed by an *in situ* double decarboxylation.[16, 41, 42]

A recent noteworthy advance in the conversion of biosourced ferulic acids to biostyrenes involves *N*-heterocyclic carbene mediated decarboxylation to afford vinylphenols in high yield.[43]

Importantly, the Knoevenagel/double-decarboxylation protocol has been reported to afford reasonable yields of sterically hindered products such as 2,6-dimethoxy-4-vinylphenol. Successful transformation with sterically demanding substrates was required by our design of veratrole-diluents containing both allyl and vinyl substituents. *See the experimental section for complete details of synthetic preparations.*



Scheme 2.2. Preparation of 3-allyl-5-vinylveratrole from vanillin

To prepare a novel veratrole-diluent which contained multiple types of vinyl substituents (Scheme 2.2), vanillin was allylated in acetone or EtOH to afford 4-(allyloxy)-3-methoxybenzaldehyde. Without complete isolation, the mixture of allylated phenol and allyl bromide was subjected to solvent-free aromatic-Claisen rearrangement[44, 45] which furnished 3-allyl-4-hydroxy-5-methoxybenzaldehyde in 95% yield over two steps. Purification was accomplished by recrystallization from DCM and Hex. The allylated formylphenol was subjected to Knoevenagel condensation in similar fashion as described for vanillin.[16]

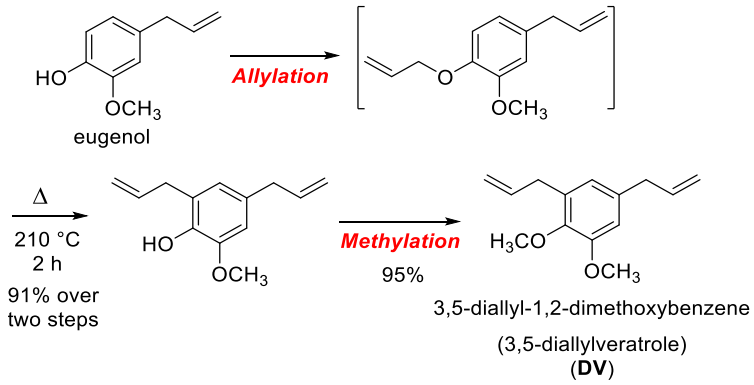
2.1.3.2. Process Solvent: CPME

With a mind towards future sale-up, toluene was seamlessly replaced with cyclopentylmethyl ether (CPME)[46] as solvent in this key transformation and functioned equally well without significant change to the yield or facility of workup. CPME gained notoriety as a

green solvent despite its petrochemical lineage. It is an ethereal solvent, but unlike its brethren, is not prone to formation of peroxides. It can be made anhydrous by drying with activated molecular sieves and forms a positive azeotrope with H_2O.

Additionally, it is not as volatile (boiling point of 106 °C) as compared to other ethereal solvents such as 1,4-dioxane, DME, 5-methyltetrahydrofuran, THF, or diethyl ether. CPME is readily synthesized from methylation of cyclopentanol or from addition of MeOH to cyclopentene. CPME is relatively stable to acids in both homogeneous and heterogeneous conditions. It has a low heat of vaporization coupled with a high boiling point which makes it recovery by rotary evaporation highly efficient and has a narrow explosion range compared to many ethereal solvents.[46]

2.1.3.3. Phenolic Masking



Scheme 2.3. Preparation of 3,5-diallylveratrole from eugenol.

The hydroxyl group substituted with either an *ortho* or *para* relationship to the aromatic aldehyde of formyl phenols was vital in their transformation from aldehydes to vinyl groups. Therefore, an additional constraint was placed on our synthesis: the hydroxyl could not be modified until late in the synthesis of 1-allyl-2,3-dimethoxy-5-vinylbenzene or 3-allyl-5-vinylveratrole (AVV). AVV precursor, 3-allyl-4-hydroxy-5-methoxybenzaldehyde, was masked using a potassium carbonate mediated reaction with methyl iodide to expedite the initial syntheses

of veratrole-diluents. Multiple laboratories have reported sustainable phenolic methylation strategies using green reagents such as dimethyl carbonate,[47-49] so there is further potential to prepare this type of diluent in scalable and sustainable fashion. Similar allylation/aromatic-Claisen rearrangement and methyl-capping transformations afforded 1,5-diallyl-2,3-dimethoxybenzene or 2,5-diallylveratrole (DV) from eugenol (Scheme 2.3).

2.1.3.4. Discussion of Metrics

The renewability metric known as biobased content has been promoted by the United states department of agriculture. If all the carbon in a material comes from renewable sources such as wood or agricultural waste, then it is considered 100% biobased. There exists a standardized method for radiocarbon determination of actual biobased content (ASTM D6866–18) which serves to quantify renewability by radiocarbon analysis. At this preliminary stage a discussion, theoretical biobased or bioderivable content is of great utility. Theoretical improvements in the bio-based content without sacrificing experimental thermomechanical properties of thermosets derived from DMESS were observed when styrene was replaced with veratrole diluents.

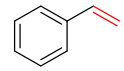
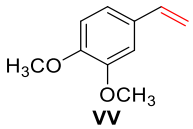
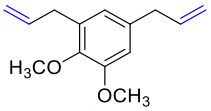
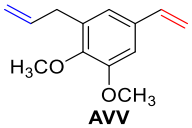
2.2. Styrene Substitution in DMESS Thermosets

2.2.1. Rheometric Analysis

Replacement of styrene as the reactive diluent with potentially sustainable alternatives—*biorenewable 4-vinylveratrole (VV), 3-allyl-5-vinyl veratrole (AVV), and 3,5-diallylveratrole (DV) (Schemes 2.1, 2.2, and 2.3)*—made the new thermosets almost completely bioderivable.[1] In the most promising thermoset, styrene (0% biobased) was replaced with AVV (>90% biobased if renewable vanillin and malonic acid were employed in its preparation as described in the experimental section).

Following preparation, the series of diluents was evaluated in formulation with dimethacrylated epoxidized sucrose soyate (DMESS). Table 2.1 summarizes the viscosities of the formulations containing ten, twenty and thirty percent by weight of the reactive diluents. Viscosity is a material's resistance to flow and the control (styrene) was the most efficient diluent as it afforded the lowest viscosity at each of the concentrations examined. The veratrole-diluents afforded viscosities an order of magnitude higher than styrene at equal weight percent dilutions. An attempt to discern specific diluent power to compare equivalent moles of reactive diluent has been made (*vide infra*).

Table 2.1. Viscosities of DMESS-diluent blends as a function of diluent amount

Reactive diluent		**Viscosity** at 10 Hz (mPa·s)		
Structure	Mol. Wt. (g/mol)	10%	20%	30%
 styrene	104	9,800	1,000	200
 VV	164	40,400	10,300	2,600
 DV	218	29,600	6,700	1,600
 AVV	204	35,300	9,000	1,900

Thermosets were prepared, analyzed and tabulated by A. Z Yu and J. M. Sahouani of Prof. Dean Webster's research group. Adapted with permission from Yu, A. Z.; Serum, E. M.; Renner, A. C.; Sahouani, J. M.; Sibi, M. P.; Webster, D. C., Renewable Reactive Diluents as Practical Styrene Replacements in Biobased Vinyl Ester Thermosets. *ACS Sus. Chem. Eng.* **2018**, 6 (10), 12586-12592. Copyright 2018 American Chemical Society.

At the lowest dilution studied—*ten percent by weight of reactive diluent*—the formulation viscosities could be sorted into ascending order with styrene <DV<AVV<VV. This trend provided the first indication that allyl substituents played an important role in lowering viscosity: a major achievement of this work! Allyl substitutions could counter developments of increasing the molecular weight and steric bulk of other residual functionalities installed on reactive vinyl diluents.

Only the styrene-DMESS formulation with thirty percent by weight of diluent displayed a viscosity below 500 mPa·s—*the value widely considered acceptable for industrial processing of resin formulations*.[31] Atom for atom, all the diluents were comparable with styrene which became apparent when considering the various molecular weights of the series (Table 2.1); when modifying colligative properties such as viscosity, the molar concentration of resin in diluent plays a much greater role than the weight fraction. From this perspective, the twenty percent by weight biobased diluent-DMESS blends could be ordered in ascending viscosity with fewer allyl substituents DV<AVV<VV. All the twenty percent by weight formulations actually compared favorably with the ten percent by weight styrene-DMESS formulation!

2.2.1.1. Evaluating Specific Diluent Effects

To properly illustrate the molar relationship between diluent species, resin and viscosity, the precise molecular weight or weight distributions of both the resin and diluents would be required. While a generalized structure for DMESS may be drawn, and while determination of a useful olefin equivalent weight by iodine titration was performed, it would be potentially misleading to convert that equivalent weight to an average molecular weight since the exact structural distribution of DMESS is not well-defined. However, to establish a semi-quantitative relationship between molar concentration of diluent per unit weight of resin, placing weight

percent diluent in the numerator and that diluent's weight in the denominator affords a quotient which has the strange units of moles diluent/100 g resin formulation. When these values are plotted as concentrations on the abscissa with viscosity measurements on the ordinate, a striking trend becomes apparent (Fig. 2.1).

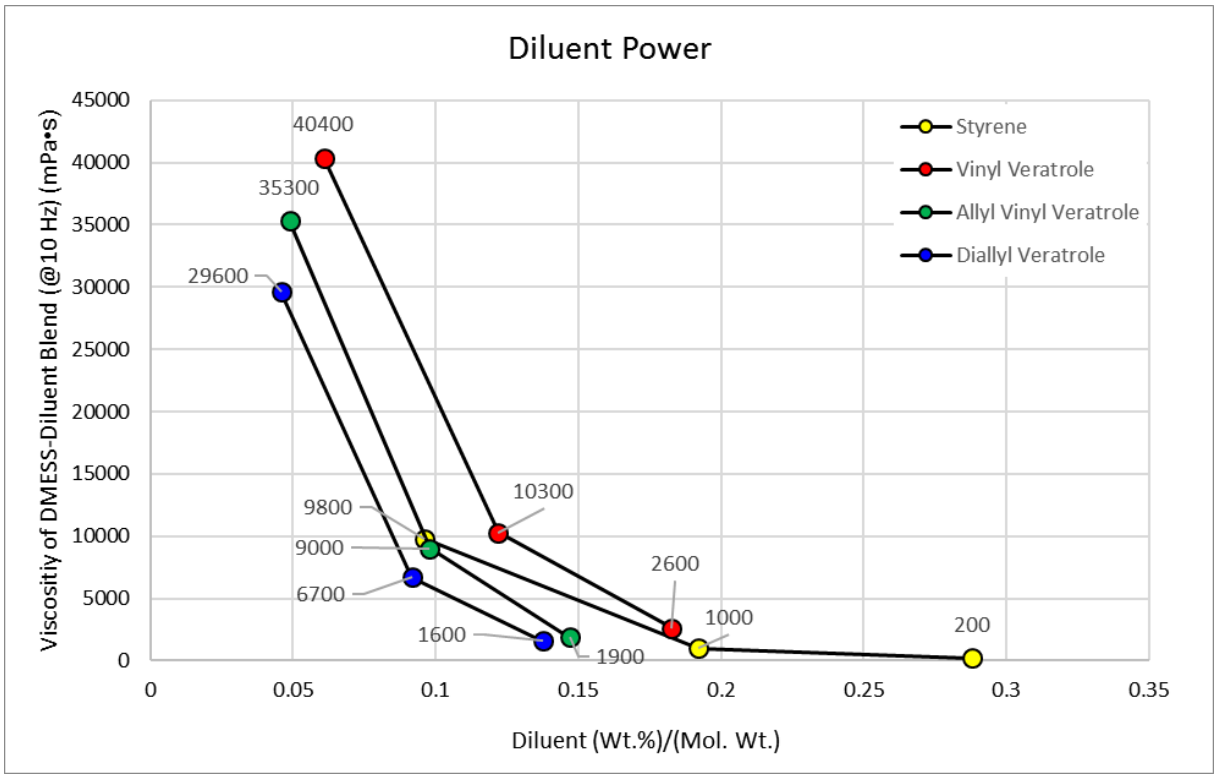


Fig. 2.1. Relationship between (moles diluent/100 g resin formulation) and viscosity

Allylated veratrole diluents are actually more powerful in terms of viscosity reduction per mole of diluent than is styrene. Vinyl veratrole alone was a weaker diluent and illuminated the negative impact on viscosity resulting from simply substituting a biomass derivable veratrole-ring for a petroleum derived benzene-ring. Coincidentally, styrene and allyl vinyl veratrole affect DMESS formulations to nearly the same degree at approximately 0.1 mol/100 g resin dilution. The relationship between molar dilution of DMESS resins and viscosity is nonlinear. It looks like it could be an exponential or described by some other power law. When the log base 10 of the ordinate values from Fig. 2.1 were plotted against the abscissa values from Fig. 2.1, the data could

be characterized by linear functions (Fig. 2.2). This has allowed quantification of the differential diluent power of these veratrole diluents compared with styrene and DMESS resin at least over the narrow range studied.

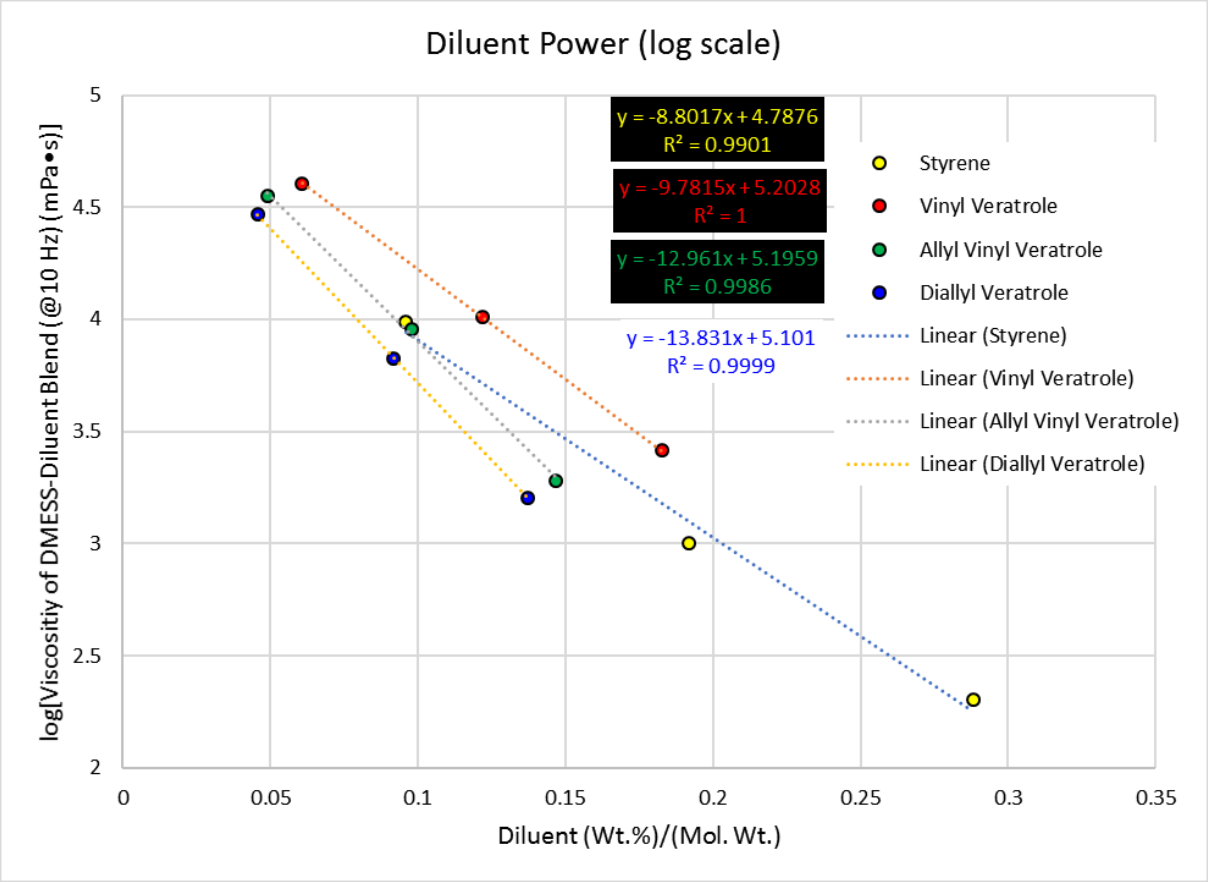


Fig. 2.2. Linearized relationship between log[viscosity] *versus* diluent (moles/100 g resin)

Right away, the linearity of the relationships in Fig. 2.2 can be observed by the coefficient of determination (R^2 value) associated with each trend. However, there is quite a bit of qualitative difference between the ordinate intercepts of veratrole diluents and styrene which is obviously false. Theoretically the intercept values should all be the same since zero moles of diluent per 100 g of resin formulation should correspond to the viscosity of the undiluted DMESS resin. This aberration has been attributed to the broader range of viscosity data collected for styrene by virtue of its low molecular weight.

These observations indicate that the well-defined relationship may be limited to low diluent concentration. The slope values for these functions should correspond with diluent power, with larger magnitude negative values indicating greater diluent power. From Fig. 2.2, it would seem that styrene is actually a less powerful diluent than all tree veratrole diluents examined; this seems abnormal due to the qualitative relationships illustrated in Fig. 2.1 and is a secondary indication that higher molar dilutions cannot be included in this type of linearization.

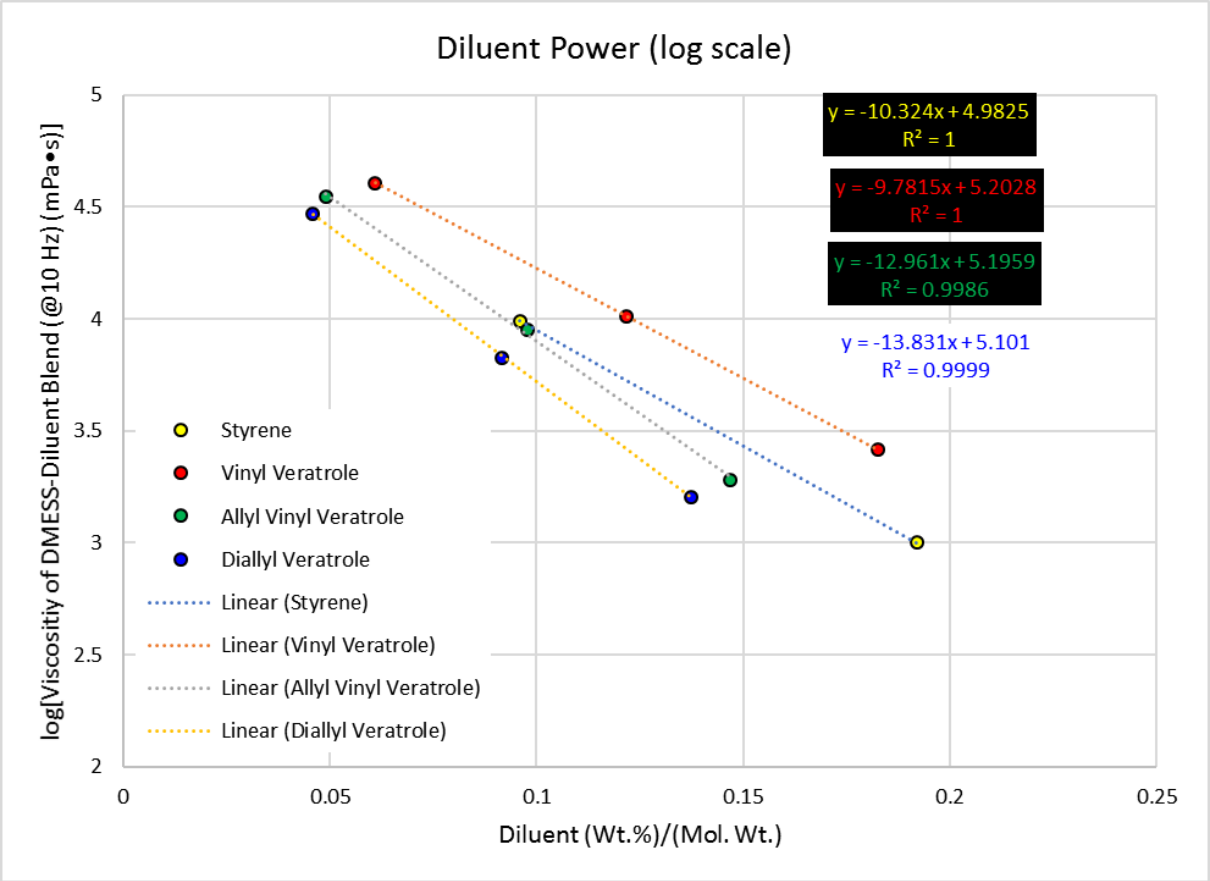


Fig. 2.3. Linearized relationship between log[viscosity] *versus* diluent (moles/100 g resin) excluding styrene at 30% by weight.

When the data for thirty percent by weight styrene was discarded, the ordinate intercept values were in closer agreement (Fig. 2.3). The average value for that intercept was 5.12 which corresponds to a predicted viscosity of undiluted DMESS resin: 132,000 (mPa·s) at 10 Hz. Unfortunately that value could not be compared or calibrated with an experimental value, since it

was way outside the range of the ARES Rheometer employed during this study.[1] The slope values from Fig. 2.3 now align with the expected trend in diluent power: DV>AVV>>styrene>VV. The change in diluent power going from AVV to styrene was a whopping 2.6 in contrast to a difference of 0.9 between DV and AVV or 0.5 for the difference between styrene and VV. The validity of these determined values is nebulous; with increased validation, this type of rheological assessment could one day be used to assign diluent power to different moieties and serve as ammunition in a quantitative structure proper relationships model with predictive power.

2.2.2. Thermomechanical Evaluation of DMESS Thermosets

Table 2.2. Thermomechanical properties of thermosets of DMESS cured at 70 °C for 1 h, 90 °C for 1 h, and 150 °C for 2 h

Reactive diluent (30 % by weight)	% Gel	$T_{5\%}$ (°C)	T_g (°C)	E' at T_g + 60 °C (MPa)	v_e (mol/m^3)
Styrene	99.7	330	85	178	17,100
VV	99.4	318	101	76	7,000
DV	93.1	308	76	45	4,400
AVV	98.6	327	84	145	13,900

Thermosets were prepared and analyzed by A. Z Yu and J. M. Sahouani of Prof. Dean Webster's research group. Adapted with permission from Yu, A. Z.; Serum, E. M.; Renner, A. C.; Sahouani, J. M.; Sibi, M. P.; Webster, D. C., Renewable Reactive Diluents as Practical Styrene Replacements in Biobased Vinyl Ester Thermosets. *ACS Sus. Chem. Eng.* **2018**, 6 (10), 12586–12592. Copyright 2018 American Chemical Society.

Thermosets were prepared from formulations containing thirty percent by weight of diluent *via* peroxide-initiated thermal curing[26] and the thermomechanical properties have been summarized in Table 2.2. Generally, thermosets with reactive diluents containing only a vinyl group displayed the highest gel contents (99.7% for styrene and 99.4% for VV), indicating excellent incorporation of the diluent into the polymer network. AVV, with both aliphatic and aromatic substituted primary olefins, gave a slightly lower gel content (98.6%) than styrene (99.7%) or VV (99.4%). Furthermore, DV—*which contained two primary aliphatic olefins and no*

aromatic olefin—showed the lowest gel content (93.1%). The % gel serves as an indication of diluent incorporation through its modulation of crosslink density by subjecting cured thermosets to exhaustive Soxhlet extraction; only small molecules and oligomers will dissolve while the fully cured network can only swell forming a gel.

Thermosets formulated with styrene began to degrade thermally at 330 °C, and displayed a glass transition at 85 °C. Those thermosets also led to the greatest crosslink density (ν_e) of the series (17,100 mol/m^3) derived from the storage modulus (E', 178 MPa) at 60 °C above the glass transition by rubber elasticity theory.[50-52] Styrene analog, VV, was not expected to function as a drop-in replacement due to enhanced resonance stabilization afforded to the benzyl-radical by balancing the effect of two methoxy substituents upon a veratrole core—*termed a veratryl radical*.[53] The net effect of two methoxy substituent groups depresses the relative propagation rate of veratryl radicals in a typical chain polymerization as compared to styrene homopolymerization.[54] Thermosets formulated with VV as compared to styrene displayed lower thermal stability (318 °C), higher glass transition temperature (101 °C), lower storage modulus (E', 76 MPa) 60 °C above T_g, and less than half the cross-link density (7,000 mol/m^3) despite their high % gel content (99.4 *versus* 99.7). Compared to styrene, the glass transition temperatures (T_g) of the thermosets were higher when VV was used. The two methoxy substituents provided steric bulk with corresponding increases observed in the T_g.

The presence of phenylpropene (allyl) moieties was expected to enhance chain-transfer reactions during the curing of thermosets; this could be desirable due to the high degree of functionality embodied by DMESS macromonomers. Alternatively, chain-transfer could also lead to an incomplete network with inferior thermomechanical properties which could leech unreacted diluent into the environment. The reduced gel content (93.4%) encountered in formulations using

DV can be attributed to the slower propagation and higher degree of chain transfer or termination present in greatly stabilized allylic/veratrylic radicals. Thermal stability of thermosets prepared with DV were the lowest of the series (onset of degradation 308 °C) as were values for glass transition (76 °C), storage modulus (45 MPa), and crosslink density (4,394 mol/m^3). These values indicated the propagation of free radical polymerization in the presence of DV was relatively slow.

The thermal stabilities determined for the DMESS-thermosets with biobased styrene replacements were generally high (308–330 °C), and comparable to formulations utilizing styrene; of particular interest, the thermosets containing AVV closely matched the properties of those from styrene—*onset of thermal degradation was 327 °C*. Appending an allyl substituent upon the vinylveratrole-core, as in AVV, depressed the T_g—*down from 101 °C with VV to 84 °C*—to closely match that of styrene-formulations (85 °C) with the second highest storage modulus (145 Mpa); also, the cross-link densities (13,930 mol/m^3) for AVV-DMESS-thermosets were most comparable with formulations containing equivalent weight percentages of styrene (17,090 mol/m^3). The increase in crosslink density between formulations containing VV *versus* AVV suggested that the allyl group contributed to network formation as it underwent slow intermolecular propagation upon chain-transfer rather than immediate termination.

2.2.2.1. Evaluation of Tensile Properties

The intermediate dual-functionality of AVV created a system which was readily incorporated into the thermosetting network propagated by free radical polymerization at the vinyl position. Once incorporated, the AVV residues were still actively engaging in chain transfer reactions and crosslinking thanks to the secondary pendant functionality of the allylic moiety. These combined features may have facilitated intermolecular—*versus intramolecular*—crosslinking between DMESS branches which would account for the increased toughness observed

in AVV opposed to VV and DV diluted DMESS thermosets (Table 2.3). Despite containing half the molecular concentration of diluent, DMESS thermosets formulated with AVV overlapped the range of determined toughness from those with styrene. In terms of toughness, thermosets prepared with styrene and AVV were significantly superior to those prepared with VV and. DMESS-thermosets formulated with AVV displayed greater tensile strengths compared with DMESS-thermosets diluted with styrene and much greater than those diluted with VV or DV. The Young's modulus determined for DMESS-thermosets diluted with AVV were far greater than those prepared from styrene, VV, or DV. Ranges in the % elongation were all overlapping with styrene and DV displaying the greatest upper limits.

Table 2.3. Tensile properties of thermosets of DMESS (90% methacrylation) and different diluents cured at 70 °C for 1 h, 90 °C for 1 h, and 150 °C for 2 h.[26]

Reactive diluent (30% by weight)	Tensile strength (MPa)	Young's modulus (MPa)	Elongation (%)	Toughness (10^{-2} J)
Styrene	13.6–20.1	431–503	4.2–6.8	3.9–9.3
VV	10.0–12.2	372–426	3.4–4.8	2.1–3.9
DV	7.3–9.0	226–260	4.5–5.5	2.4–3.8
AVV	17.2–21.6	686–718	3.4–4.8	4.0–7.0

Thermosets were prepared and analyzed by A. Z Yu and J. M. Sahouani of Prof. Dean Webster's research group. Adapted with permission from Yu, A. Z.; Serum, E. M.; Renner, A. C.; Sahouani, J. M.; Sibi, M. P.; Webster, D. C., Renewable Reactive Diluents as Practical Styrene Replacements in Biobased Vinyl Ester Thermosets. *ACS Sus. Chem. Eng.* **2018**, 6 (10), 12586–12592. Copyright 2018 American Chemical Society.

Overall, the novel structure of AVV showed promise as a bio-based styrene substitute in terms of thermomechanical and tensile properties of the thermosets at comparable weight percent formulations. This result was consistent with expectations generated from the study of VV and from investigations utilizing vinyl ester derivatives prepared from eugenol wherein useful polymeric materials were prepared by combination of a reactive vinyl group comprising a reactive methacrylic ester and the less reactive allyl moiety.[55]

2.2.3. Chapter Conclusions

Biorenewable reactive diluents of practical importance have been prepared from chemicals of low toxicity: vanillin and eugenol. These scalable veratrole-diluents were investigated as possible styrene replacements in a series of thermosets prepared from dimethacrylated-epoxidized-sucrose soyate (DMESS). One novel veratrole-diluent performed similarly to styrene when formulated at 30% by weight of diluents: 3-allyl-5-vinylveratrole. Excitingly, this was only about half the molar concentration of veratrole-diluent compared with styrene. The dual functionality and methoxy substitutions of the veratrole-diluent was designed to diminish chances of worker exposure due to its higher molecular weight and expected lower volatility. This innovation is the first example of such a direct substitution in high-performance vinyl ester thermosets. A resin derived from table sugar and soybean oil was effectively formulated for thermosetting materials applications specifically by incorporation of lignin derivable reactive diluents.

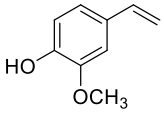
2.3. Experimental

2.3.1. General Methods

Unless otherwise stated, all commercially procured materials were used as received without further purification. Melting points were collected on a REACH Devices RD-MP digital melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were collected on a Bruker Avance 400 MHz instrument and processed with Topspin software. Infrared spectra were collected with a Nicolet™ iS™ 10 FTIR Spectrometer using a diamond sample plate for ATR and processed using Omnix. High resolution mass spectra were collected on Waters Synapt G2-Si high definition mass spectrometer and were processed using MassLynx. Unless otherwise stated, all reactions were stirred magnetically with PTFE coated spin-bars. All mention of silica gel refers to Sorbtech standard grade silica gel: 230-400 mesh.

2.3.2. One Pot Knoevenagel Condensation/Double Decarboxylation

2.3.2.1. 2-Hydroxy-1-methoxy-5-vinylbenzene[1]



^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.95 (d, *J*=1.7 Hz, 1H), 6.93 (dd, *J*=8.1, 1.8 Hz, 1H), 6.88 (d, *J*=8.0 Hz, 1H), 6.65 (dd, *J*=17.5, 10.9 Hz, 1H), 5.66 (s, 1H), 5.60 (dd, *J*=17.5, 0.9 Hz, 1H), 5.14 (dd, *J*=10.9, 0.8 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.7, 145.8, 136.8, 130.4, 120.2, 114.5, 111.6, 108.1, 56.0; IR (ATR, diamond, neat film from $CDCl_3$ solution, cm^{-1}): 3509, 3433, 3086, 3005, 2939, 2843, 1594, 1510, 1463, 1417, 1364, 1267, 1235, 1204, 1151, 1120, 1029, 987, 900, 854, 819, 790, 705, 575, 554, 436.

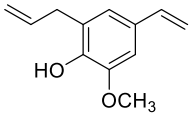
This compound has been previously reported by Nomura *et al.*[39] Also reported in many recent works.[56-60] Notably it has been prepared recently from lignin-derived aromatic acids.[43] Based on the procedure of Aouf *et al.*,[16] a 250 mL round-bottom flask was charged with vanillin (2.029 g, 13.3 mmol, 1.0 eq.), malonic acid (2.057 g, 19.8 mmol, 1.5 eq.), and toluene (53 mL). The mixture was submerged in an oil bath, stirred beneath a H_2O-cooled condenser, and formed a colorless-transparent solution which contained undissolved white solid residue. Dry piperidine (6.5 mL, 66 mmol, 4.9) was added *via* syringe. Immediately, the white solids clumped together, and the solution became yellowish green. Argon was flushed through the apparatus for ten min.

The solids dissolved upon heating (oil bath at 115 ºC); the reaction mixture was a medium brownish yellow solution. Following two h of reflux, the reaction flask was removed from the oil bath and allowed to cool with stirring. The reaction mixture was analyzed with thin layer chromatography (TLC) and compared with vanillin; 2:1 Hex/EtOAc development solvent, and UV visualization. R_f values were as follows: vanillin: 0.30; reaction mixture: 0.0, 0.05, 0.49.

When cool, the reaction mixture was poured through a funnel into a 250 mL round-bottom flask; acetone was used to aid transfer, but 95% EtOH was required to transfer a yellow, oily

residue at the bottom of the flask. The reaction mixture was concentrated *in vacuo*. To the remaining orange-brown oil was added (50 mL of toluene, which was subsequently removed *in vacuo)* twice to increase the fraction of piperidine removed from the reaction mixture. The concentrate was purified by flash column chromatography[61] using Hex and EtOAc as the solvent. Column fractions containing product (TLC R_f 0.49) were combined, concentrated to a constant mass and characterized by NMR and FTIR. The product appeared as a colorless oil: 1.361 g or 68% of the theoretical maximum.

2.3.2.2. 3-Allyl-2-hydroxy-1-methoxy-5-vinylbenzene[1]



HRMS $[C_{12}H_{15}O_2]^+$ Calcd.: 191.1072: found 191.1073; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.84 (d, *J*=1.9 Hz, 1H), 6.81 (d, *J*=1.8 Hz, 1H), 6.62 (dd, *J*=17.5, 10.8 Hz, 1H), 6.01 (ddt, *J*=16.6, 10.1, 6.6 Hz, 1H), 5.71 (s, 1H), 5.58 (dd, *J*=17.5, 0.9 Hz, 1H), 5.05–5.13 (m, 3H), 3.91 (s, 3H), 3.41 (dt, *J*=6.5, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.6, 143.5, 136.9, 136.6, 129.6, 125.7, 121.1, 115.7, 111.4, 106.1, 56.2, 34.0; IR (ATR, diamond, neat film, cm^{-1}): 3518, 3082, 3005, 2976, 2938, 2903, 2841, 1731, 1601, 1494, 1463, 1435, 1412, 1361, 1288, 1237, 1208,1106, 1074, 1045, 988, 692, 937, 897, 868, 846, 786, 753, 688, 618, 559, 436.

This material has appeared in a table reported by Sinha *et al.* wherein they have attempted to expand the substrate scope of substituted ferulic acids which could be decarboxylated to afford phenolic styrenes. However a yield was not reported nor was any characterization data.[62] From their work, it is apparent that wild type whole organisms—*Pantoea agglomerans strains in their case*—may be unsuited to direct conversion of highly substituted ferulic acids. Replacement of toluene (*vide infra)* with the preferable cyclopentylmethyl ether (CPME)[46] was made in order to evaluate the effectiveness of a large scale process solvent in this transformation.

A 300 mL round bottom flask was charged with 3-allyl-4-hydroxy-5-methoxybenzaldehyde (pale yellow solid, 4.916 g, 25.6 mmol, 1 eq.), and CPME (100 mL). The mixture was stirred; a light-yellow solution resulted. Dry piperidine (12.4 mL, 169.0 mmol, 6.6 eq.) was added to the stirring reaction solution which transitioned to an orange color but remained a complete solution.

Malonic acid (5.678 g, 54.6 mmol, 2.1 eq.) was added to the stirring solution in which it partially dissolved to form a turbid light orange mixture from which a red-jelly phase separated. The mixture was stirred for 30 min, during which time an exotherm was noted as the outer walls of the flask had become warm (from 21 to 31 °C). The mixture was fitted beneath a condenser and heated to reflux under positive nitrogen pressure by slowly heating the oil bath (from ambient to 130 °C over 1 h). The mixture was refluxed under positive nitrogen pressure for 5 h. TLC analysis indicated at least two motile species and the results were as follows: Hex, broad spot extending from R_f=0.2 to the origin | Hex:EtOAc 6:1 vol:vol slightly tailing spot from R_f=0.47-0.27 and elongated spot from R_f=0.09 to the origin when the UV-254 stained silica gel plates were visualized under shortwave UV light. Both the motile and obstinate spots reacted with potassium permanganate stain to afford light green spots on a fuchsia background. The mixture was acidified by pouring it into a mixture of concentrated hydrochloric acid (14 mL, ~170 mmol) and crushed-ice (~150 mL) with vigorous hand stirring. EtOAc was used to replace diethyl ether in this aqueous workup.

The mixture was transferred to a 500 mL separatory funnel with DI H_2O employed to assist the transfer, EtOAc (200 mL) was used to further assist the transfer and partitioning of reaction mixture. H_2O (150 mL) was added and the mixture was transferred to a 1000 mL separatory funnel, shaken vigorously then allowed to partition. The top layer was light-amber and clear, the bottom

layer was turbid and slightly pink. Saturated sodium chloride was added but the turbidity of the bottom layer did not improve. The aqueous layer (bottom, 450 mL) was removed, and tested acidic to universal indicator paper. The organic extract was washed with DI H_2O (3 × 150 mL). During the washing, the organic phase seemed to become a darker amber color. The mixture was washed a final time with saturated sodium chloride (100 mL). The amber solution (300 mL) was dried (anhydrous magnesium sulfate). TLC analysis indicated that the mixture was partially purified by this extraction; there was only a round motile spot R_f =0.44 to 0.33 and a faint orange spot at the origin which was immobile when visualized under shortwave UV following development in Hex:EtOAc 6:1. The motile spot reacted strongly with potassium permanganate stain, while the spot at the origin reacted only faintly.

The amber solution was isolated by gravity filtration through a plug of cotton, concentrated by rotary evaporation under reduced pressure, adsorbed onto silica gel and formed a bright red wet slurry before drying to a light peach free-flowing slurry. The product—*3-allyl-4-hydroxy-5-methoxystyrene*—was isolated by flash column chromatographic separation using a gradient from 0% EtOAc in Hex to 5% in five column volumes followed by an isocratic domain at 5%. The fractions containing 3-allyl-4-hydroxy-5-methoxystyrene were combined, concentrated by rotary evaporation under reduced pressure to afford a colorless oil: constant mass of 2.534 g, 13.3 mmol, 52% of the theoretical maximum.

2.3.2.3. 3-Allyl-2-hydroxy-1-methoxy-5-vinylbenzene[1]

Alternatively, a 2 L round bottom flask was charged with 3-allyl-4-hydroxy-5-methoxybenzaldehyde (36.33 g, 189 mmol, 1 eq. of powdery yellow solid). A jointed vertical vacuum take-off adapter was modified to facilitate nitrogen sparging through-out the reaction by fitting a length of PTFE tubing through the sidearm and out the male joint. The yellow powder

was suspended in toluene (780 mL) and the mixture formed a slightly red solution above solid residue. Piperidine (93 mL, 940 mmol, 5 eq.) was dispensed into the reaction mixture and the color of that mixture darkened to blood-red as it was hand swirled at room temperature. Malonic acid (31.22 g, 204 mmol, 1.1 eq.) was added to the toluene mixture; the malonic acid did not completely dissolve at room temperature.

Nitrogen was sparged through the reaction mixture as it was stirred and submerged in an oil bath beneath a moisture-trap and condenser. The flask was wrapped in foil to assist distillation and to protect it from light. Wet distillate was observed when the oil bath had reached 100 °C. The mixture was distilled for 2 h and H_2O was observed collecting in the bottom of the trap: ~2 mL collected.

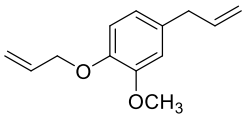
The mixture was stirred as the oil bath cooled to 25 °C and concentrated by rotary evaporation under reduced pressure to remove most of the piperidine. The residue was a dark red oil which did not form a complete solution when diluted with diethyl ether. The mixture was partitioned in a 1.0 L separatory funnel with DI H_2O, and dark sludgy residue was observed. The mixture was acidified by the addition of concentrated HCl—*first the mixture turned black, and all the color resided in the organic layer*. Concentrated HCl was added dropwise with intermittent shaking, the dark color gave way to an amber one which persisted after the aqueous layer tested deep red on universal indicator paper. The volume of the aqueous layer was ~700 mL when isolated.

The organic layer was shaken with H_2O to wash the mixture of nitrogenous bases, but the mixture emulsified. Saturated ammonium chloride was added; the mixture eventually partitioned. The volume of the aqueous layer upon isolation (which tested mildly acidic) was ~500 mL. The organic solution was washed again with H_2O and saturated ammonium chloride was added to

dispel the emulsion. This washing tested nearly neutral to universal indicator paper: volume of that aqueous washing was ~500 mL. The residual ethereal solution was red-amber and looked like it contained quite a bit of H_2O, it was washed with saturated sodium chloride (~100 mL), isolated and dried (anhydrous sodium sulfate). Analysis by TLC indicated that there was a very major motile fraction. The dried ethereal solution (~500 mL) was gravity filtered through a plug of cotton and the red solution was concentrated by rotary evaporation under reduced pressure. The dark red oily residue was adsorbed onto silica gel to afford a yellow-orange free-flowing slurry under reduced pressure. The slurry was purified by flash column chromatography. The fractions which contained the first motile peak were combined, collected and concentrated in a 2 L recovery flask to afford a colorless oil which crystalized upon chilling to -10 °C. The mass of 3-allyl-4-hydroxy-5-methoxystyrene was 19.48 g of ghostly-yellow oil (54 %).

2.3.3. Alkylation of Electron Rich Phenols

2.3.3.1. 4-Allyl-1-(allyloxy)-2-methoxybenzene[1]

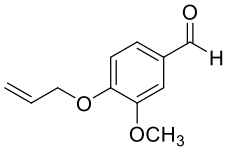


^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.82 (d, *J*=8.0 Hz, 1H), 6.72 (d, *J*=1.9 Hz, 1H), 6.70 (dd, *J*=8.0, 1.9 Hz, 1H), 6.08 (ddt, *J*=17.3, 10.7, 5.3 Hz, 1H), 5.96 (ddt, *J*=16.9, 10.1, 6.7 Hz, 1H), 5.39 (dq, *J*=17.3, 1.6 Hz, 1H), 5.27 (dq, *J*=10.5, 1.4 Hz, 1H), 5.04–5.11 (m, 2H), 4.59 (dt, *J*=5.4, 1.5 Hz, 2H), 3.86 (s, 3H), 3.34 (d, *J*=6.68 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 149.5, 146.5, 137.8, 133.7, 133.2, 120.5, 115.7, 113.7, 117.9, 112.4, 70.2, 56.0, 39.9; IR (ATR, diamond, neat film, cm^{-1}): 3078, 3003, 2976, 2965, 2907, 2830, 1639, 1589, 1509, 1464, 1419, 1334, 1258, 1229, 1141, 1026, 994, 915, 850, 802, 746, 656.

Reported recently by Mahapatra *et al.*[63] A 1.0 L round bottom flask was charged with eugenol (32.86 g, 200 mmol, 1 eq.), potassium carbonate (60.83 g, 440 mmol, 2.2 eq.), and acetone (200 mL HPLC grade). The lightly amber liquid turned yellow upon contact with carbonate and

took on a greenish tinge upon hand swirling. Allyl bromide (19 mL, 220 mmol, 1.1 eq.) was added to the hand swirled slurry at room temperature and rinsed in with acetone (200 mL HPLC grade). The flask was sealed beneath a condenser with cold H_2O flowing, and the headspace of the flask was flushed with argon and kept under an argon balloon. The mixture was lowered into a prewarmed oil bath (35 °C) and heated to reflux (oil bath temp set to 80 °C) for 18 h. The reaction mixture was separated by suction filtration through a finely-fritted-glass-Büchner funnel. The filtrate was an amber color and was concentrated by rotary evaporation under reduced pressure. The concentrate was an amber oil which was used directly in an aromatic-Claisen rearrangement.

2.3.3.2. 4-(Allyloxy)-3-methoxybenzaldehyde[1]



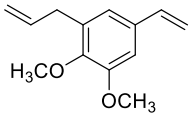
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.84 (s, 1H), 7.41–7.43 (m, 2H), 6.97 (d, *J*=8.7 Hz, 1H), 6.08 (ddt, *J* =17.2, 10.7, 5.4 Hz, 1H), 5.44 (dq, *J*=17.3, 1.6 Hz, 1H), 5.34 (dq, *J*=10.5, 1.3 Hz, 1H), 4.70 (dt, *J*=5.4, 1.4 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 190.9, 153.5, 149.9, 132.2, 130.2, 126.6, 118.8, 111.9, 109.3, 69.8, 56.0; IR (neat film from Hex/EtOAc solution, cm^{-1}): 3081, 2938, 2834, 2721, 1678, 1584, 1505,1463, 1423, 1395, 1337, 1263, 1230, 1132, 994, 933, 865, 806, 781, 729, 660, 632, 590, 566.

Following modifications of the procedure reported by Bräse *et al.*,[64] a 300 mL round bottom flask was charged with vanillin (7.78 g, 51 mmol, 1 eq.), and HPLC grade acetone (100 mL). The mixture was stirred vigorously, and a complete-colorless solution formed. Dimethyl sulfoxide (3.6 mL, 51 mmol, 1 eq.) was added to increase the solubility of potassium vanillate in the reaction medium. Potassium carbonate (10.49 g, 77 mmol, 1.5 eq.) was added; the reaction mixture became slightly turbid but still held no color. Allyl bromide (4.6 mL, 53 mmol, 1.05 eq.) was added by syringe.

Within 15 min of warming, the reaction mixture had formed a thick slurry tinted ghostly yellow and was refluxed under argon for 8 h. TLC analysis indicated completion. No movement when eluted with Hex. Using a vol/vol mixture of 6:1 Hex:EtOAc, the R_f of the dark motile spot was 0.22; only a faint spot remained on the baseline, both reacted with potassium permanganate stain. The mixture was concentrated by rotary evaporation under reduced pressure, mixed with ice, then allowed to partition in a 500 mL separatory funnel. The organic phase was washed with 2 × 100 mL of DI H_2O, followed by 80 mL saturated aqueous sodium chloride. The EtOAc extract (~160 mL) was isolated, dried (anhydrous magnesium sulfate), adsorbed onto silica gel and purified by flash chromatography using Hex/EtOAc. There was one major eluate observed, the fractions comprising that peak were combined, concentrated *in vacuo* to constant mass: light yellow oil, 9.04 g, 47 mmol, 92% of the theoretical maximum. This was an improvement from the reported 85%.

To evaluate the efficiency of this reaction in another solvent consistent with the principles of green chemistry and following the example of Kaufman *et al.*,[44] this transformation was performed utilizing absolute EtOH at one half the concentration with no dimethyl sulfoxide additive. The product isolated was 8.96 g, or 92%. Although the purity of the final isolated 4-(allyloxy)-3-methoxybenzaldehyde was comparable, the ethanolic reaction was yellow throughout and contained some impurities which were less polar than the product.

2.3.3.3. 3-Allyl-1,2-dimethoxy-5-vinylbenzene[1]



HRMS $[C_{13}H_{17}O_2]^+$ Calcd.: 205.1228: found 205.1225; HRMS $[C_{13}H_{16}O_2Na]^+$ Calcd.: 227.1048: found 227.1109; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.86 (d, *J*=2.0 Hz, 1H), 6.82 (d, *J*=2.0 Hz, 1H), 6.64 (dd, *J*=17.5, 10.9 Hz, 1H), 5.98 (ddt, *J* =16.8, 10.2, 6.6 Hz, 1H), 5.64 (dd, *J*=17.6, 0.8 Hz, 1H), 5.19 (dd, *J*=10.8, 0.7 Hz, 1H), 5.04–5.10 (m, 2H), 3.88 (s, 3H),

3.81 (s, 3H), 3.40 (dt, *J*=6.5, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.9, 147.1, 137.3, 136.7, 133.9, 133.6, 120.6, 115.8, 113.0, 108.0, 60.8, 55.8, 34.2; IR (ATR, diamond, neat film, cm^{-1}): 3082, 3003, 2936, 2830, 1637, 1581, 1489, 1463, 1433, 1407, 1285, 1231, 1181, 1111, 1078, 1006, 989, 944, 901, 864, 846, 779, 748, 690, 553.

A 50 mL round bottom flask was charged with 3-allyl-4-hydroxy-5-methoxystyrene (2.642 g, 13.9 mmol, 1 eq. of ghostly-yellow oil), and anhydrous *DMF via* syringe (15 mL). A colorless solution formed. The flask was lowered into an oil bath and anhydrous potassium carbonate (4.269 g, 30.9 mmol, 2.2 eq.) was added. The colorless solution took on a light-yellow color. Iodomethane (1 mL, 16.1 mmol, 1.2 eq.) was added and the mixture slowly transitioned to a creamy peach slurry over 13 h as it was stirred in a 40 °C oil bath sealed with a yellow capplug. White solid settled from a pale-yellow solution upon cooling. The reaction mixture was poured over 250 mL of crushed ice with vigorous hand stirring. The flask was rinsed repeatedly with diethyl ether into the icy-mixture.

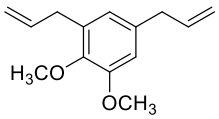
The mixture was transferred to a 500 mL separatory funnel, shaken, and allowed to partition while it was still ice cold. The two colorless clear phases were isolated from one another, then the ethereal solution was rinsed twice more with 100 mL H_2O and once with 100 mL saturated sodium chloride. The organic solution was isolated, dried (sodium sulfate) and concentrated to constant mass by rotary evaporation under reduced pressure. The mass of the colorless oil obtained thereof was 2.839 g (99% crude yield).

In a scaled-up preparation, a 300 mL round bottom flask was charged with 3-allyl-4-hydroxy-5-methoxystyrene (19.478 g, 102 mmol, 1 eq. of ghostly-yellow oil). The flask was also charged with potassium carbonate (30.427 g, 220 mmol, 2.2 eq.) and *DMF* (60 mL). The mixture

was stirred, and a bright yellow solution developed which contained white-residual solid even upon heating and stirring in an oil bath set to 40 °C.

Iodomethane (7 mL, 112 mmol, 1.1 eq.) was added dropwise—*the bright yellow color disappeared right away*—and the mixture became creamy then white within 5 min before turning light peach 30 min after the addition, the mixture was capped and stirred for six h. The mixture was pulled from the oil bath, allowed to cool, then poured over 400 mL of ice. Diethyl ether (300 mL) was added and the mixture was transferred to a 1.0 L separatory funnel. A bit of L(+) ascorbic acid was added to reduce any iodine since the aqueous layer was looking a bit pink. The aqueous layer held some yellow color, while the ether was colorless following shaking with the ascorbic acid. The ethereal solution was washed with 2 × 300 mL H_2O, then once with 300 mL saturated sodium chloride. The organic solution was isolated, dried (sodium sulfate), and concentrated to a light-yellow oil by rotary evaporation under reduced pressure—*constant mass of oil: 20.69 g (99% of the theoretical maximum yield)*.

2.3.3.4. 3,5-Diallyl-1,2-dimethoxybenzene[1]



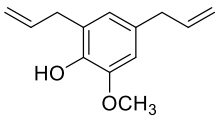
HRMS $[C_{14}H_{18}O_2Na]^+$ Calcd.: 241.1205, found: 241.1225; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.62 (d, *J*=2.0 Hz, 1H), 6.61 (d, *J*=2.0 Hz, 1H), 5.91–6.03 (m, 2H), 5.03–5.13 (m, 4H), 3.85 (s, 3H), 3.79 (s, 3H), 3.40 (dt, *J*=6.6, 1.4 Hz, 2H), 3.33 (d, *J*=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 152.7, 145.4, 137.6, 137.5, 135.9, 133.8, 122.0, 115.9, 115.6, 110.9, 60.8, 55.8, 40.2, 34.2; IR (ATR, diamond, neat, cm^{-1}): 3078, 3004, 2977, 2936, 2902, 2831, 1638, 1588, 1489, 1463, 1429, 1331, 1286, 1181, 1145, 1107, 1075, 1011, 994, 958, 909, 840, 783, 757, 715, 672, 600, 553.

Previously reported by Zbiral, Wessely, and Joerg.[65] A round bottom flask was charged with 3,5-diallylguaiacol (9.663, 47.3 mmol, 1 eq.) and anhydrous *DMF* (10 mL). Potassium

hydroxide (3.28 g, 58.5 mmol, 1.2 eq.) was added and a dark solution formed. Iodomethane (3.2 mL, 51.4 mmol, 1.1 eq.) was added dropwise to the stirring reaction mixture under dry-nitrogen and sealed with a yellow cap-plug. The mixture was warmed in an oil bath (40 °C) for six h by which time creamy solid precipitate was observed and the color of the residual solution had lightened to amber. The mixture was partitioned between diethyl ether and DI H_2O. The H_2O was tinted slightly pink and the organic phase was light amber. The organic solution was washed 3 × 100 mL DI H_2O and once with 100 mL saturated sodium chloride solution. The extract was isolated, dried (anhydrous sodium sulfate) and adsorbed onto silica gel. The mixture was purified by flash chromatography with a 0 to 5% gradient of EtOAc in Hex over 20 column volumes. The very motile and only eluate peak's fractions were combined, concentrated to constant mass by rotary evaporation: 9.76 g of colorless light oil (95% of the theoretical maximum).

2.3.4. Aromatic Claisen Rearrangement of Electron Rich Phenols

2.3.4.1. 3,5-Diallyl-2-hydroxy-1-methoxybenzene[1]



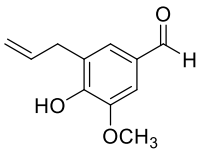
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.59 (s, 2H), 5.91–6.07 (m, 2H), 5.58 (s, 1H), 5.04–5.12 (m, 4H), 3.87 (s, 3H), 3.40 (dt, *J*=6.5, 1.4 Hz, 2H), 3.31 (d, *J*=6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.4, 141.7, 138.0, 136.9, 131.3, 125.7, 122.2, 115.6, 115.5, 109.1, 56.1, 40.1, 34.0; IR (ATR, diamond, neat, cm^{-1}): 3526, 3077, 3004, 2904 2843, 1638, 1604, 1495, 1463, 1434, 1365, 1282, 1233, 1210, 1147, 1106, 1073, 994, 949, 910, 842, 793, 754, 715, 670, 599, 555.

Reported recently by Serra *et al.*[66] The concentrated-eugenol-allylation (theoretical maximum of 200 mmol) was charged into a 100 mL round bottom flask and was submerged in an oil bath beneath a distillation trap and a condenser. The headspace was flushed with argon and the oil bath was heated (215–220 °C) as distillate was collected for 2.3 h. The reaction solution was

orange. Upon cooling the reaction mixture was analyzed by ^{1}H NMR. The mixture appeared to contain circa 5 mol% eugenol, it remains unclear whether the eugenol was residual substrate from the *O*-allylation or from deallylation during the aromatic-Claisen rearrangement. The orange solution was adsorbed onto silica gel and purified by flash chromatography (Hex:EtOAc gradient from 0% EtOAc to 10% in 15 column volumes). The first peak to elute was clearly very major and the second minor eluates smelled distinctly of eugenol. The major fractions were combined, concentrated by rotary evaporation under reduced pressure to a constant mass of 37.13 g (186 mmol or 91% of the theoretical maximum over two steps).

To establish the necessity of protecting the aromatic-Claisen rearrangement from oxygen, a 250 mL round bottom flask was charged with *O*-allyleugenol (37.305 g, 183 mmol of light-yellow oil). The flask was affixed to a distillation receiver/condenser. The mixture was lowered into a preheated oil bath (215 °C) for 2 h then raised from the bath and allowed to cool overnight. The oil had turned dark red, and then to black. Silica gel was added to adsorb the oil, which was chromatographed using Hex and EtOAc. The major and most motile eluate peak's fractions were combined and concentrated to afford 25.816 g 3,5-diallylguaiacol (0.126 mole, 71% of the theoretical maximum).

2.3.4.2. 5-Allyl-4-hydroxy-3-methoxybenzaldehyde[1]



^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.80 (s, 1H), 7.31 (s, 2H), 6.33 (s, 1H), 6.05–5.95 (m, 1H), 5.14– 5.08 (m, 2H), 3.95 (s, 3H), 3.46 (dt, *J*=6.6, 1.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 191.3, 149.5, 147.0, 135.7, 129.2, 128.1, 126.2, 116.5, 107.1, 56.4, 33.6; IR (ATR, diamond, neat film from $CDCl_3$ solution, cm^{-1}): 3210, 3076, 2969, 2940, 2852, 1664, 1640, 1604, 1588, 1496, 1468, 1457, 1425, 1402, 1336, 1301, 1255, 1200, 1186, 1141, 1115, 1069, 992, 964, 912, 847, 731, 674, 648, 619, 586, 538.

Kaufman *et al.,* also described the aromatic Claisen rearrangement of 4-(allyloxy)-3-methoxybenzaldehyde to afford 5-allyl-4-hydroxy-3-methoxybenzaldehyde wherein a solid with a melting point range of 82–84 °C was reported following dissolution in 1,2-dichlorobenzene, reaction at 180–185 °C for 12–16 h and purification through a short silica gel column.[44] Sahal *et al.* have prepared 5-allyl-4-hydroxy-3-methoxybenzaldehyde by neat microwave irradiation.[45]

A 100 mL round bottom flask was charged with *O*-allylvanillin (white crystalline solid at -10 °C, 21.42 g, 111.4 mmol, 1 eq.). The flask was fitted beneath a condenser and the headspace was flushed with dry nitrogen. Under positive nitrogen pressure, the white crystalline solid thawed to afford a colorless oil. The mixture was stirred neat—*with heating (205 °C oil bath)*—for 3.3 h. The product (light amber crystalline solid upon cooling) appeared to have completely converted by NMR. The pale yellow crystalline solid was chipped and scraped into a 10 mL beaker and triturated with Hex (75 mL). The solid residue was isolated by suction filtration, pressed dry, then chopped and spread on paper. The mass of the isolated 3-allyl-4-hydroxy-5-methoxybenzaldehyde was 19.10 g, 99.4 mmol, 89% of the theoretical maximum yield. Melting point range of the crude solid: 84–85 °C. The material could be column purified to afford white crystalline solid, melting point range: 87–89 °C

Vanillin could be allylated followed by neat heating to afford 5-allyl-4-hydroxy-3-methoxybenzaldehyde without intermittent chromatographic purification since the allylphenol product could be recrystallized, thus avoiding two chromatographic purifications. A 1 L round bottom flask was charged with vanillin (30.39 g, 200 mmol, 1 eq.), potassium carbonate (41.48 g, 305 mmol, 1.5 eq.), and acetone (200 mL). The mixture was composed of a colorless slightly turbid solution above white powdered solid. Allyl bromide (19 mL, 220 mmol, 1.1 eq.) was added by syringe. The mixture was lowered into a preheated (75 °C) oil bath beneath a condenser and drying

tube charged with indicated Drierite. The flask was wrapped in aluminum foil to protect the allyl bromide from light. The mixture was refluxed for 20 h (overnight). The previously chalky white reaction mixture had taken on a faintly-yellow hue. The reaction mixture was separated by suction filtration through a jointed (24/40) fine fritted Büchner funnel directly into a 500 mL recovery flask. The mixture was concentrated by rotary evaporation under reduced pressure.

The faintly yellow-green residue was diluted with diethyl ether in a 500 mL separatory funnel and washed with DI H_2O (3 × 300 mL and once with saturated sodium chloride)—*The yellow color dissipated with the washings*. The mixture was concentrated by rotary evaporation under reduced pressure and the yellow oil crystallized upon chilling to -10 °C but melted again when allowed to warm to room temperature. The yellow oil was transferred to a fresh 300 mL single neck round bottom flask 24/40 and had a mass of 41.010 g (106 % of the theoretical yield) and presumably contained some residual allyl bromide. The light-yellow oil was stirred over an oil bath (210–215 °C) beneath a condenser and distillation receiver, but NOT under inert atmosphere. The material became amber as the reaction stirred and allyl bromide was observed to collect initially during the 4 h of reaction. When raised from the oil bath to cool, the mixture afforded an amber orange solid with some liquid on top inner walls of the flask. The total volume of the distillate collected was ~0.8 mL.

The solid did not dissolve in boiling hexane but was made to dissolve by the addition of DCM to afford a red amber solution. Another distillation receiver was added to collect DCM from the boiling reaction mixture (~50 mL). When the DCM was removed, the Hex phase separated from a lower more viscous orange oil. The residue was stirred vigorously as it cooled to room temperature and spongy yellow solid precipitated. The mixture was broken up with a stainless-steel spatula and diluted with Hex. The material became powdery and free flowing when triturated

with Hex. The yellow powdery solid was isolated by suction filtration through a 150 mL glass Büchner funnel, dried on the filter, chopped and spread on paper to air dry overnight. The solid was suitable for use in the Knoevenagel condensation/decarboxylation synthesis of phenolic styrenes: Mass was 36.33 g, 95% of the theoretical maximum after 2 steps.

2.4. References

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3. STRUCTURAL ELUCIDATION OF ACETOACETYLATED LIGNIN

Another outcome of Dakota Biocon was the team-up of Eric Michael Serum and Eric Michael Krall (Sibi and Webster research groups respectively) at North Dakota State University. The focus of EMK throughout the duration of Dakota Biocon (and beyond) was the preparation of macromolecular resins by chemical modification of technical lignins. Specifically, EMS was approached to consult in matters of organic synthesis and spectrometric characterization of technical lignins when modified with acetoacetic ester functionality. This led to a collaborative communication in *Green Chemistry* which described characterization of pre- and post-modified lignins as well as several model compounds by action of *tert*-butyl acetoacetate.[1] The contents of this chapter detail EMS's contribution to that work.

3.1. Acetoacetylation and Lignin Modification

acetoacetic acid acetoacetic acid

Fig. 3.1. Structure of acetoacetic acid and acetoacetate ester

While the hydroxyl functionalities in any mono or polyol offer a diverse array of possible interconversions, transesterification[2] with acetoacetate esters was selected for its potential to improve the processability of technical lignins as well as offer orthogonal (complimentary) masking of phenols as compared to alkylation protocols.[3] Acetoacetate esters and the parent structure of acetoacetic acid (Fig. 3.1) contain two enolizable positions. The most acidic position in both molecules (excluding carboxylic acid) forms what is known as a thermodynamic enolate. This acidic position is between the carbonyls and is considered an active methylene. The relative acidity of that position drives most of the chemistry associated with acetoacetylated resins as it is

naturally nucleophilic. This natural tendency to form new carbon–carbon bonds with electrophiles may be readily enhanced by acid or base catalysis.

3.1.1. Incorporation of Acetoacetate Functionality

Reports in the early 1990's out of the Eastman Chemical Company Research Laboratories describe catalyst-free reaction of various nucleophiles with *tert*-butyl acetoacetate under conditions of industrial and preparative relevance[4] as well as preparation of coatings derived from acetoacetylated resins.[5] Eastman Chemical Products also released details of acetoacetyl chemistry in thermoset coatings.[6] Importantly, the acetoacetyl functionality can be incorporated into a variety of resins and contains potential for a wide array of potential crosslinking reactions. Furthermore, formation of biproducts was found to vary depending on concentration and mode of addition.[4]

While acetoacetylated materials may be prepared from reaction with diketene, the reactivity and lachrymator properties of said compound created an impetus for so-called 'diketene-free' acetoacetylation technologies; the culmination of which was a protocol for transacetoacetylation with *tert*-butyl acetoacetate (TBAA). TBAA was preferred over all other acetoacetic esters owing to its increased reactivity, which is fifteen to twenty fold greater than primary alkoxy analogs, and amenability to industrial scale-up.[4] The only significant limitations of transacetoacetylation initially included: (1) sluggish reaction with phenols, (2) proclivity of allyl alcohols to undergo Carroll rearrangement[7] upon modification, and (3) lowered yields of primary unhindered amines attributed to formation of enamine side products.

Typically, modification of an alcohol moiety with *tert*-butyl acetoacetate requires heating (between 100 and 150 °C) equimolar amounts of substrate and reagent in concentrated solution (sometimes neat) which significantly simplifies isolation of the product.[4] Often resins prepared thusly may require no purification for application. The reaction is not typically inhibited by *tert*-

butanol, which led to the development of a green protocol utilizing recycled reaction byproduct as solvent (*vide infra*).

3.1.2. Property Modulation of Technical Lignins

Anything which disrupts hydrogen bonding between different segments of lignin macromolecules should improve the solubility of technical lignins. Specifically, ethylene glycol has been shown to solubilize lignin by intercalating between macromolecular hydrogen bonded network at room temperature.[8] Incorporation of acetoacetyl functionality into polyhydroxylated resins reduced solution viscosities and glass transition temperatures of those resins.[6] This phenomenon is likely to improve the processability of lignin in similar fashion as acetylation or silylation which was recently reported.[9]

Classically, it was not uncommon to use very harsh conditions and reagents such as acetyl bromide to solubilize technical lignins and the model compounds utilized for structural elucidation.[10] Depending on the reaction conditions, treatment with acetyl bromide may result in one of several valuable changes in the lignin structure. These include α-ether cleavage, benzylic bromination, and acetylation.[11] Recently, a solvent-free and catalyst free acetylation protocol was published which utilized microwave irradiation to achieve similar results while substituting carboxylic anhydrides for acetyl bromide.[12]

The mildness of *tert*-butyl acetoacetate modification in comparison is quite benign. Another very mild lignin modification which increased the hydrophobicity and therefore the processability of technical lignins was enzymatic esterification with fatty acids in ionic liquids.[13] However, the value of acetoacetic ester functionalization lies in the diversity of its crosslinking reactions (*vide infra*).

3.1.3. Reactivity of Acetoacetates

Acetoacetic esters are considered ambiphilic.[14] The versatility of crosslinking options may be the greatest advantage to resin formulations containing acetoacetic esters.[6] There are two chemically distinct sites for reactive crosslinking (Fig. 3.2): (1) the active methylene is nucleophilic, while (2) the carbonyl of the ketone is electrophilic. The reactivities of both groups is mild enough that self-condensation is only a problem during extreme curing schedules.

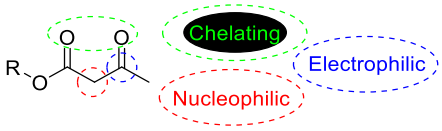
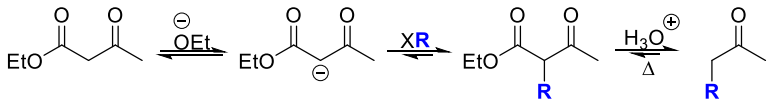


Fig. 3.2. Reactive sites and their proclivities in acetoacetic esters

The active methylene can react with traditional crosslinkers of polyols such as melamine and isocyanates while engendering improved processability. Additionally, Michael reactions with acrylates and Knoevenagel condensation with aldehydes can occur at room temperature.[6] Another ambient cured platform is reaction of the ketonic carbonyl with amine crosslinkers typically used in preparation of thermosets with epoxy resins. Especially interesting and unique, the twin carbonyls of acetoacetic esters connote the ability of their resins to act as strong chelators. This could create entirely new applications for any polymeric materials derived thereof in the field of ion exchange resins (widely used in affinity column chromatography).

In the field of organic synthetic chemistry, acetoacetate chemistry has been driven by its similarity to malonic esters: active methylene alkylation followed by decarboxylation. The acetoacetic and malonic ester syntheses provide great utility as illustrated by their employment in radiolabeled syntheses of fatty esters.[15] A generalized illustration of the acetoacetic ester synthesis has been included (Scheme 3.1). Classically, Claisen condensation affords ethyl acetoacetate from the base mediated self-condensation of anhydrous EtOAc.[16] It is important to understand the

known chemistry of a reactive functional group, such as the acetoacetate group, when exploring its applications in sustainable materials science; especially when considering future project potential and while characterizing side products in resin modification or crosslinking reactions.



Scheme 3.1. Generalized acetoacetic ester synthesis

In the acetoacetic ester synthesis (Scheme 3.1), ethyl acetoacetate is activated by deprotonation of the active methylene with sodium ethoxide or sodium hydride at low but not cryogenic temperature. The choice of base is critical if intermediate β-ketoesters are to be isolated. Only hydrides with their extremely selective basicity or ethoxide with its non-productive reaction at the ester carbonyl may be used in these cases. The thermodynamic enolate is thus the major species in solution when an electrophile (XR) is introduced.

While capture of the electrophile is technically reversible, and there is a chance for oxygen's alkylation, this synthesis is extremely chemoselective for carbon–carbon bond formation. This phenomenon is attributed to that type of bond's great relative strength and the relative polarizabilities of carbon nucleophiles and carbon electrophiles. Finally, a new ketone is revealed typically by the process of acidic hydrolysis with concomitant evolution of carbon dioxide.

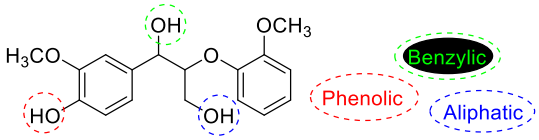
3.2. Lignin Model Compounds

Elucidation and quantification of modified lignin structure was facilitated by employing a series of readily prepared model compounds which isolate the major hydroxyl containing moieties characteristic of lignin. The determination of lignin structure relies heavily on use of nuclear magnetic resonance spectroscopy[17, 18] and has often been supplemented by use of model

compounds.[10, 19-21] Additionally, model compounds find use in developing methodologies for lignin valorization.[8, 22-24]

3.2.1. Representative Small Molecule Lignin Substitutes

There will be multiple strategies for developing useful model compounds for any complex system. These strategies will differ primarily in their level of complexity. An optimization must be reached between effort required to process the data collected and the predictive ability of the model. Recently, the complexity of useful models for lignin has even been extended to synthetic pseudo-lignoid polymers.[25] If a model system is too simple, it will have no predictive ability. If a model system is too complex, it will offer no advantage over working with the complete system.



1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol

Fig. 3.3. Trifunctional lignin model compound with β-O-4 linkage

With those optimization parameters in mind, consider 1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol (also known as guaiacylglycerol-β-(2-methoxyphenyl) ether) which was initially considered as a candidate for acetoacetylation in our collaborative study (Fig. 3.3). Although not particularly relevant to Kraft lignins,[17] guaiacylglycerol-β-(2-methoxyphenyl) ether contains one of the more sensitive linkages recurrent in native lignin known as the β-O-4 linkage and commonly serves on a panel of model compounds.[10, 11, 20-24, 26-28] Owing to this demand, facile and selective preparation of guaiacylglycerol-β-(2-methoxyphenyl) ether and its analogs has been the subject of several research articles.[29-33]

However, the goal of our study[1] was never focused solely model compounds. Sufficient evidence was presented during the initial discussion meetings between EMS and EMK to indicate that (Indulin AT) Kraft lignin could in fact be acetoacetylated under some conditions. Therefore,

there was not a need to overcomplicate the model compounds used in an acetoacetylation survey unless preliminary results were not useful in facilitating the interpretation of modified lignin. Additionally, ignoring labile linkages would not preclude application of a simple model compound strategy since even a lignin first strategy has been shown to cleave the β-O-4 linkage.[34]

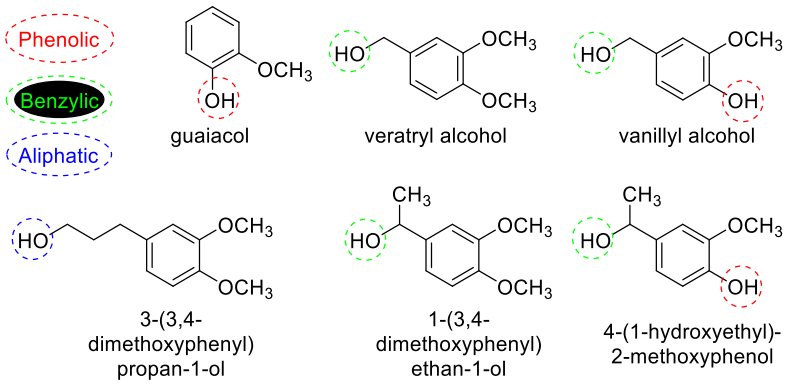


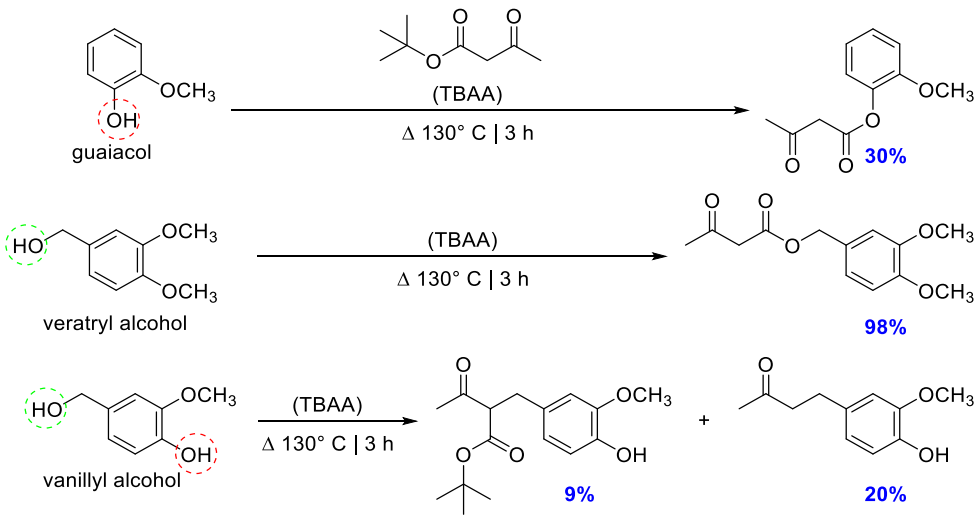
Fig. 3.4. Readily accessible lignin model compounds for acetoacetylation

Consideration of viable lignin model compounds was constrained to small, commercially available or readily prepared chemicals (Fig. 3.4). The series included commercially available guaiacol, veratryl alcohol, and vanillyl alcohol. Additionally, 3-(3,4-dimethoxyphenyl)propan-1-ol was prepared from commercially available eugenol while 1-(3,4-dimethoxyphenyl)ethan-1-ol and 4-(1-hydroxyethyl)-2-methoxyphenol were prepared from apocynin (acetovanillone). This short series of accessible model compounds embodies each of the three predominant hydroxylic environments contained in technical lignins. One shortcoming of this series was a lack of residual sulfur modified functionalities carried over from the Kraft process.

3.2.2. Acetoacetylation of Model Compounds

Standard acetoacetylation conditions[4] were adopted and slightly modified to begin investigation of catalyst-free transacetoacetylation of *tert*-butylacetoacetate (1.1 molar equivalents, neat) with simple lignin model compounds at 130 °C for three h. The liberation and distillation of *tert*-butanol was assisted by steady nitrogen sparging which also served to protect

reaction mixtures from atmospheric oxygen. Following reaction, the liquid residues were adsorbed onto silica gel and purified by flash column chromatography. The results of the initial screening utilizing only commercially available guaiacol, veratryl alcohol, and vanillyl alcohol have been illustrated in Scheme 3.2.

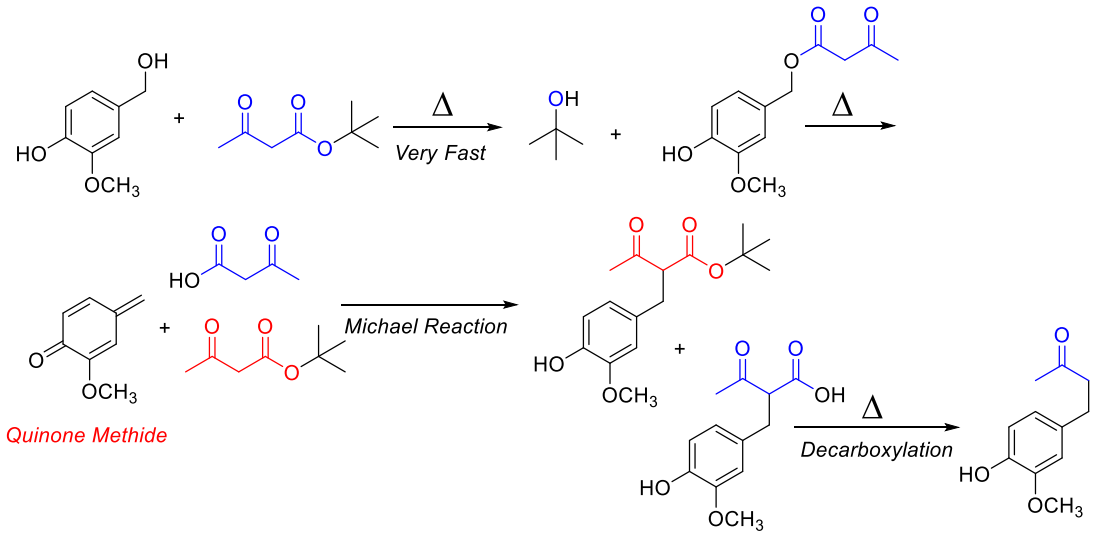


Scheme 3.2. Comparison of neat catalyst-free acetoacetylation: phenolic *versus* benzylic hydroxyls

Unsurprisingly, these reaction conditions afforded a low isolated yield of acetoacetylated product (2-acetoacetoxyanisole) when guaiacol was the substrate (30%) in contrast to an excellent yield of clean acetoacetylated product (4-(acetoacetoxymethyl)veratrole) when veratryl alcohol was the substrate.[4] Strangely, no product of transacetoacetylation could be isolated from the reaction mixture of vanillyl alcohol. Instead products resembling an acetoacetic ester synthesis were observed. These could be explained by formation of a quinone methide intermediate followed by recombination or interception by nucleophilic acetoacetate moieties (Scheme. 3.3).

From the acetoacetylation of veratryl alcohol (Fig. 3.5), it seems plausible that vanillyl alcohol also undergoes complete and likely rapid transacetoacetylation with concomitant evolution of *tert*-butanol (observed). The fate of 4-(hydroxy-3-methoxybenzyl)-3-oxobutanoate (5-

(acetoacetoxymethyl)guaiacol) at 130 °C is herein proposed to include elimination of acetoacetic acid with concomitant dearomatization to form a reactive quinone methide intermediate. The natural nucleophilicity of active methylene compounds describes both acetoacetic acid, TBAA and any other acetoacetate esters in the mixture. Additionally, activity as an electrophile or alkylation of 2-methoxy-4-methylenecyclohexa-2,5-dien-1-one by a Michael donor is very energetically-favorable due to a renewal of aromaticity.



Scheme 3.3. Rationalization of transacetoacetylation with vanillyl alcohol

A similar mechanism has been invoked at low temperature for the preparation 4-phenyl-2-buanones from desilylation of *p*- silylether substituted acetoacetoxy esters.[35] Indeed, the role of quinone methide intermediate chemistry has been implicated in the biological polymerization of monolignols and the role NADPH reduction of those intermediates can explain some of the benzylic substitution patterns found in lignin.[36]

Perhaps unsurprisingly, more than one discreet small molecule product of Michael addition was observed while the total yield of identifiable isolates was relatively low (29%): 20% of 4-(4-hydroxy-3-methoxyphenyl)butan-2-one from recombination and 9% of *tert*-butyl 2-(4-hydroxy-3-methoxybenzyl)-3-oxobutanoate from interception of the quinone methide by TBAA. It must be

noted that acetoacetic acid is thermally unstable and would be expected to undergo rapid decarboxylation at 130 °C.[37] Thus thermolysis of 5-(acetoacetoxymethyl)guaiacol could have led to a build-up of the reactive intermediate, 2-methoxy-4-methylenecyclohexa-2,5-dien-1-one, which would be capable of engaging in addition reactions with acetoacetate moieties leading to oligomerization.

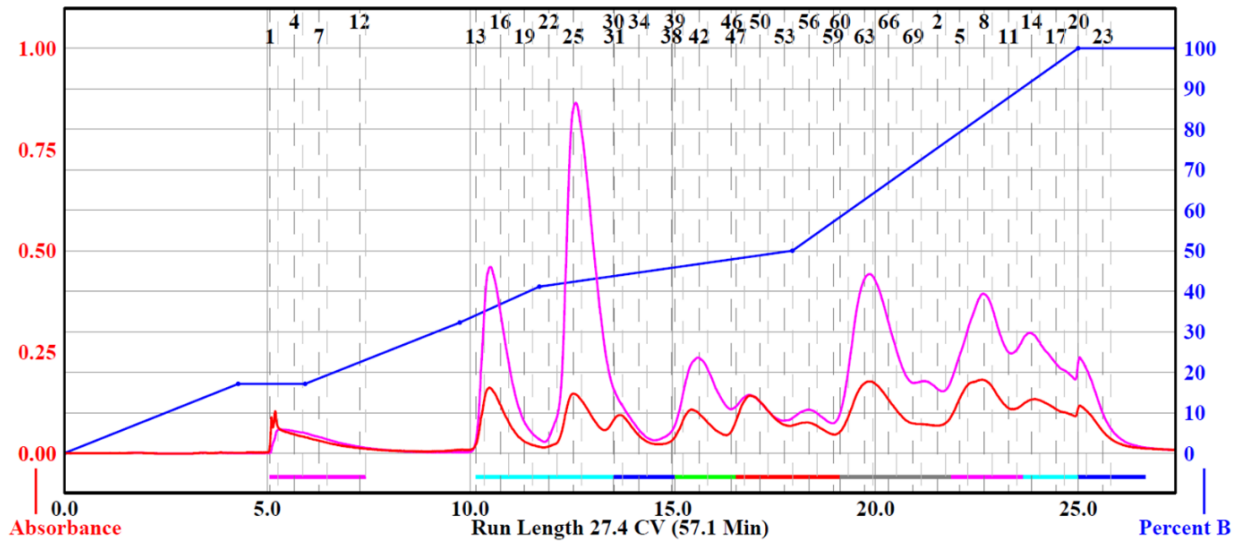


Fig. 3.5. Preparative chromatogram from the thermally induced reaction between *tert*-butyl acetoacetate and vanillyl alcohol

Since approximately 30% of phenolic hydroxyls could be expected to have undergone transacetoacetylation with TBAA, the rest of the mass balance likely was made up of oligomers. Transesterification of *tert*-butyl 2-(4-hydroxy-3-methoxybenzyl)-3-oxobutanoate should also be considered very likely under the reaction conditions. Indeed, when observing the preparative chromatogram from the thermally induced reaction of TBAA and vanillyl alcohol, a forest of products can be observed. (Fig. 3.5). The well-defined products of the reaction could be identified by ^{1}H NMR in deuterated chloroform ($CDCl_3$, compare Figs. 3.6 to 3.7 and 3.8). Key features are well resolved, and spectral data has been listed in the experimental section. For example, in each spectrum a phenolic hydroxyl can be observed around 5.5 ppm. Vanillyl alcohol (Fig. 3.6) contains

no aliphatic resonance peak (only a broad hydroxylic peak) upfield from the methoxy CH_3 resonance peak around 3.9 ppm.

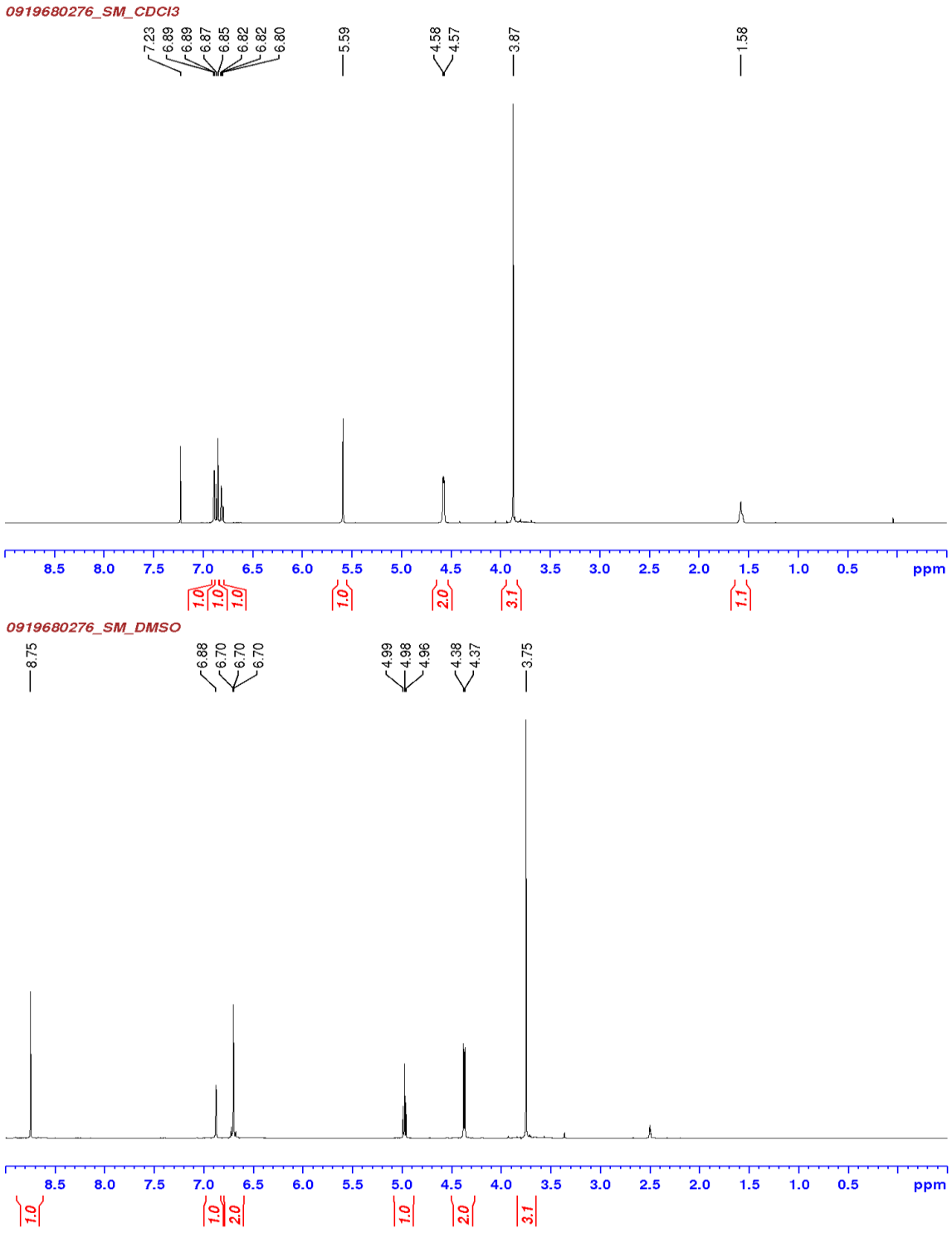


Fig. 3.6. ^{1}H NMR spectra vanillyl alcohol (in $CDCl_3$ on top, in DMSO on bottom)

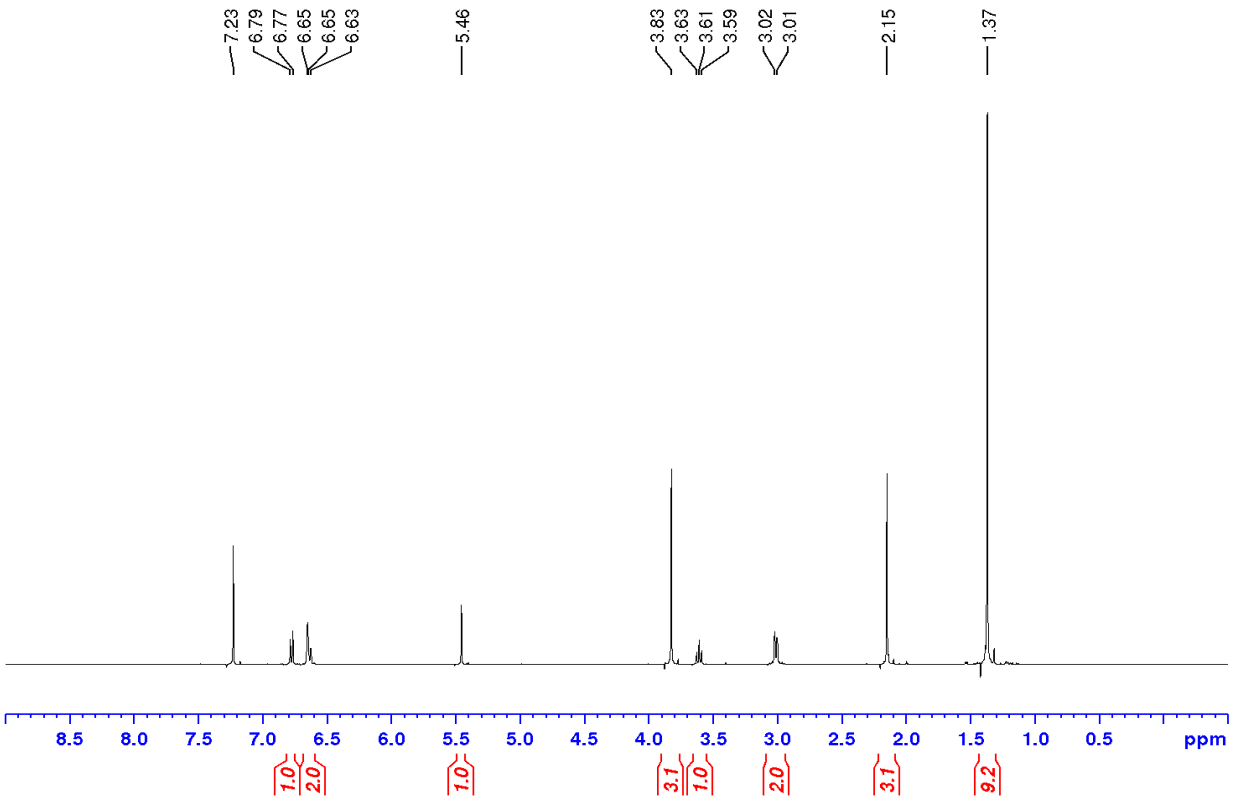


Fig. 3.7. ^{1}H NMR of fractions 13–19 from Fig. 3.5. Identified as *tert*-butyl 2-(4-hydroxy-3-methoxybenzyl)-3-oxobutanoate

The ^{1}H NMR spectrum for fractions 13–19 (Fig. 3.7) contained sound evidence supporting incorporation of *tert*-butyl acetoacetate. To enumerate: (1) a striking peak around 0.9 ppm which integrates to nine protons relative to the aromatic methoxy peak around 3.8 integration of three protons, (2) a peak attributed to an acetate CH_3 group integrating for three protons around 2.2 ppm, (3) diastereotopic protons corresponding to the acetoacetate methine and benzylic methylene protons around 3.5 and 3.0 ppm respectively. The ^{1}H NMR spectrum for fractions 23–28 (Fig. 3.8) contained evidence consistent with its identification as 4-(4-hydroxy-3-methoxyphenyl)butan-2-one; namely presence of an acetate CH_3 group (around 2.2 ppm) and a two carbon methylene chain (around 2.75 ppm).

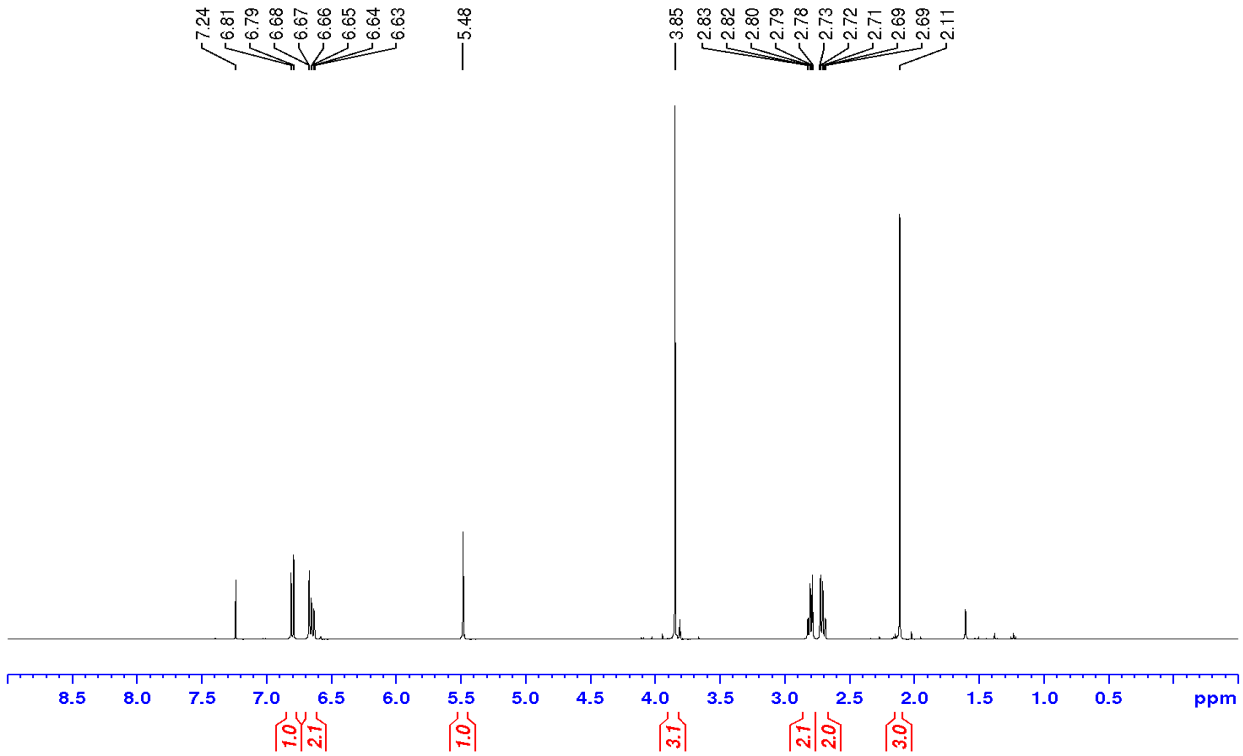


Fig. 3.8. ^{1}H NMR of fractions 23–28 from Fig. 3.5. Identified as 4-(4-hydroxy-3-methoxyphenyl)butan-2-one

3.2.3. Acetoacetylation of Lignin Model Compounds and Quantitative NMR

The reactions of TBAA and vanillyl alcohol were further investigated by employing a more sophisticated experiment. The same acetoacetylation was carried out with some refinements: (1) reaction temperature was closer to 100 °C as maintained by a thermoregulated oil bath, (2) aliquots of the reaction mixture were pulled periodically and analyzed by ^{1}H NMR against an internal standard, and (3) the reaction was stopped following only two h of reaction and separated by flash column chromatography (Fig. 3.9).

At first glance, the relatively mild conditions employed leading to Fig. 3.9 contrast with those of Fig. 3.5 in the diversity of products. A major eluate peak appeared which was composed of TBAA (fractions 2–6). There were only two other significant eluate peaks corresponding to 4-(4-hydroxy-3-methoxyphenyl)butan-2-one and *tert*-butyl 2-(4-hydroxy-3-methoxybenzyl)-3-

oxobutanoate which were the only well-defined products isolated from the high temperature reaction. Noticeably, the forest of oligomerized products was not very prominent at the two-h mark of the low temperature experiment.

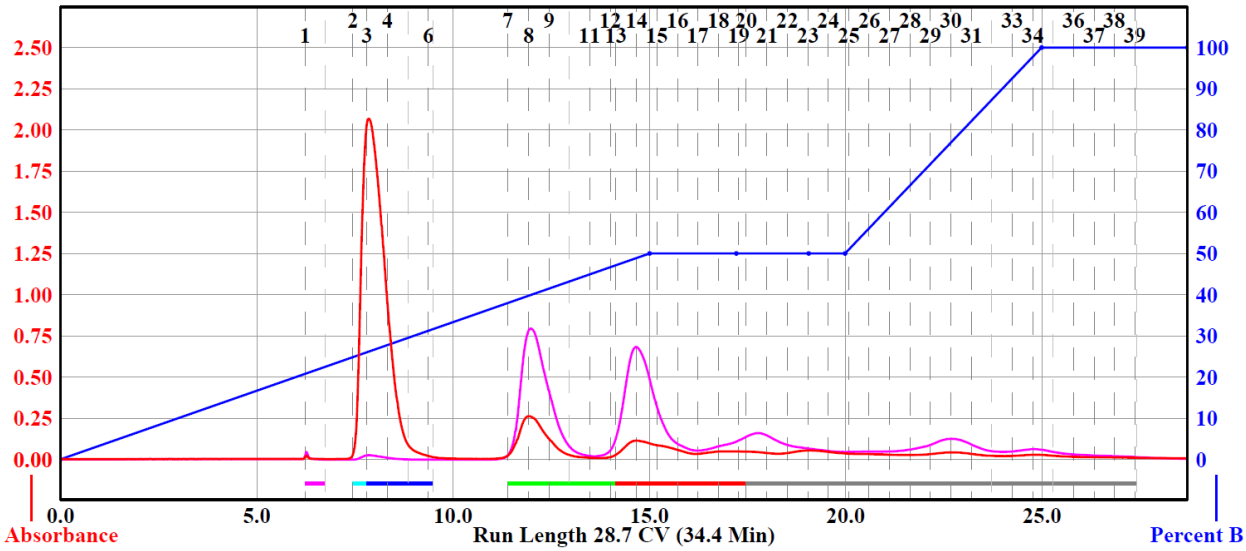


Fig. 3.9. Acetoacetylation of vanillyl alcohol at 100 °C separated at two h of reaction time

When the proton NMR spectra of the periodic aliquots were analyzed, the appearance of both isolated products and disappearance of vanillyl alcohol was noted. The desired products of transacetoacetylation, such as 5-(acetoacetoxymethyl)guaiacol, could not be observed. As the relative concentration of vanillyl alcohol fell during the reaction, so did the relative concentration of TBAA. The relative molar concentrations of thermolysis products, 4-(4-hydroxy-3-methoxyphenyl)butan-2-one and *tert*-butyl 2-(4-hydroxy-3-methoxybenzyl)-3-oxobutanoate, rose.

While Fig. 3.10 serves to qualitatively illustrate the changes in reaction mixture composition throughout the transacetoacetylation reaction, the methodology described herein was amenable to actual quantification by addition of an internal standard (nitromethane). An internal standard allows for the calculation of a calibration factor which can reliably convert relative

integration values into corresponding weights of identified material. Knowledge of two weights became crucial; the weight of each aliquot was recorded prior to addition of deuterochloroform, as was the weight of internal standard.

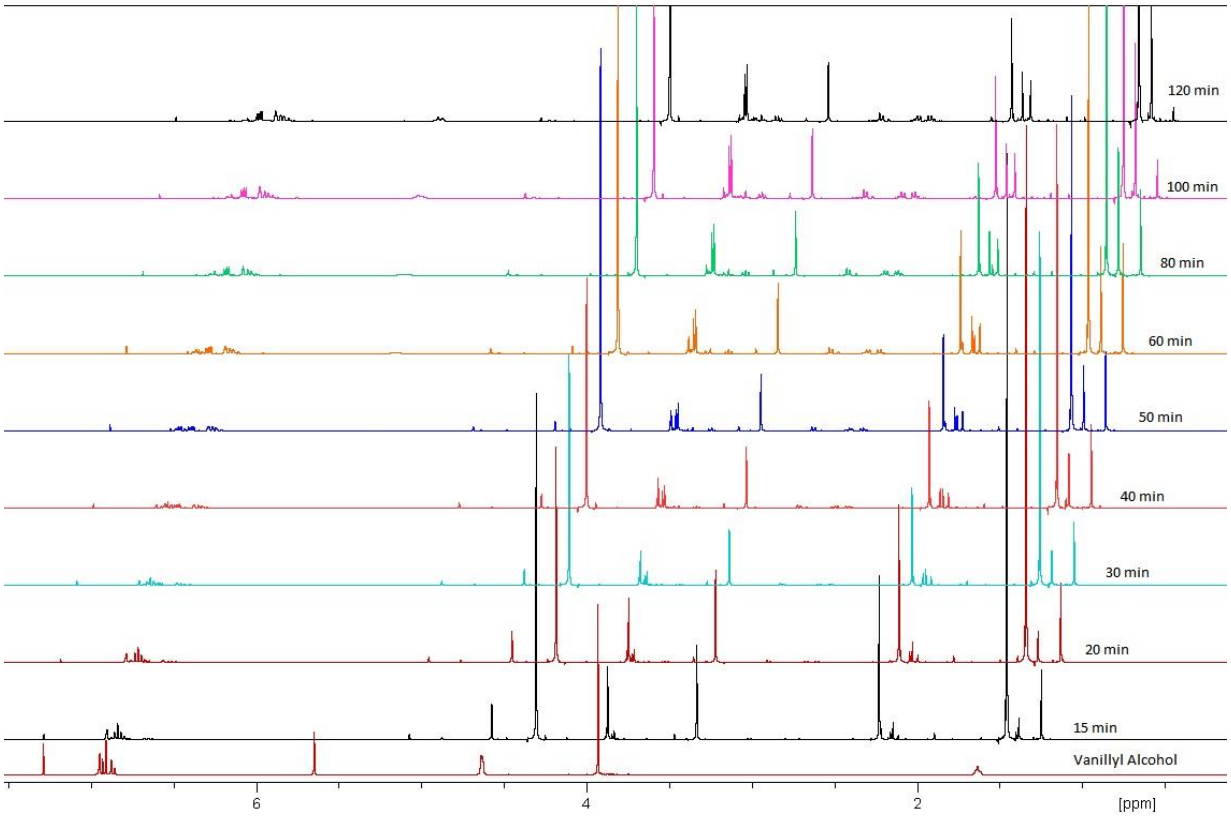


Fig. 3.10. Offset overlay of some ^{1}H NMR spectra collected from treatment of vanillyl alcohol and TBAA at 100 °C over two h

Thus, the weight percentage of each NMR resolved component of the neat reaction mixture could be determined. This contrasts with determination of NMR yields by normalized integration which is only suitable for well-defined systems which contain only known species. Overall, this technique was able to track the consumption of vanillyl alcohol and appearance of 5-(acetoacetoxymethyl)guaiacol-thermolysis products. The results have been plotted together in Fig. 3.11. The initial concentrations of TBAA and vanillyl alcohol were calculated not from quantitative NMR analysis but from the initial reaction components under the assumption that each was 100% pure.

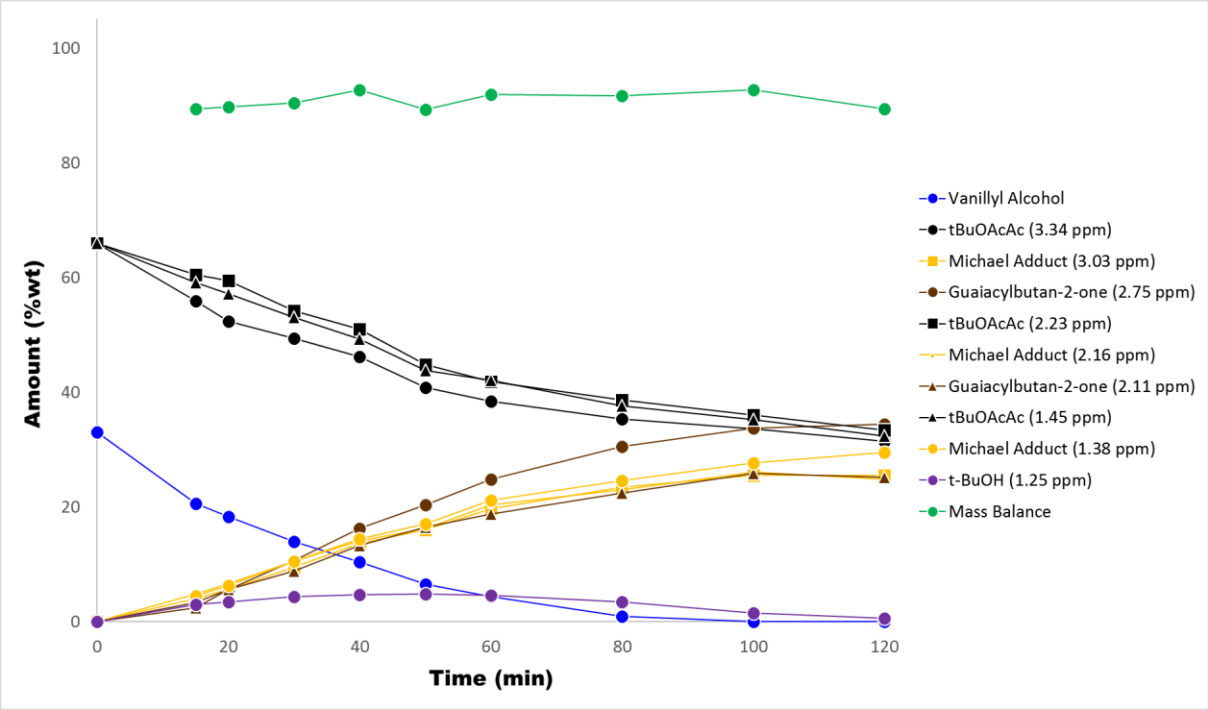


Fig. 3.11. One-pot preparation and thermolysis of 5-(acetoacetoxymethyl)guaiacol. Results of quantitative ^{1}H NMR analysis

Equation 3.1 was used to determine the masses of reaction components during the reaction cross sectioning of model compounds based on: (1) mass of standard, (2) mass of aliquot and (3) relative integration values of the standard compared with individual peaks absolutely assigned to the reaction components.

$$\text{Reaction Component(g)} = \frac{\text{Reaction Component}\left(\frac{\text{g}}{\text{mol}}\right) \times \text{Standard (g)}}{\text{Standard}\left(\frac{\text{g}}{\text{mol}}\right)} \times \left(\frac{\left(\frac{\text{Reaction Component(integration)}}{^{1}\text{H per Molecule of Reaction Compoent}} \right)}{\left(\frac{\text{Standard(integration)}}{^{1}\text{H per Molecule of Standard}} \right)} \right) \quad (3.1)$$

$$\text{Concentration of Reaction Romponent (wt.\%)} = \frac{\text{Reaction Component(g)}}{\text{Aliquot (g)}} \times 100 \quad (3.2)$$

Equation 3.2 describes the determination of concentration of an identifiable reaction component in terms of weight percentage as a relationship between the determined weight of reaction component by quantitative ^{1}H NMR (from Equation 3.1) to the observed weight of

periodically collected aliquot. When the results—*concentration of reaction components in weight percentage*—were plotted against time as in Fig. 3.11, the changing reaction mixture could be visualized from the composite image created by these cross-sections.

The green line tracks the calculated mass balance as the reaction proceeded and should have been at 100% for a clean reaction. Its steady hovering around 90% indicated that species were always present in the reaction mixture which were not identified. Initially this was likely due to production of unidentified 5-(acetoacetoxymethyl)guaiacol, and later in the reaction this was attributed to oligomerization. If the reaction had proceeded longer than two h, the mass balance would likely have continued to decline as more oligomerized products were formed. Notably, *tert*-butanol could be resolved from TBAA, indicating the power of this quantitative ^{1}H NMR technique to differentiate between related moieties of different functional groups. A clear build-up to a steady state of *tert*-butanol was observed during the course of transacetoacetylation at the primary alcohol. Later in the reaction, the amount of *tert*-butanol dropped off as it was removed by nitrogen assisted distillation and it was no longer replenished by transacetoacetylation reactions with TBAA.

TBAA could be tracked by changes at three resonance frequencies: 3.34 ppm (methylene), 2.23 ppm (methyl) and 1.45 ppm (*tert*-butyl). While all three signals led to similar quantitation, the value determined from the methylene proton resonances was consistently lower than that determined from the methyl or *tert*-butyl resonance peaks. This was attributed to the acetoacetic preponderance to undergo enolization, which shifted a small portion of the methylene resonance to the vinyl region of the NMR spectrum. Importantly, the general shape of the loss of TBAA from the reaction mixture matches the general shape of vanillyl alcohol loss. This is a strong indication

that these two species were in fact reacting. The vanillyl alcohol only contained one trustworthy resonance signal which was suitable to quantification: the benzylic methylene around 4.5 ppm.

While primary or phenolic acetoacetates were not identified, two resolved resonance peaks could be used for each of the previously identified thermolysis products; Labeled as guaiacyl-butan-2-one, 4-(4-hydroxy-3-methoxyphenyl)butan-2-one could be tracked by changes in the regions of 2.75 ppm (combined methylene chain) and 2.11 ppm (methyl). The disagreement in the quantification was attributed to the rise in overlapping resonances from unidentified oligomerization products around 2.75 ppm as the reaction progressed. Referred to as Michael adduct in Fig. 3.11, *tert*-butyl 2-(4-hydroxy-3-methoxybenzyl)-3-oxobutanoate was tracked by changes observed in the regions of 3.03 ppm (methine) and 1.38 ppm (*tert*-butyl ester) which both led to consistent quantification.

Limitations encountered in this experiment included lack of resolved resonance frequencies associated with acetoacetylated product, and difficulty encountered in preparation of NMR samples during the initial reaction when employing substrate with low solubility. Also, there was private debate regarding the applicability of these results to lignin, since there are almost zero primary benzylic alcohol moieties and there are sparingly few benzylic alcohol residues of any kind substituted *ortho* or *para* to a free phenol (the positions required to engage in quinone methide formation).

3.2.3.1. Acetoacetylation of α-Methylvanillyl Alcohol

To address these valid concerns while taking advantage of the powerful quantitative NMR strategy, the methodology was extended to acetoacetylation of 4-(1-hydroxyethyl)-2-methoxyphenol or α-methyl vanillyl alcohol (Figs. 3.12 and 3.13). Several advantages were endemic to this slightly more complicated model compound which was prepared by graduate

researcher Catherine A. Sutton by reaction of vanillin with a superstoichiometric excess of methyl magnesium bromide. Those advantages included an aliphatic methyl group which could be used to track acetoacetylation and a substitution pattern more analogous to technical lignins.

The diol substrate, 4-(1-hydroxyethyl)-2-methoxyphenol, was dispersed in two molar equivalents of TBAA and heated in an oil bath (100 °C) for two h with nitrogen sparging as aliquots were taken periodically by undergraduate researcher Rebecca Haller. Like vanillyl alcohol, α-methylvanillyl alcohol was a white crystalline solid at room temperature and was not miscible with TBAA at room temperature. However, the mixture became a homogeneous solution within two min of heating and there were no issues with precipitation of reaction components during aliquot collection. Following two h of reaction, the slightly yellowed viscous solution was adsorbed onto silica gel and separated by flash column chromatography (Fig. 3.12). What a difference a methyl group made!

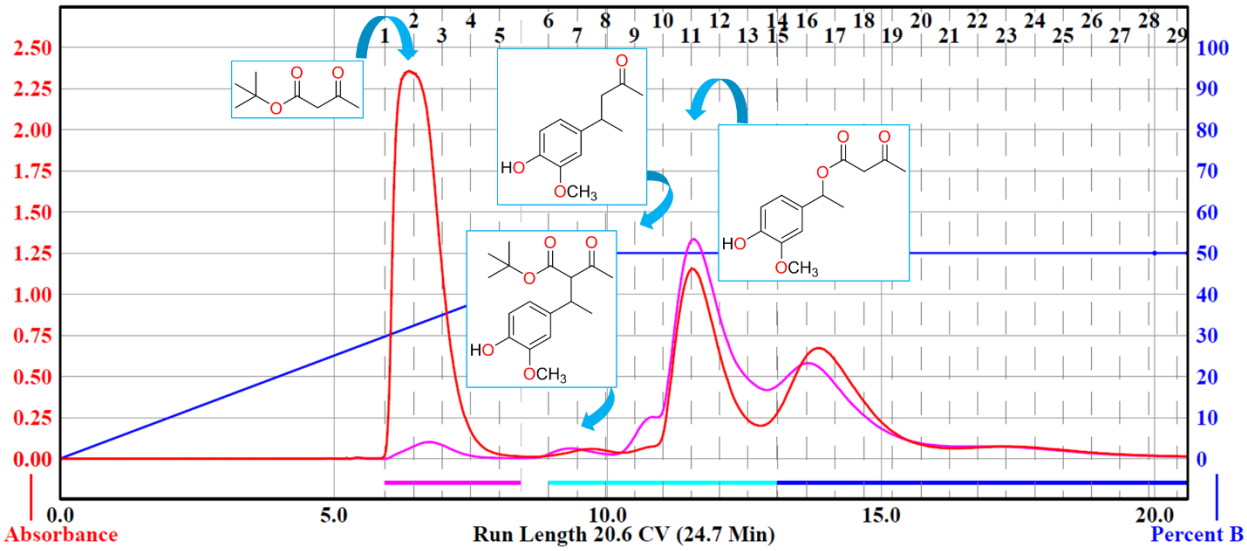


Fig. 3.12. Preparative chromatogram from acetoacetylation of α-vanillyl alcohol with TBAA

The periodic aliquots were also amenable to quantitation with nitromethane as the internal standard and the results have been plotted in Fig. 3.13. Remarkably different trends were observed in the mass balance of the reaction mixture and stability of 1-(4-hydroxy-3-methoxyphenyl)ethyl-

3-oxobutanoate (mono acetoacetylated α-methylvanillyl alcohol). Correspondingly lower concentrations of thermolysis products from the decomposition of 1-(4-hydroxy-3-methoxyphenyl)ethyl-3-oxobutanoate were observed. Strikingly, the pattern of alcohol disappearance again closely matched the disappearance of TBAA during the initial sixty min of reaction. The concentration of *tert*-butanol was also similar in both reactions.

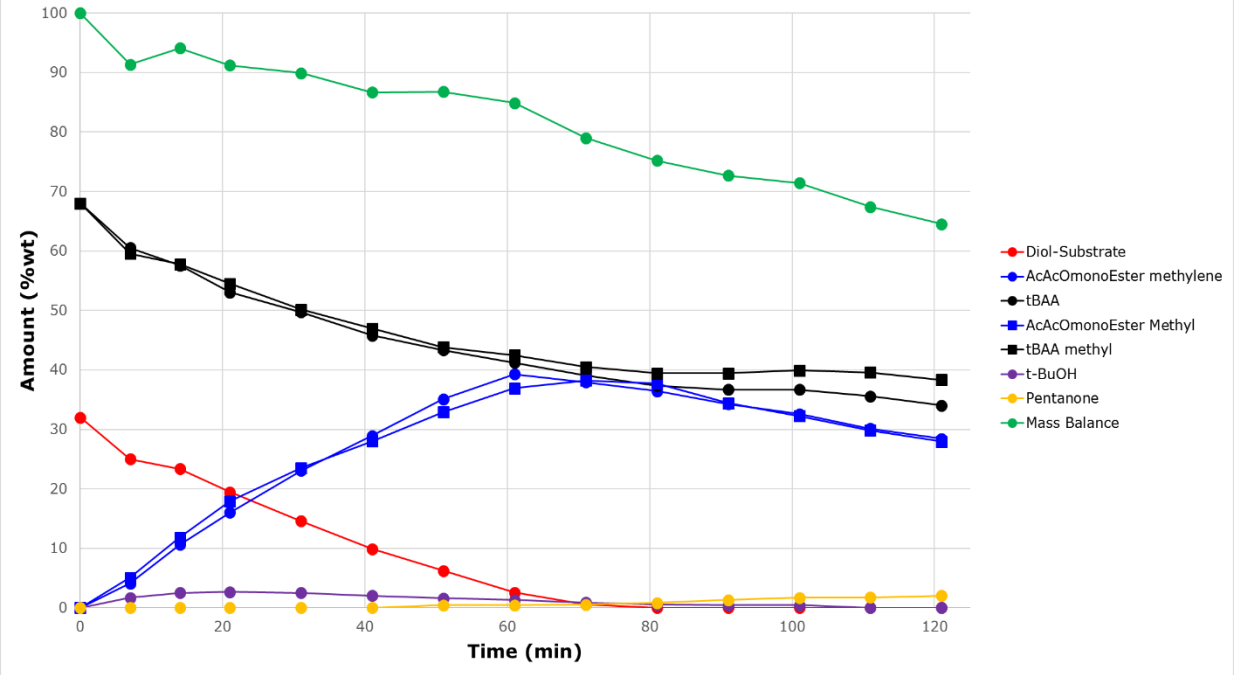


Fig. 3.13. Acetoacetylation of 4-(1-hydroxyethyl)-2-methoxyphenol at 100 °C. Results of quantitative ^{1}H NMR analysis

The relatively constant drop in the mass balance could have been due to further acetoacetylation of the phenolic hydroxyl which could also explain the gentle descent from the plateau observed in TBAA concentration around 120 min. However, NMR analysis of the tail fractions indicated a diverse mixture of oligomerized products was present and likely the cause of dropping mass balance. In contrast to the acetoacetylation of vanillyl alcohol, there was never a very large concentration of products from acetoacetic ester synthesis such as 4-(4-hydroxy-3-methoxyphenyl)pentan-2-one (labeled as pentanone in Fig. 3.13). The different outcomes of these

experiments indicate that switching from a primary benzylic alcohol *para* to a phenol to a secondary benzylic alcohol *para* to a phenol was enough to shift the mechanism of degradation.

Some possible explanations have been enumerated: (1) the quinone methide forms in both cases, but derivatization by Michael addition is very sensitive to steric hinderance thus leading to the disparity in product outcomes, (2) the quinone methide forms in the first case with vanillyl alcohol but not in the second, in other words the secondary benzylic acetoacetoxy moiety decomposes in a totally different way than the primary acetoacetoxy moiety and faster than quinone methide imine formation, and (3) there was never a quinone methide, only bimolecular substitution which is retarded by steric hinderance.

Firstly, a similar rate of quinone methide formation was discarded as an explanation. Careful analysis described in the literature has characterized quinone methides as electron deficient species which are stabilized by electron donating substituents.[38] So all other things being equal, the presence of additional methyl stabilization should have should have made 1-(4-hydroxy-3-methoxyphenyl)ethyl-3-oxobutanoate (from α-methylvanillyl alcohol) more prone to quinone methide formation. Instead, it is stable enough to be the primary isolated product after two h of reaction.

The second supposition seems favorable over the first. To expand on this argument, consider the qualitatively similar trend in changing diol concentration (tracked in both reactions) and in the disappearance in TBAA (compare Fig. 3.11 with Fig. 3.13; the rates of TBAA loss are practically identical in both cases during the initial sixty min of reaction. The concentration drops from around 66 weight percent to around 40 weight percent in that time. Therefore, the rate of benzylic acetoacetoxy formation is similar but the stability of the intermediates is very much different.

The third discussion point is precluded by the initial reaction screening related in this chapter wherein transacetoacetylation of TBAA by veratryl alcohol was compared with vanillyl alcohol. If the benzylic acetoacetoxy moiety was simply a leaving group capable of activating the material towards nucleophilic substitution, there is no way to reconcile the nearly quantitative yield of 4-acetoacetoxyveratrole after three h at 130 °C with the results collected in Scheme 3.2.

3.2.3.2. Isolating the Common Hydroxyl Groups of Lignin

Further studies have aided the elucidation lignin model compound acetoacetylation, and assisted interpretation of complex spectra collected from acetoacetylated technical lignins.[1] Quantitative ^{1}H NMR experiments were completed with three representative lignin model compounds which contained only a single hydroxylic environment each. The selected compounds, 1-(3,4-dimethoxyphenyl)ethan-1-ol, 3-(3,4-dimethoxyphenyl)propan-1-ol, and guaiacol (Fig. 3.4), isolate each hydroxyl environment while conserving electronics similar to lignin.

Conserving lignin-like electronic structure was important since side reactions could be related to the electronic stabilization or destabilization of powerful mesomeric electron donors such as alkoxy ethers upon an aromatic ring. Additionally, the peak-shift of NMR resonance signals could be modulated by differential substitutions. By employing guaiacol and veratrole rings, electronics akin to coniferyl alcohol (one of three common monolignols) were conserved.

It was expected that the aliphatic hydroxyl containing lignin model compounds (1-(3,4-dimethoxyphenyl)ethan-1-ol and 3-(3,4-dimethoxyphenyl)propan-1-ol) would be the most susceptible to transacetoacetylation but that benzylic esters may be unstable[39, 40] under the reaction conditions. Without the aid of catalyst, acetoacetylation of the phenolic hydroxyl was expected to proceed with comparative lethargy based on literature reports and the initial comparisons between guaiacol, veratryl alcohol and vanillyl alcohol (Scheme 3.2).

Reaction cross sections of the neat reaction mixtures heated to 130°C over time were collected and analyzed by previously described (*vide supra*) quantitative ^{1}H NMR method and utilized nitromethane as an internal standard. Extrusion of *tert*-butanol was facilitated by nitrogen sparging. The higher reaction temperature was selected to push the limits of acetoacetoxy stability and the quantitative NMR analysis.

3.2.3.1. Acetoacetylation of a Secondary Benzylic Alcohol

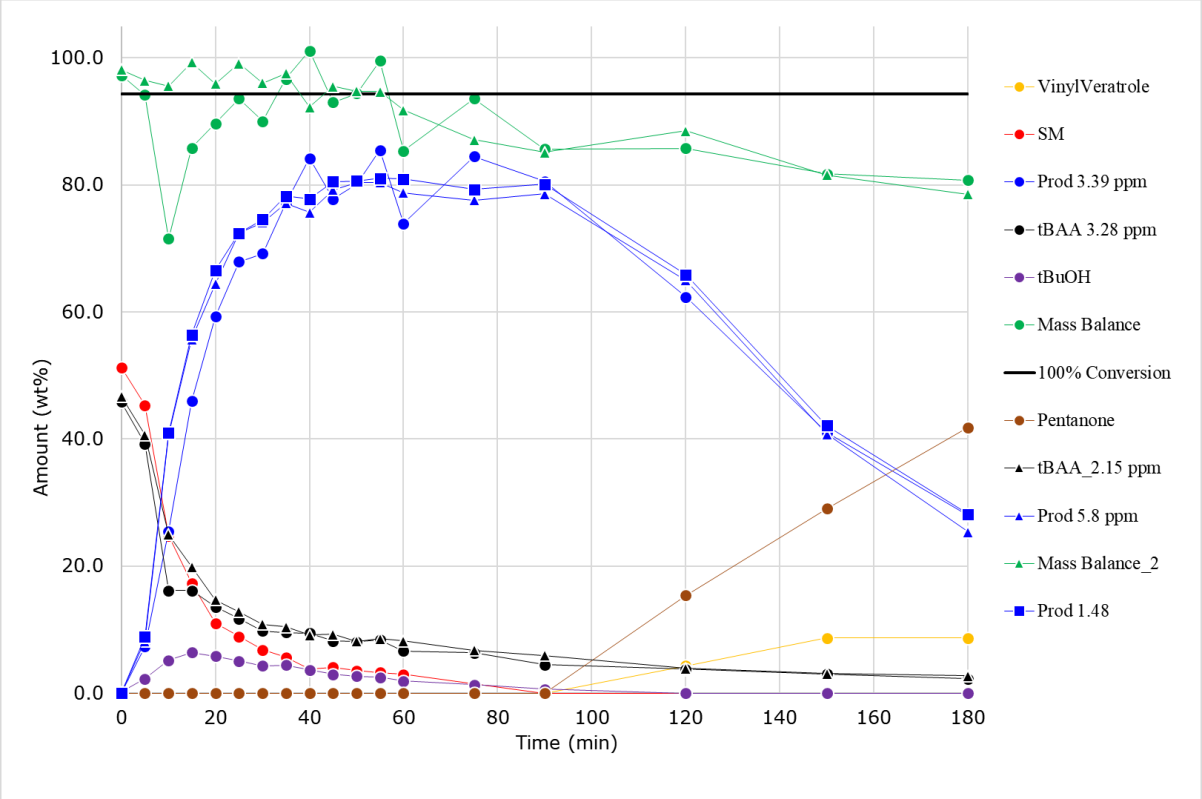


Fig. 3.14. Acetoacetylation of 1-(3,4-dimethoxyphenyl)ethan-1-ol. Results of ^{1}H NMR analysis

Lignin's benzylic hydroxyls have been represented in this section by 1-(3,4-dimethoxyphenyl)ethan-1-ol. In this case, the analogous electronic environment to that of the larger lignin macromolecule could significantly impact the stability of secondary benzylic hydroxyl moieties upon acetoacetylation. Fig. 3.14 illustrates the ramifications of acetoacetylating 1-(3,4-dimethoxyphenyl)ethan-1-ol. Qualitatively similar to the reaction of α-methylvanillyl

alcohol (Fig. 3.13), a plateau in the formation of 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate (labeled as Prod and illustrated in blue, Fig. 3.14) was reached with corresponding depletion of starting materials: 1-(3,4-dimethoxyphenyl)ethan-1-ol in red and TBAA in black. Also, the concentration of *tert*-butanol (purple) spiked then dropped steadily.

A difference in the time course of developing changes between the reaction illustrated in Fig. 3.13 and that of 3.14 was observed; the concentration of 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate reached a maximum in 40 min at 130 °C whereas the peak in 1-(4-hydroxy-3-methoxyphenyl)ethyl 3-oxobutanoate took 60 min at 100 °C. The stability of 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate also seemed to be higher than 1-(4-hydroxy-3-methoxyphenyl)ethyl 3-oxobutanoate since its concentration plateaued for almost an h at the high temperature of 130 °C in contrast to the peak-like rise and fall of 1-(4-hydroxy-3-methoxyphenyl)ethyl 3-oxobutanoate at 100 °C. This could be viewed as evidence that yet another mechanism for decomposition was in effect. Additionally, there is no facile route to formation of a quinone methide from 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate since its phenolic hydroxyls are masked as sturdy ethereal functionalities.

The observed decomposition of 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate was very unexpected, since the early experiment consuming veratryl alcohol was so clean and high yielding compared with vanillyl alcohol (Scheme 3.2). It was expected that 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate would form rapidly and remain stable in the reaction mixture. The decomposition of 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate corresponded with detection of vinyl veratrole. Note that no 5-vinylguaiacol was observed in the reaction which formed 1-(4-hydroxy-3-methoxyphenyl)ethyl 3-oxobutanoate (Fig. 3.13).

Thermolysis products previously associated with formation of a quinone methide followed by recombination with an acetoacetate anion have been identified as derivatives of spontaneous elimination of the acetoacetate anion to afford a secondary carbenium stabilized by the electron-rich veratryl ring. Similar products from the different reaction mixtures do not seem as strange once quinone methides are viewed as highly resonance stabilized *p*-alkoxy carbenium intermediates.[41] To further understand how secondary benzylic acetoacetate esters may decompose without quinone methide intermediacy, the components of the reaction mixture were isolated (Fig. 3.15).

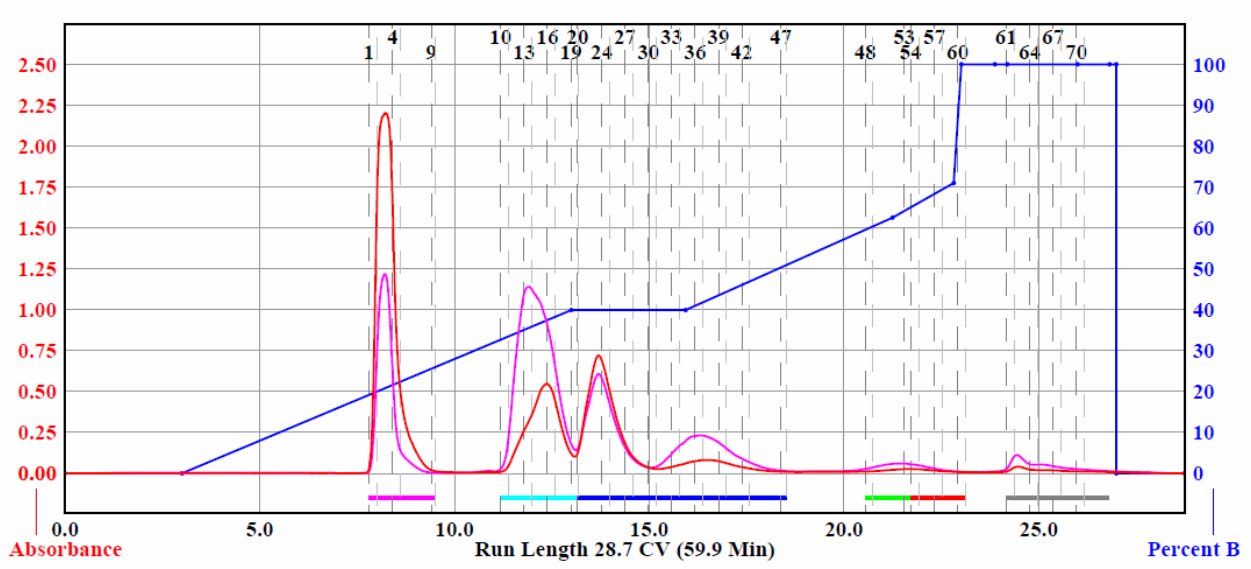


Fig. 3.15. Flash chromatogram of degradation products observed in the preparation of 1-acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane

In Fig. 3.15, fractions 1–9 contained 4-vinylveratrole; fractions 10–18 contained 4-(3,4-dimethoxyphenyl)-2-pentanone; fractions 20–27 contained 1-acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane; fractions 31–47 contained a complex mixture of methoxylated aromatic products according to NMR characterization. The viscous residue was further analyzed by HRMS spectrometry (Fig. 3.16). Some plausible structures were proposed corresponding to the observed peaks (usually ionized with sodium) (Schemes 3.4–3.9).

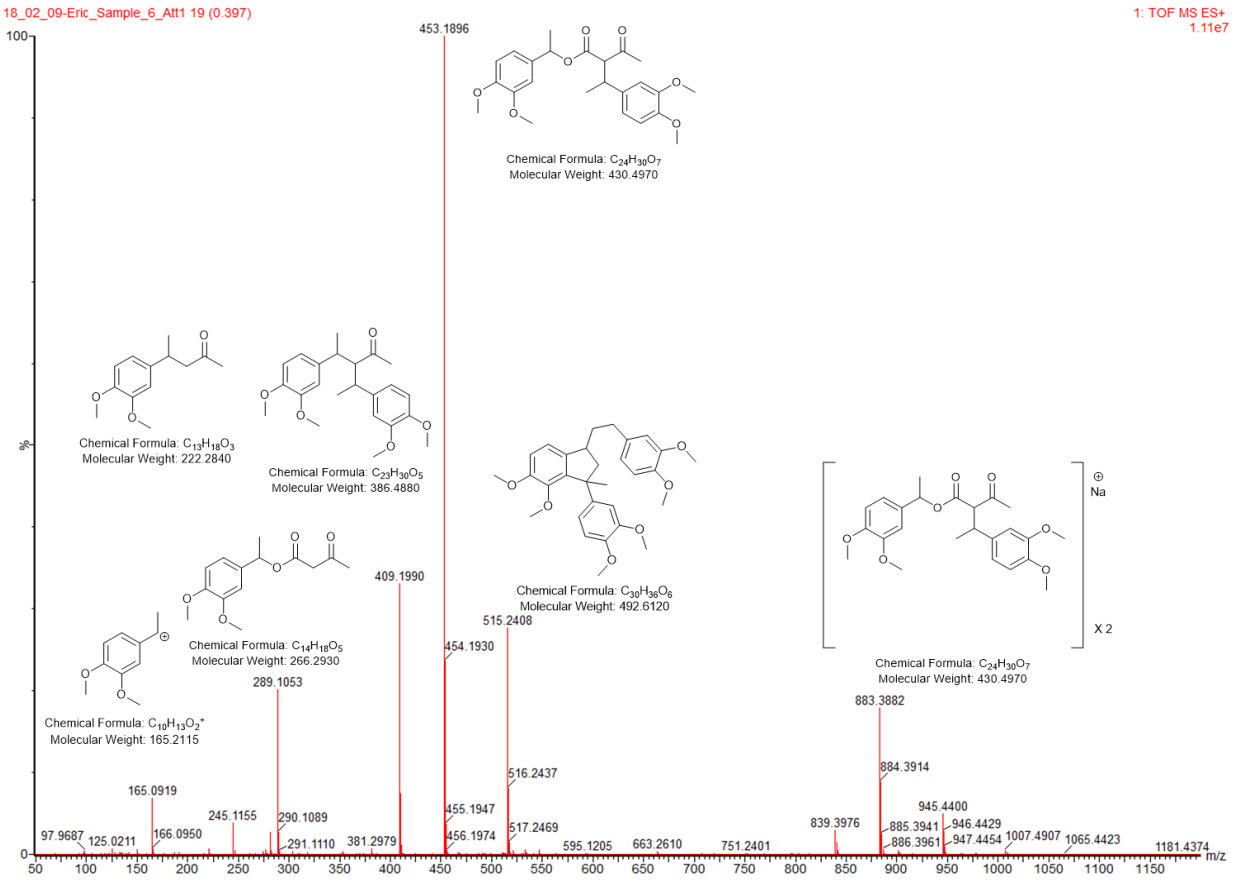
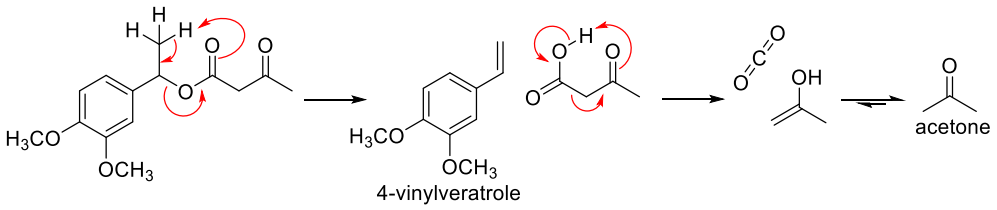
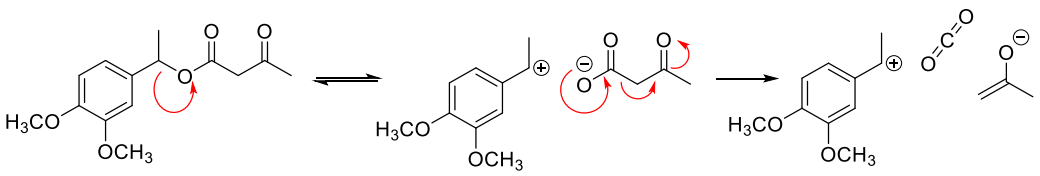


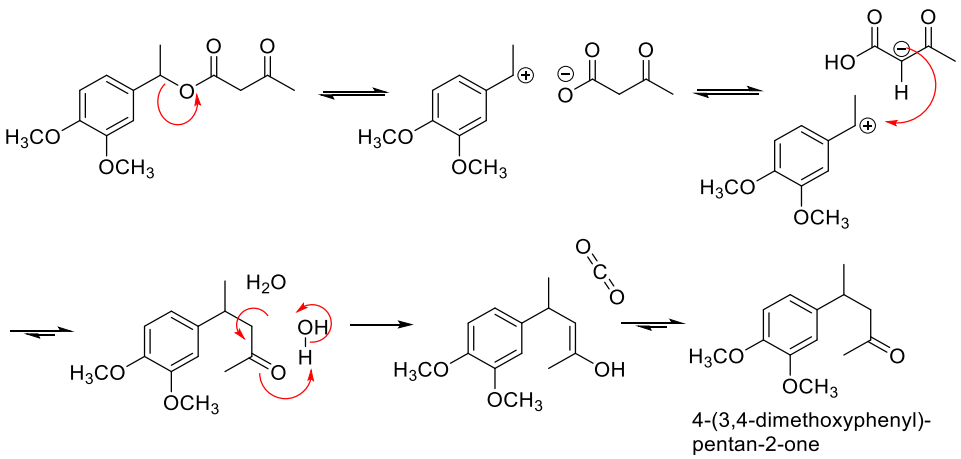
Fig. 3.16. HRMS of additional degradations products observed during the preparation of 1-acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane



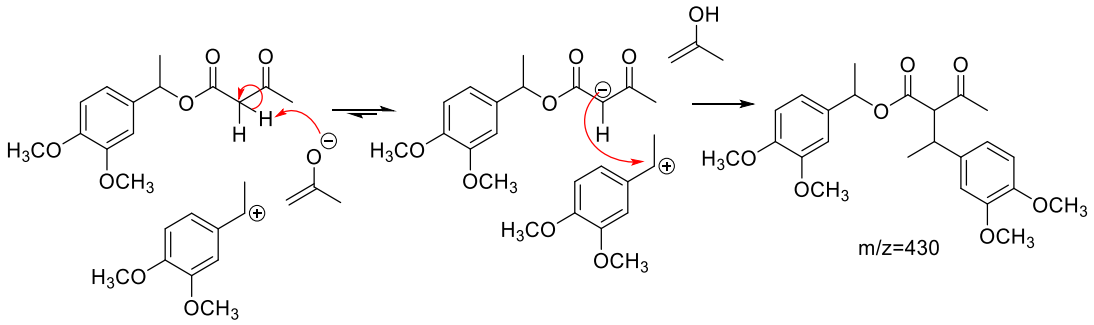
Scheme 3.4. Proposed mechanism for decomposition of 1-acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane to afford 4-vinylveratrole and acetone



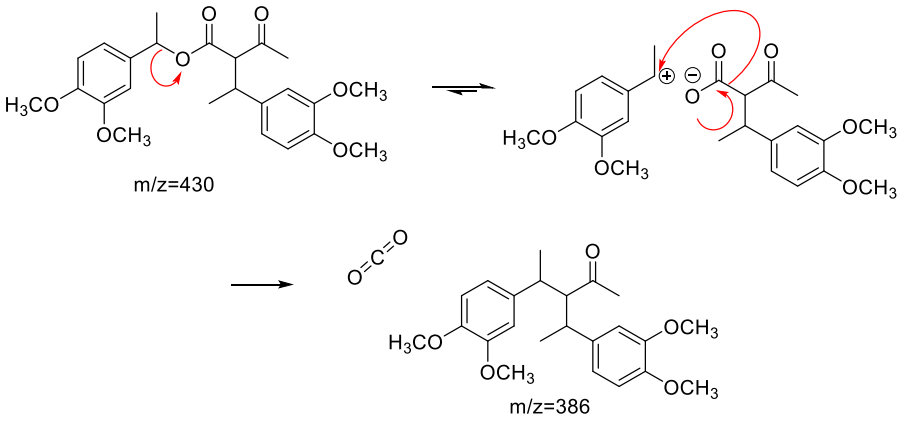
Scheme 3.5. Proposed mechanism for the generation of a secondary carbenium intermediate from the thermal decomposition of 1-acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane



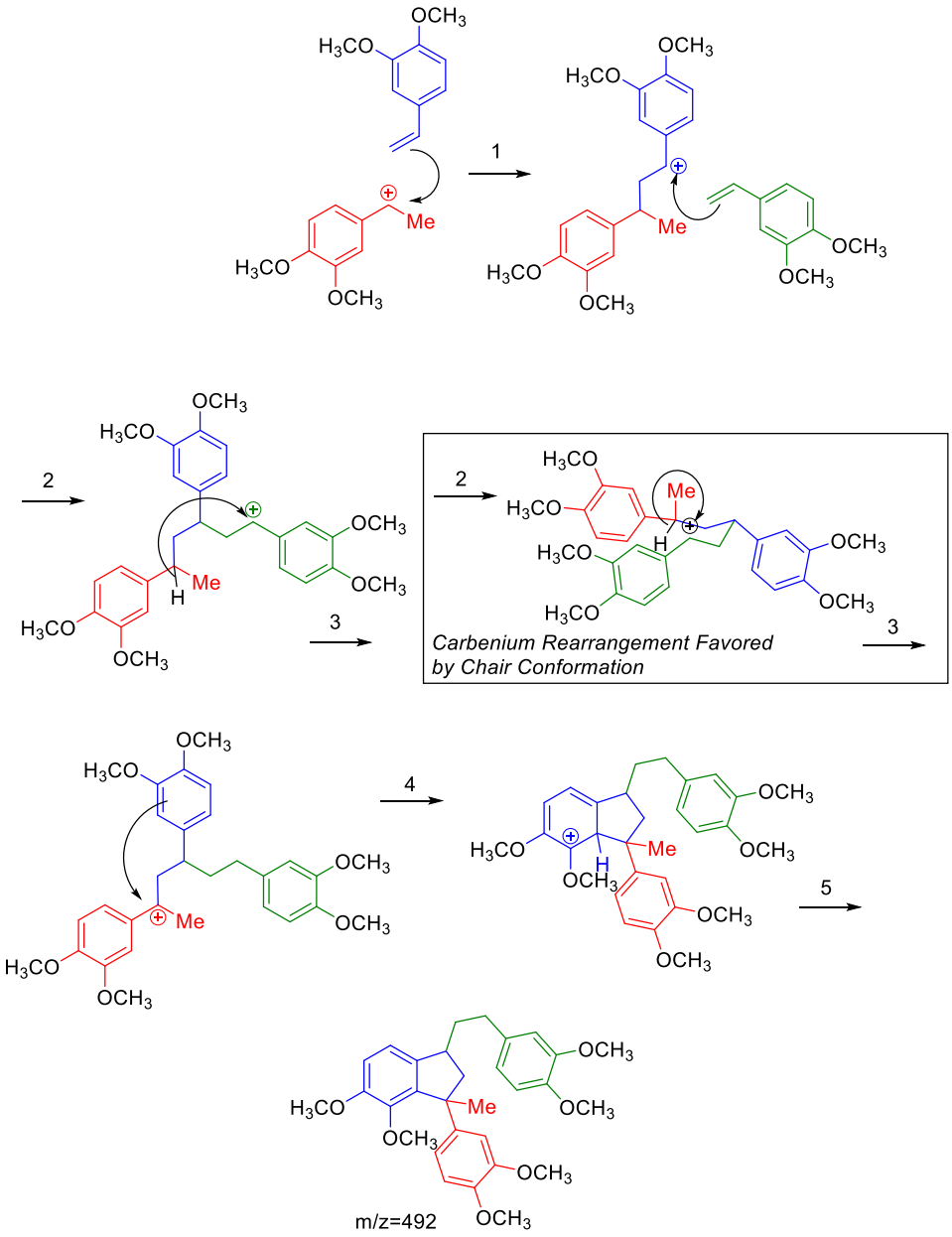
Scheme 3.6. Proposed mechanism for generation of 4-(3,4-dimethoxyphenyl)-pentan-2-one from 1-acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane.



Scheme 3.7. Proposed mechanism for the decomposition of 1-acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane to afford species with m/z=430



Scheme 3.8. Proposed mechanism for heterolytic cleavage, decarboxylation and recombination of species with m/z=430 to afford species with m/z=386.



Scheme 3.9. Proposed mechanism for the formation of a species with m/z=492 and which consumed 4-vinylveratrole

The presence of vinyl veratrole and its trimer suggested that a limited amount of the veratryl-carbenium can undergo proton abstraction from the α-methyl group in the model compound (Scheme 3.4). Veratryl-carbenium formation (Scheme 3.5) most often led to recombination with the nucleophilic acetoacetate enolate followed by subsequent decarboxylation to afford 4-(3,4-dimethoxyphenyl)pentan-2-one (Scheme 3.6). Additional minor products

indicated that trapping of the carbenium with 1-(3,4-dimethoxyphenyl)ethyl-3-oxobutanoate (Scheme 3.7) could lead to crosslinking of acetoacetylated-lignin corresponding with the loss of secondary acetoacetoxy moieties and (Scheme 3.8).

The relatively high mass balance throughout the reaction (illustrated in green, Fig. 3.14) which only slowly depleted with time along with the plateau in 4-vinylveratrole concentration (illustrated in gold) indicated that something was consuming the reactive olefin as more acetoacetate product from the reaction degraded. It was surmised that once the concentration of vinylveratrole was high enough, a steady state was achieved between its production by hydrogen atom abstraction and its consumption in a cationic oligomerization reaction. (Scheme 3.9).

3.2.3.2. Acetoacetylation of a Primary Aliphatic Alcohol

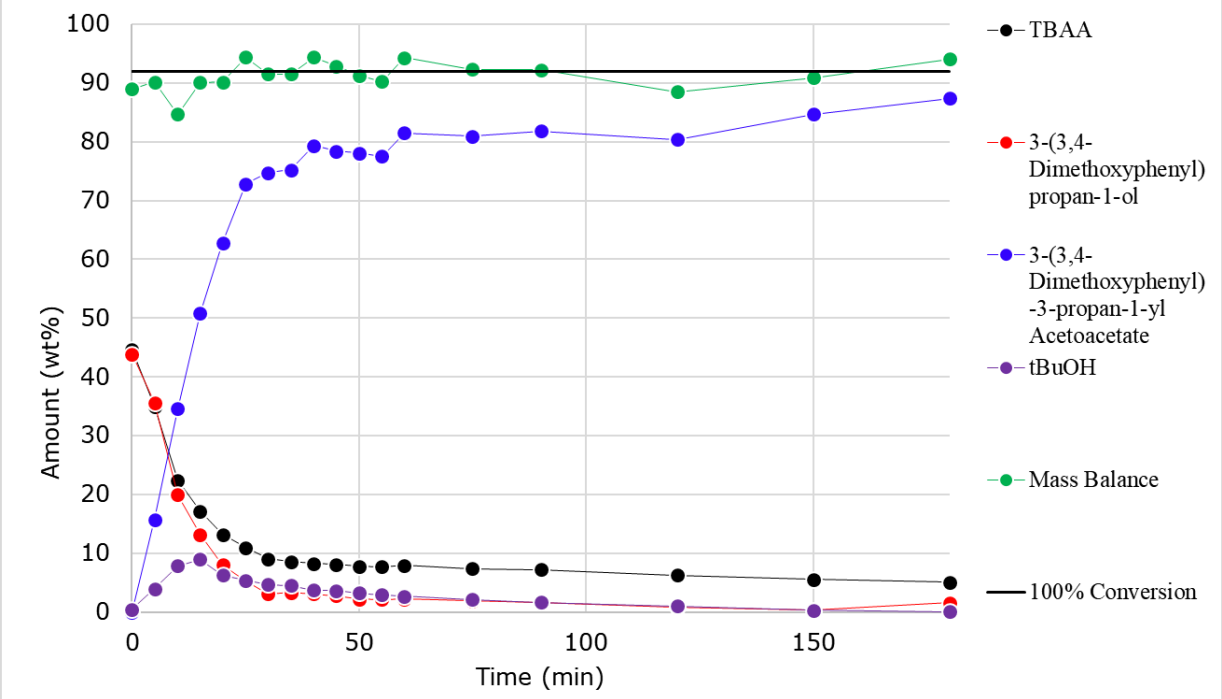


Fig. 3.17. Acetoacetylation of 3-(3,4-dimethoxyphenyl)propan-1-ol

The aliphatic alcohol, 3-(3,4-dimethoxyphenyl)propan-1-ol, was chosen to model primary aliphatic hydroxyls in Kraft lignin because of its low volatility and its facile preparation from

eugenol. mono alcohol substrate, 3-(3,4-dimethoxyphenyl)propan-1-ol, rapidly reacted with TBAA at 130 °C creating a plateau in product concentration within 40 min. The general method for quantitative NMR analysis afforded cross sections of a clean reaction as indicated by a mass balance which never dropped overall (Fig. 3.17, illustrated in green).

The product, 3-(3,4-dimethoxyphenyl)propyl-3-oxobutanoate, was formed immediately upon heating of the reaction mixture (illustrated in blue). The loss of the starting materials (3-(3,4-dimethoxyphenyl)propan-1-ol and TBAA) corresponded well with the formation of acetoacetate ester. The amount of the product never decreased, which indicated the relative stability of this ester linkage even at elevated temperatures corroborated by no observed side products.

3.2.3.3. Acetoacetylation of an Aromatic Alcohol

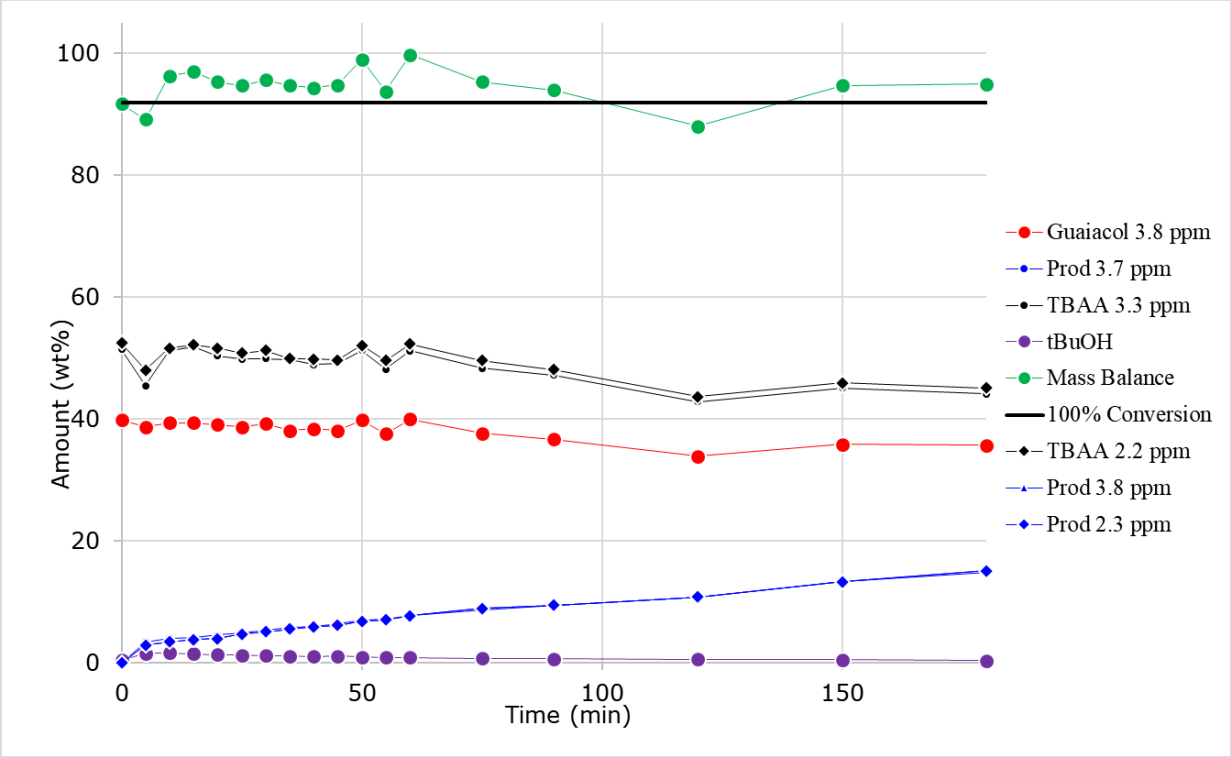


Fig. 3.18. Acetoacetylation of guaiacol

Guaiacol was returned to as a model because of its popular use as a representative structure for lignin phenolic hydroxyl groups.[17] Additionally, application of the quantitative NMR technique

afforded a time resolved visualization of the reaction mixture when TBAA was not rapidly consumed. Compared with the aliphatic hydroxyls (Figs. 3.11, 3.13, 3.14 and 3.17), phenolic guaiacol was hardly reactive towards TBAA (Fig. 3.18).

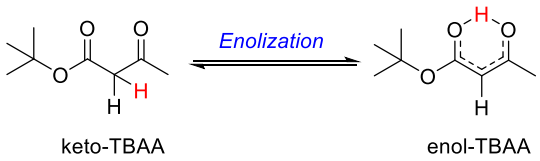
Starting materials—*TBAA in black and guaiacol in red*—in the reaction mixture steadily decreased over the course of the reaction. The production of 2-acetoacetoxyanisole (illustrated in blue) was observed immediately at the onset of heating and steadily increased over the course of the reaction; the amount of acetoacetylated product never rose much above 15 weight percent. Again, the steady rise in the amount of product closely matched the loss of both starting materials, which indicated the stability of even the phenolic ester at elevated temperatures. This observation suggested that complete acetoacetylation of lignin may be possible given sufficient reaction time, but that selective modification of practically all aliphatic and benzylic hydroxyls should be possible while leaving phenolics unchanged.

3.3. Acetoacetylation of Lignin

Acetoacetylation[2, 4] of polyols such as cellulose[42] offers complementary chemoselectivity to established lignin modification reactions which include phenolic coupling to oxiranes.[3, 43] Decreased hydrogen bonding is also a hallmark of acetoacetylated polyols. Acetoacetylation was only recently reported for lignin[1] and remains an active line of inquiry.

3.3.1. Advantages of Acetoacetate Resin Synthesis from Technical Lignins

In the case of lignin, selective modification of aliphatic alcohols over phenols could offer significant benefit to its resins as compared with simple aliphatic polyols due to the adhesive properties of polyphenols.[44] The acetoacetate group adds further value to polyol resins by providing access to crosslinking through a wide variety of mechanisms.[6]



Scheme 3.10. Tautomerization of TBAA

Direct preparation of acetoacetylated macromolecular resins from a variety of technical lignins offers an exquisite opportunity for accessing sustainable thermosets. Like cellulose and other polysaccharides, the polyhydroxylated structure of lignin offers many synthetic handles for modification. Unlike polysaccharides, the strength of lignin macromolecules and the physical properties of their mixtures depends on multiple types of crosslinks besides hydrogen bonding. Selective modification of surface hydroxyls in nanocrystalline or micro fibrillated cellulose without sacrificing performance through disruption of crystallites is extremely challenging.

Additional benefits include closing the loop of paper pulping or EtOH fermentation by utilization of crude exudates without further refinement. TBAA (Scheme 3.10) has been developed as an efficient reagent to acetoacetylate alcohols in concentrated solution with no catalyst.[4] Any strategy for preparing value-added products from acetoacetylated lignin would require quantification of the degree to which acetoacetylation had occurred. Such a technique would have to account for acetoacetate enolization.

3.3.1.1. Characterization Challenges of Acetoacetylated Lignins

The thrust of this collaborative research focused on adding value to Indulin AT Kraft lignin in a catalyst-free fashion by acetoacetylation and interpretation of the resulting modified structure**.** A self-imposed constraint on this technology was that it should have future applicability to additional technical lignins. Hydroxyl content of lignin has been determined using various methods.[18, 45] However, because acetoacetate moieties readily tautomerize (Scheme 3.10) it is difficult to track the amount of lignin-acetoacetylation by methods which rely on hydroxyl-group

derivatization and subsequent quantitative analysis by nuclear magnetic resonance (NMR) spectroscopy.

Significantly, in deuterated chloroform solution, proton spectra show between 5–20% contribution from the enol form.[4] A direct quantification of readily determined proton NMR spectra would offer significant improvement to the state of the art and was envisioned as a natural development in the quantitative ^{1}H NMR protocol established for lignin model compound acetoacetylation (*vide supra*). A reliable method could also find future applicability in developing small scale screening reactions for determining relative rates of cross-linking reactions.

The robust information regarding functional group interconversions gleaned through infrared spectroscopy offers one facile approach to the qualitative determination of resin acetoacetylation. The twin carbonyl stretching bands contributed by acetoacetic esters were expected to be distinct from the carbonyl background of most technical lignins. Comparison of overlays between unmodified lignins, their acetoacetylated products, and acetoacetylated model compounds in combination with the power of total attenuated reflectance techniques allowed for rapid determination of effective reaction conditions.

3.3.2. Acetoacetylation of Kraft Lignin

Kraft lignin (Indulin AT) was functionalized by reaction with TBAA in the absence of a catalyst by simple heating in similar reaction to that employed during model compound reaction cross-sectioning and closely related to reported methods for preparing acetoacetylated resins.[46] TBAA is a poor solvent for lignin however, so 1,4-dioxane was used as a co-solvent due to its ability to interface the reaction components without unduly complicating the ^{1}H NMR spectrum. The reaction flask was placed in an oil bath kept at 130 °C, but the temperature inside the reaction flask was maintained closer to 101 °C due to refluxing 1,4-dioxane.

The course of the reaction was followed by different spectroscopic techniques. As the dioxane and *tert*-butanol were removed by distillation, the viscosity of the black liquid resin increased. There was significant difficulty encountered in removing aliquots for NMR analysis during the acetoacetylation of lignin due to its great viscosity and vitrification upon cooling. Fortuitously, the vitrified lignin could be isolated from the reaction components by IPA-trituration.

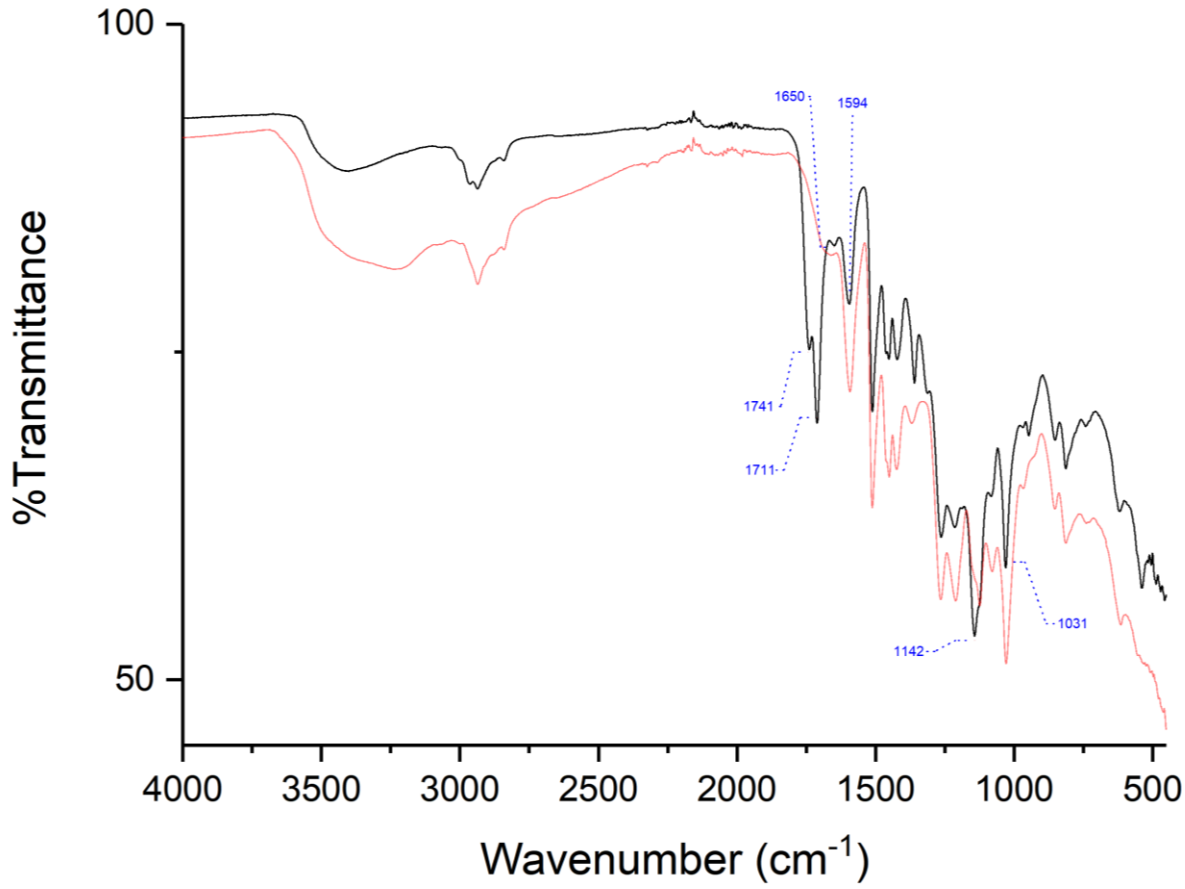


Fig. 3.19. Acetoacetylated (Indulin AT) Kraft lignin (washed with IPA and vacuum dried) in black; (Indulin AT) Kraft lignin in red; FTIR (ATR, neat powder)

Extent of lignin-functionalization was assessed by comparison of FTIR spectra before and after treatment with TBAA (Fig. 3.19). Partial esterification was evident by the identification of two carbonyl stretches at 1741 and 1711 cm^{-1}. These carbonyl-stretching features are extremely

characteristic of acetoacetate esters and were clearly introduced during the reaction with TBAA. Notably, very little else changed in the FTIR spectrum.

Comparison of ^{1}H NMR spectra (Figs. 3.20 and 3.21) revealed several distinct changes from the unmodified lignin which have been attributed to acetoacetylation and formation of tert-butyl ethers. Acetoacetylated Kraft lignin displayed a broadening of the peak at 3.8 ppm, and new peaks appeared at 2.1 ppm, 1.4 ppm and 0.9 ppm. The broadening of the peaks resulted from incorporation of acetoacetate moieties into the irregular macromolecular network.

The methylene protons (3.8 ppm) were not resolved from the methoxy resonances. The broad peak at 2.1 ppm resulted from the terminal methyl group of the acetoacetate moieties and offered an opportunity to determine the molal concentration of acetoacetic esters which had been incorporated into the network. These peaks were identified as overlapping methyl groups of acetoacetate moieties (2.1 ppm) in their keto and enol tautomers.

The findings from the model compounds suggested that the aliphatic and benzylic hydroxyls in Kraft lignin were successfully acetoacetylated; however, it is likely that the benzylic acetoacetate moieties decomposed under the conditions employed. Evidence supporting lignin modification followed by thermolysis of benzylic acetoacetate moieties and subsequent recombination or cross-linking was detected. The development of a resonance peak at 1.4 ppm in the ^{1}H spectrum (Fig. 3.20) could be attributed to quinone methide intermediacy and Michael reaction to afford methylene bound TBAA derivative esters. Such *tert*-butyl 2-substituted acetoacetate esters showed exactly the same signature at 1.4 ppm when observed following the reaction between vanillyl alcohol and TBAA (Fig. 3.7). However, there was no clear indication of styrene formation. Remarkably, there was no evidence of non-acetoacetate carbonyl resonances

near 208 ppm analogous to 4-(3,4-dimethoxyphenyl)pentan-2-one in the acetoacetylated lignin (Figs. 3.20 and 3.21).

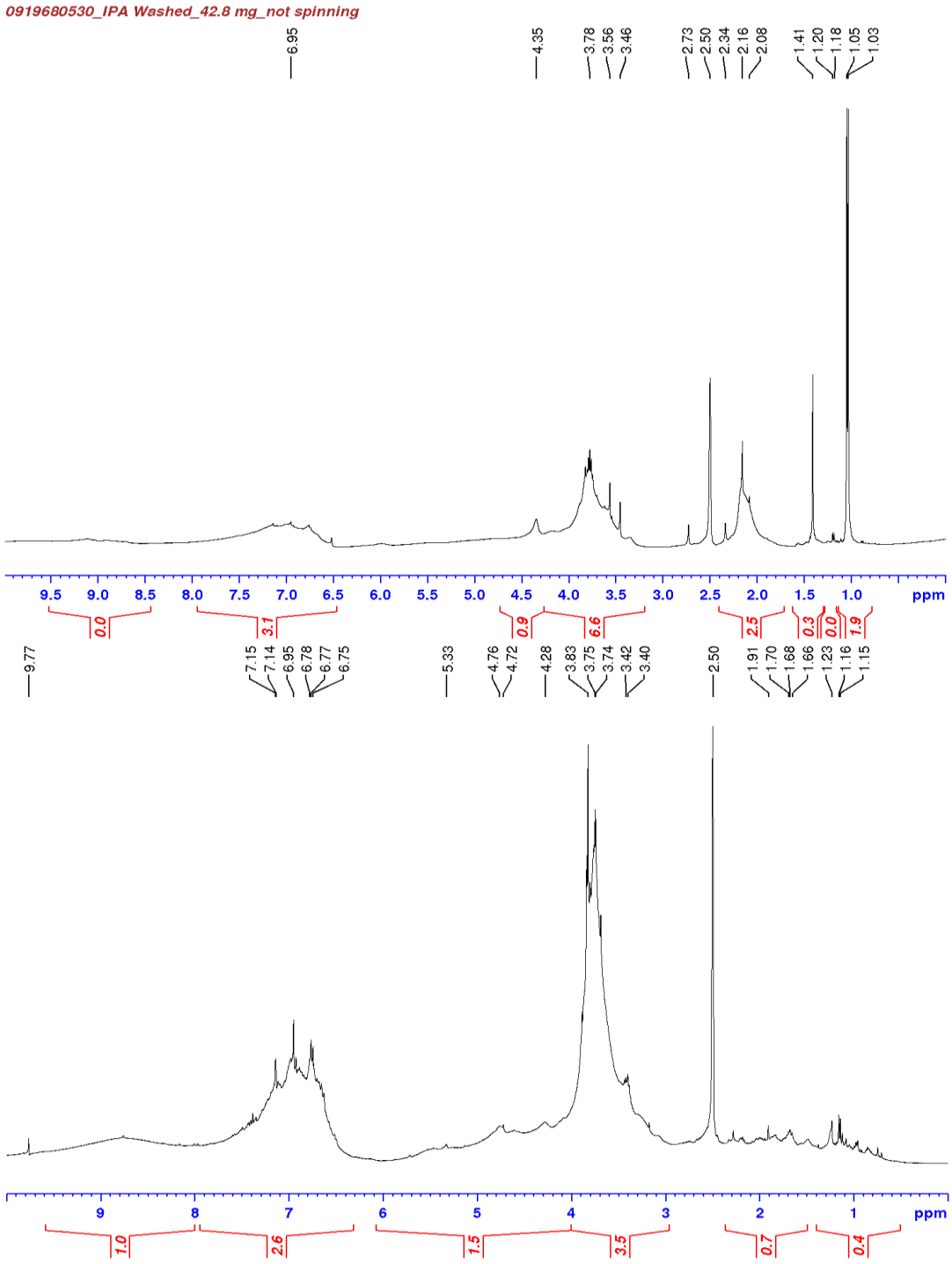


Fig. 3.20. Acetoacetylated (Indulin AT) Kraft lignin (washed with IPA and vacuum dried) over (Indulin AT) Kraft lignin; ^{1}H NMR (DMSO-d_6); ^{1}H NMR (DMSO-d_6)

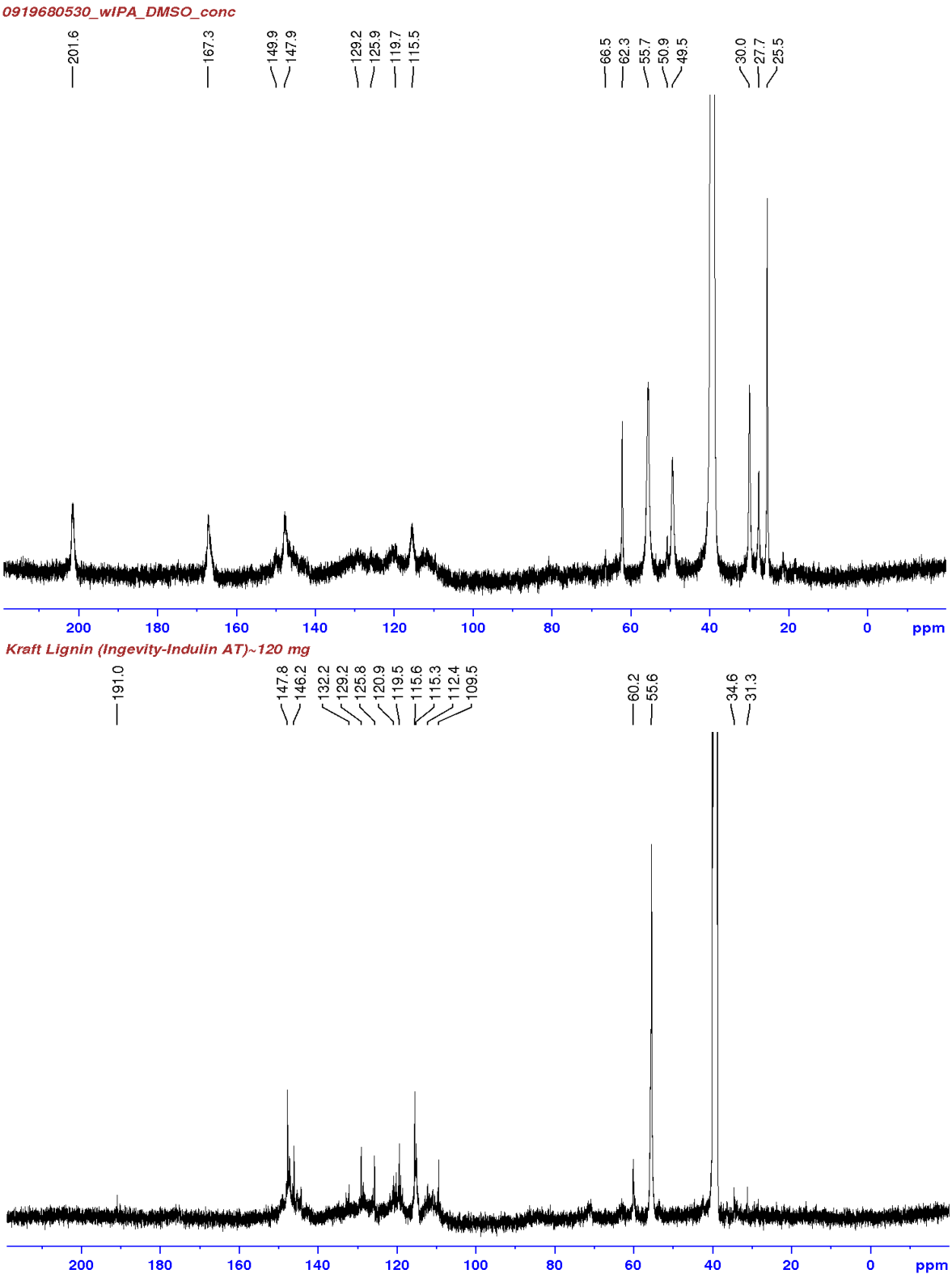


Fig. 3.21. Acetoacetylated (Indulin AT) Kraft lignin (washed with IPA and vacuum dried) overlay with (Indulin AT) Kraft lignin; ^{13}C NMR (DMSO-d_6)

While there was no evidence of *tert*-butyl ether formation in the model compounds investigated, the strong signals at 0.9 ppm in the ^{1}H NMR along with pronounced signals at 25 and 62 ppm in the ^{13}C NMR spectra (Fig. 3.20: ^{1}H NMR and Fig. 3.21: ^{13}C NMR) were interpreted as incorporation of *tert*-butyl ethers into the lignin network. This was a very surprising outcome of the thermolysis since *tert*-butanol is a very weak nucleophile. Decomposition was very different between the lignin and models, but the models could be combined to facilitate interpretation of the lignin.

The macromolecular network of which lignin is composed created conditions which could not otherwise be modeled. It has been supposed that dioxane and *tert*-butanol (from surface reactions with TBAA) led to swelling of the lignin network which facilitated high temperature homogenization of the reaction mixture. Furthermore, *tert*-butanol formed as the product of transesterification deep within the network would not have easily cleared the system as observed in the lignin model compound experiments.

When benzylic acetoacetic esters began eliminating acetoacetate, the temperature dependent formation of carbon dioxide was unaffected by the network and so chances for alkylation with ketone generating acetoacetate enolates diminished relative to carbenium-trapping by TBAA. TBAA is not very effective at penetrating an unmodified lignin network but at the same time would have undergone rapid transesterification upon penetration. As *tert*-butanol was liberated, it would not have been able to escape the reaction mixture due to increased viscosity which would have favored eventual reaction with *tert*-butanol due to low concentrations of TBAA inside the network. These factors combined to facilitate the unpredicted but reasonable formation of *tert*- ethers in Kraft lignin treated with TBAA and polar aprotic solvent at 130 °C.

Just as in FTIR (Fig. 3.19), there was no observed diminution of existing peaks (Figs. 3.20 and 3.21): an indication of the largely preserved lignin network during modification by transacetoacetylation. According to comparison with NMR spectral data, there was minimal acetoacetate functionalization at phenolic hydroxyls. This assertion was supported by a lack of upfield broadening observed for the lignin methoxy peaks between 3 and 4 ppm (Figs. 3.20 and 3.21). This was likely related to the apparent competition between *tert*-butanol and guaiacol which would have been complicated by the 100 °C reaction temperature and by the network blocking removal of *tert*-butanol by distillation in concert.

3.3.3. Quantification of Lignin Functionalization

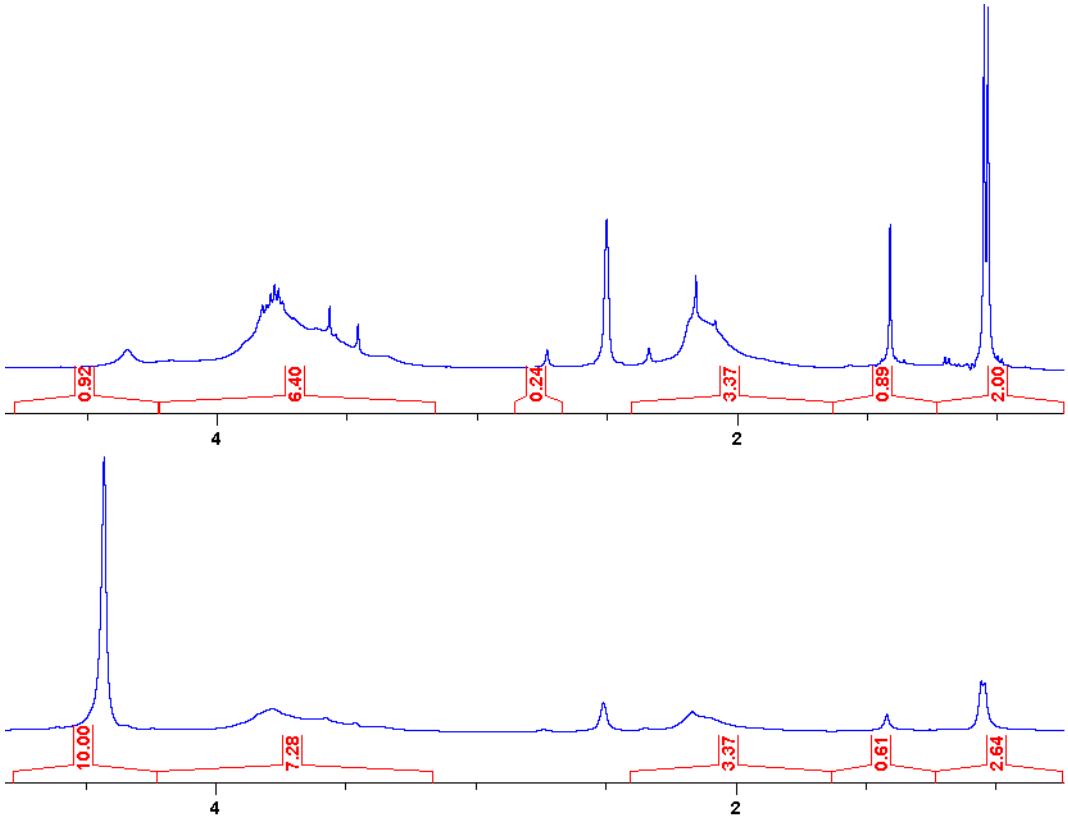


Fig. 3.22. Quantification of acetoacetylated (Indulin AT) Kraft lignin (DMSO-d6, nitromethane standard)

To estimate the degree of acetoacetate functionalization afforded by this method, a known amount (42.8 mg) of modified lignin was dissolved in anhydrous deuterated dimethyl sulfoxide by vortex mixing and heating in an NMR tube. A ^{1}H NMR spectrum was collected (Fig. 3.22 top). A nitromethane standard (15.2 mg) was added and reanalyzed (Fig. 3.22 bottom). The region assigned to the nitromethane standard was set to 10 H. The acetoacetate methyl groups' resonance peak was integrated and was 3.37 H. The same signal in the original spectrum was set to 3.37 H, then the region which became occluded by the nitromethane standard was integrated in the original spectrum (0.92 H). This quantification assumed that the broad peak appearing at 2 ppm in the modified lignin spectrum was solely due to addition of acetoacetate moieties. Equation 3.3 was derived from Equations 3.1 and 3.2. It describes the determination of acetoacetate functionality in units of molality (moles per kilogram): 2.16 mol/kg.

$$\mathrm{Molality}_{\mathrm{OAcAc}} = m_{\mathrm{OAcAc}} = \frac{\mathrm{OAcAc}_{\mathrm{mole}}}{\mathrm{Modified\ Lignin}_{\mathrm{kg}}}$$

$$= \frac{\left(\frac{\mathrm{Mass}_{\mathrm{NO_2Me(g)}}}{\mathrm{Molar\ Mass}_{\frac{\mathrm{NO_2Me(g)}}{\mathrm{NO_2Me(mole)}}}}\right)_{\mathrm{NO_2Me(mole)}} \times \left(\frac{\mathrm{OAcOAc}_{\mathrm{integration}}}{\mathrm{NO_2Me}_{\mathrm{integration}}}\right)_{\frac{\mathrm{OAcOAc}_{\mathrm{mole}}}{\mathrm{NO_2Me}_{\mathrm{mole}}}}}{\left(\frac{\mathrm{Sample\ Mass}_{\mathrm{g}}}{1000_{\frac{\mathrm{g}}{\mathrm{kg}}}}\right)_{\mathrm{kg}}}$$

$$= \frac{\left(\frac{0.0152_{\mathrm{NO_2Me(g)}}}{61.04_{\frac{\mathrm{NO_2Me(g)}}{\mathrm{NO_2Me(mole)}}}}\right)_{\mathrm{NO_2Me(mole)}} \times \left(\frac{3.37}{(10.0-0.92)}\right)_{\frac{\mathrm{OAcOAc}_{\mathrm{mole}}}{\mathrm{NO_2Me}_{\mathrm{mole}}}}}{\left(\frac{0.0428_{\mathrm{g}}}{1000_{\frac{\mathrm{g}}{\mathrm{kg}}}}\right)_{\mathrm{kg}}}$$

$$= \frac{(0.000249)_{NO_2Me(mole)} \times (0.371)_{\frac{OAcOAc_{mole}}{NO_2Me_{mole}}}}{(0.0000428)_{kg}} = 2.16_{\frac{OAcAc_{mole}}{modified\ lignin_{kg}}} \qquad (3.3)$$

As illustrated in Fig. 3.22 there was a minor resonance which developed at ~4.4 ppm during the acetoacetylation which was not pronounced in the unmodified Kraft lignin. While the

determination was concerned with the acetoacetyl methyl groups which could be observed at ~2.1 ppm, this quantification method included adding an internal standard (nitromethane) which happened to partially overlap with the new peak at 4.4 ppm. To correct for background resonance signals in the modified lignin structure, the region assigned to the standard (4.4 ppm) was integrated before and after addition of the standard with the former subtracted from the latter in the determination as implied by Equation 3.3.

The modified Kraft lignin (Indulin AT) was determined to contain approximate functionality of 2.0 mol/kg of acetoacetate ester previously.[1] The same data was used for the current determination of 2.2 mol/kg acetoacetate, and are considered to be in close agreement. The observed variance was very susceptible to modulation by slight alterations in the phasing of NMR spectra. In future experiments, this type of uncertainty will be combated by utilization of multiple internal standards, and an expansion in the spectral width do decrease the curvature of an NMR phenomenon known as the smile.

Grafting of some *tert*-butyl acetoacetic esters to the macromolecular network could be quantified by the peak observed at 1.4 ppm (Fig. 3.22). A slight modification to Equation 3 afforded Equation 3.4 which described the molal concentration of *tert*-butylacetoacetate functionality grafted to the modified lignin by its active methylene. The determined molal concentration of methylene-grafted acetoacetate functionality (0.16 mol/kg) should be subtracted from the total acetoacetate functionality determined by acetoacetic methyl groups since they would be much less reactive in cross-linking reactions.

The corrected determination of cross-linkable acetoacetate functionality in Kraft lignin thusly modified was 2.00 mol/kg which agrees with the literature reported value.[1] The aforementioned modification to Equation 3.3, included substitution of the averaged regional

integration around 1.4 ppm (equal to 0.75H, Fig. 3.22) for the integration of aggregated acetate methyl groups around 2.2 ppm. The averaging of the signals was necessary due to variance caused by differences in phasing which could not be homogenized because the height of the internal standard peak was so much greater than the analyte peak. Substitution of targeted species also required a correction in the stoichiometric ratio between the internal standard signal (expected 3H per mole) and the *tert*-butyl ester (expected 9H per mole).

$$\text{Molality}_{\text{AcAcOtBu}} = m_{\text{AcAcOtBu}} = \frac{\text{AcAcOtBu}_{\text{mole}}}{\text{Modified Lignin}_{\text{kg}}}$$

$$= \frac{\left(\frac{\text{Mass}_{\text{NO}_2\text{Me(g)}}}{\text{Molar Mass}_{\frac{\text{NO}_2\text{Me(g)}}{\text{NO}_2\text{Me(mole)}}}}\right)_{\text{NO}_2\text{Me(mole)}} \times \left(\frac{\text{AcAcOtBu}_{\text{integration}}}{\text{NO}_2\text{Me}_{\text{integration}} \times 3}\right)_{\frac{\text{AcAcOtBu}_{\text{mole}}}{\text{NO}_2\text{Me}_{\text{mole}}}}}{\left(\frac{\text{Sample Mass}_{\text{g}}}{1000_{\frac{\text{g}}{\text{kg}}}}\right)_{\text{kg}}}$$

$$= \frac{\left(\frac{0.0152_{\text{NO}_2\text{Me(g)}}}{61.04_{\frac{\text{NO}_2\text{Me(g)}}{\text{NO}_2\text{Me(mole)}}}}\right)_{\text{NO}_2\text{Me(mole)}} \times \left(\frac{0.75}{(10.0 - 0.92) \times 3}\right)_{\frac{\text{AcAcOtBu}_{\text{mole}}}{\text{NO}_2\text{Me}_{\text{mole}}}}}{\left(\frac{0.0428_{\text{g}}}{1000_{\frac{\text{g}}{\text{kg}}}}\right)_{\text{kg}}}$$

$$= \frac{(0.000249)_{NO_2Me(mole)} \times (0.0275)_{\frac{AcAcOtBu_{mole}}{NO_2Me_{mole}}}}{(0.0000428)_{kg}} = 0.16_{\frac{AcAcOtBu_{mole}}{Modified\ Lignin_{kg}}} \quad (3.4)$$

Rising viscosity during the reaction as solvent was removed by distillation resulted in the peaks appearing at 0.9 ppm (Fig. 3.22) which have been attributed to incorporation of *tert*-butanol into the lignin network as *tert*-butyl ethers *via* trapping of benzylic-carbeniums or quinone methides. Again, these peaks were utilized to quantify the degree of *tert*-butyl ether formation: Equation 3.5. The molal concentration of *tert*-butyl ethers in acetoacetylated Kraft lignin was determined to be 0.50 mol/kg. This brought the total degree of lignin functionalization to 2.7 mole/kg.

According to the results of model compound experiments, during the two-h reaction period, circa 90% of primary aliphatic hydroxyls should have underwent modification (Fig. 3.17) and circa 66% of benzylic hydroxyls should have been modified (Fig. 3.18) and around 16% of the phenolics should have converted (Fig. 3.19). The expected hydroxyl content of (Indulin AT) Kraft lignin was about six mol/kg with about half of those attributed to phenols.[17] The non-phenolic hydroxyls were expected to be an even distribution of aliphatic and benzylic hydroxyls. This leads to a roughly predicted acetoacetate molality of 2.8 kg/mol. The results determined by the quantitative NMR results (2.7 kg/mol lignin modification) were in close agreement with the prediction generated from model compound experiments.

$$\text{Molality}_{\text{OtBu}} = m_{\text{OtBu}} = \frac{\text{OtBu}_{\text{mole}}}{\text{modified lignin}_{\text{kg}}}$$

$$= \frac{\left(\frac{\text{mass}_{\text{NO}_2\text{Me(g)}}}{\text{molar mass}_{\frac{\text{NO}_2\text{Me(g)}}{\text{NO}_2\text{Me(mole)}}}}\right)_{\text{NO}_2\text{Me(mole)}} \times \left(\frac{m_{\text{OtBu}_{\text{integration}}}}{\text{NO}_2\text{Me}_{\text{integration}} \times 3}\right)_{\frac{\text{OtBu}_{\text{mole}}}{\text{NO}_2\text{Me}_{\text{mole}}}}}{\left(\frac{\text{sample mass}_{\text{g}}}{1000_{\frac{\text{g}}{\text{kg}}}}\right)_{\text{kg}}}$$

$$= \frac{\left(\frac{0.0152_{\text{NO}_2\text{Me(g)}}}{61.04_{\frac{\text{NO}_2\text{Me(g)}}{\text{NO}_2\text{Me(mole)}}}}\right)_{\text{NO}_2\text{Me(mole)}} \times \left(\frac{2.32}{(10.0 - 0.92) \times 3}\right)_{\frac{\text{OtBu}_{\text{mole}}}{\text{NO}_2\text{Me}_{\text{mole}}}}}{\left(\frac{0.0428_{\text{g}}}{1000_{\frac{\text{g}}{\text{kg}}}}\right)_{\text{kg}}}$$

$$= \frac{(0.000249)_{NO_2Me(mole)} \times (0.0852)_{\frac{\text{OtBu}_{mole}}{NO_2Me_{mole}}}}{(0.0000428)_{kg}} = 0.50_{\frac{OtBu_{mole}}{modified\ lignin_{kg}}} \quad (3.5)$$

3.3.4. Refined Acetoacetylation Protocol

Since the conditions required for complete functionalization of either benzylic or phenolic hydroxyls were determined to be mutually exclusive, this method of technical lignin functionalization provides an interesting opportunity to create a diverse family of resins by simply

modulating the reaction timespan. An additional avenue of interest lies in exploring different swelling agents which could be incorporated into the network as reactive diluents or recycled. Indeed, the use of excess *tert*-butanol seems an excellent starting point due to its generation in the reaction mixture and preferred status as a safe solvent as compared with 1,4-dioxane.[47]

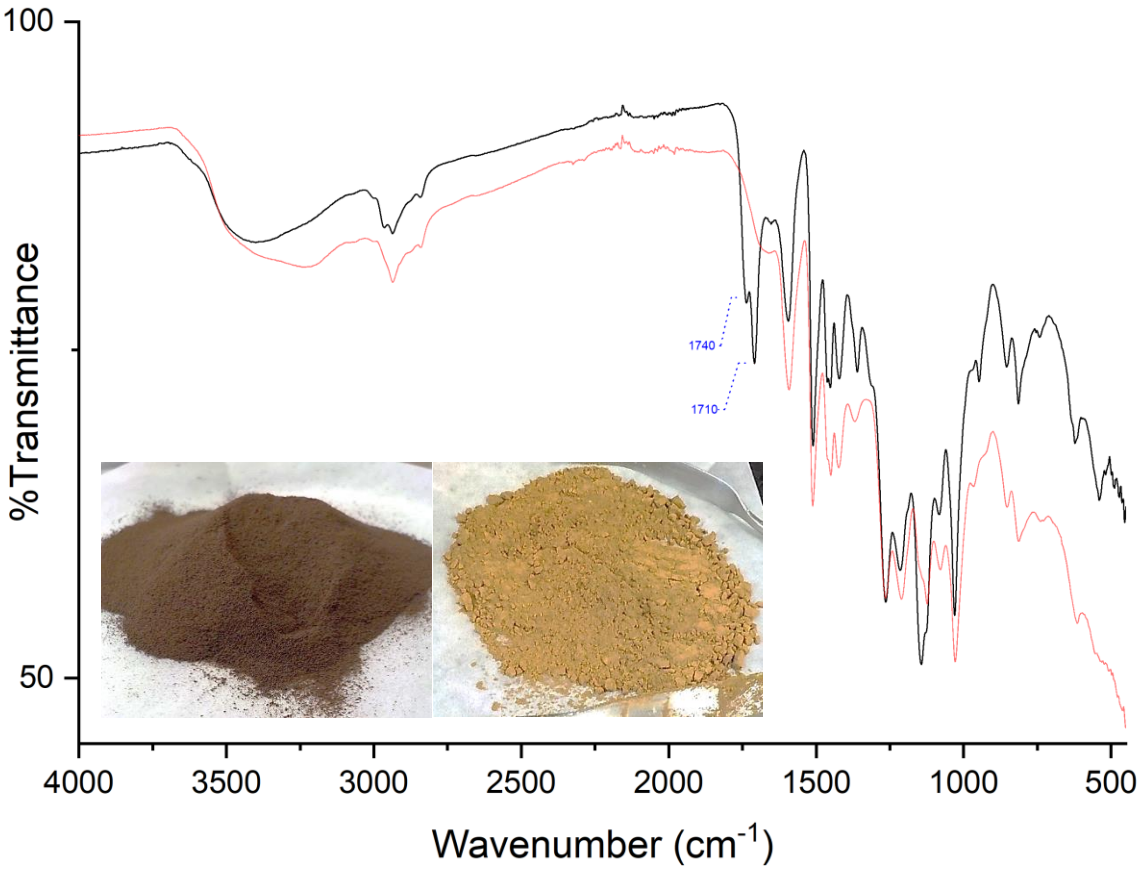


Fig. 3.23. Kraft lignin (Indulin AT, Ingevity) before (left) and after (right) acetoacetylation treatment by *tert*-butanol swelled acetoacetylation of (Indulin AT) Kraft Lignin (FTIR in Black). (Indulin AT) Kraft Lignin (FTIR in red)

When (Indulin AT) Kraft lignin was treated with TBAA in the presence of *tert*-butanol as cosolvent, a vitreous resin was again afforded which could be purified to afford a light tan solid by isopropanol-sonication. The developed method for lignin modification afforded product with lighter color than the starting materials (Fig. 3.23) and should be applicable to a variety of technical

lignins. FTIR analysis indicated acetoacetylation by appearance of the twin carbonyl-stretch frequencies at 1740 and 1710 cm^{-1} (Fig. 3.23).

3.3.5. Chapter Conclusions

The most widely available type of lignin derived from the paper pulping industries, Kraft lignin (Indulin AT), was acetoacetylated in a chemoselective fashion by an uncatalyzed reaction with *tert*-butyl acetoacetate. The amount of cross-linkable acetoacetate functionalization was determined to be 2.0 mol/kg resulting from a modest 3 h reaction time and mild workup. Quantitative NMR facilitated determination of a total functionalization of 2.7 mol/kg out of approximately 6 mol/kg possible.

Model compounds were used to facilitate interpretation of which hydroxyl environments in lignin were functionalized and to validate a quantification protocol which considered new resonances in the ^{1}H NMR spectrum to be solely attributable to incorporation of acetoacetate moieties. Out of 2.8 mol/kg predicted by preliminary experiments with select lignin model compounds determined results of 2.7 mol/kg lignin functionalization were very promising. While there was some difficulty encountered in adapting established acetoacetylation protocols, a satisfactory method for directly acetoacetylating lignin with no strenuous purification and minimal cosolvent was established which allowed for isolation of modified material in powder form. This technique was extended to include use of recycled *tert*-butanol as cosolvent.

Interpretation of model compounds under the conditions of acetoacetylation suggested that primary and benzylic hydroxyls reacted very rapidly. However, prolonged heating resulted in benzylic acetoacetate decomposition. Phenolic hydroxyls were acetoacetylated at a much slower rate than aliphatic hydroxyls. When phenolic hydroxyls were substituted *para* to benzylic hydroxyls, there was likely quinone methide intermediacy.

The neat reaction conditions employed during the study of liquid-model compounds suggests that any solubilized lignin could be directly acetoacetylated by this protocol; currently investigations into additional benign cosolvents such as *tert*-butanol or glycerol are underway. Further improvements to the quantitative analyses developed herein are also underway. Findings from these studies and the techniques described herein are currently being employed to inform the formulation of a family of bio-based organic thermoset coatings derived from catalyst free modification of technical lignins.

3.4. Experimental

3.4.1. General Methods

Unless otherwise stated, all commercially procured materials were used as received without further purification. Mass measurements of all reagents, substrates and reaction aliquots were determined on by an Accuris Analytical Series Balance. Melting points were collected on a REACH Devices RD-MP digital melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were collected on a Bruker Avance 400 MHz instrument and processed with Topspin software; Peak shifts were calibrated based on residual solvent peaks. Infrared spectra were collected with a Nicolet™ iS™ 10 FTIR Spectrometer using a diamond sample plate for ATR and processed using Omnix. High Resolution Mass Spectra were collected on Waters Synapt G2-Si high definition mass spectrometer and were processed using MassLynx. All reactions were stirred magnetically with PTFE coated magnetic spinning stir-bars unless otherwise stated. All mention of silica gel refers to Sorbtech standard grade silica gel: 230-400 mesh.

3.4.2. Acetoacetylation of (Indulin AT) Kraft Lignin

3.4.2.1. Acetoacetylation with 1,4-Dioxane cosolvent[1]

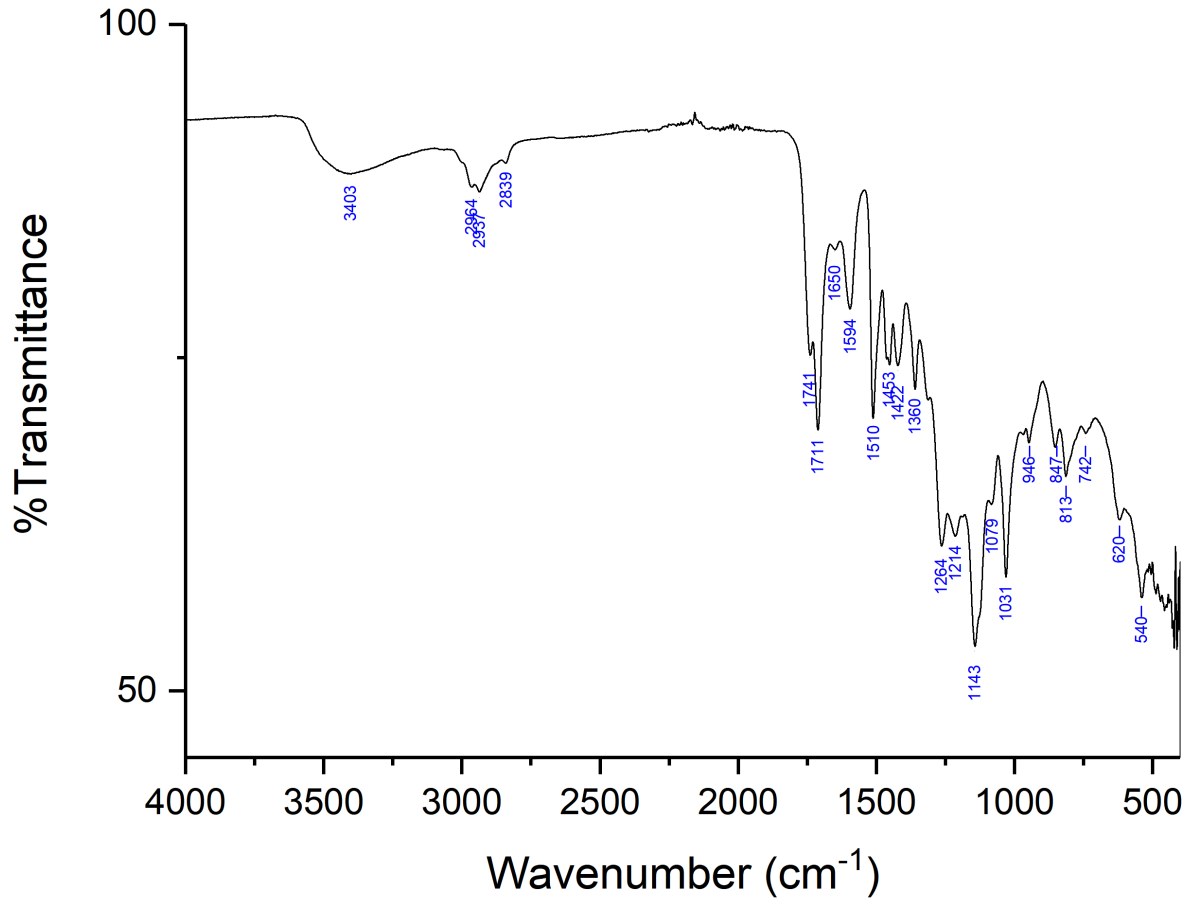


Fig. 3.24. Acetoacetylated (Indulin AT) Kraft lignin (washed with IPA and vacuum dried); FTIR (ATR, neat powder)

A 25 mL single neck round bottom flask (14/20) was charged with Kraft lignin (Indulin AT, provided by Ingevity (formerly MeadWestvaco) 2.500 g), 1,4-dioxane (7.5 g), and *tert*-butyl acetoacetate (provided by Eastman Chemical Company, 2.454 g). The flask was fitted beneath a short path distillation apparatus. The reaction was heated in a 130 °C oil bath with nitrogen sparging through the dark reaction mixture. Several aliquots were collected during the reaction mixture for analysis by ^{1}H There was significant difficulty encountered in removing aliquots during the acetoacetylation reaction as the dioxane was removed by distillation and the viscosity

of the black liquid resin increased. The reaction was aged open in a well-ventilated fume hood for 6 weeks. A portion of the vitreous black residue (1.490 g) was chipped out of the flask and triturated with isopropyl alcohol. A fine tan solid was isolated by suction filtration and vacuum drying to afford a free flowing brown solid (1.169 g). That solid was analyzed by quantitative ^{1}H spectroscopy, ^{13}C spectroscopy, and FTIR (Fig. 24); there was clear evidence of acetoacetate ester grafting at 1741 and 1711 cm^{-1}.

3.4.2.2. Acetoacetylation with tert-Butanol as Cosolvent

A 100 mL round bottom flask charged with Kraft lignin (Indulin AT, supplied by Ingevity, 3.024 g of dark brown powder) was charged into the flask. Solvent for the reaction, *tert*-butanol (5.922 g, approximately 36 mmol of hydroxyl) was added and the mixture became a slurry with obvious aggregate particles. TBAA (2.841 g, approximately 18 mmol) was added and dissolved into the reaction liquor. The reaction mixture was refluxed by heating in a 100 °C oil bath for 90 min under positive nitrogen pressure.

The reaction mixture still contained particulate, so an additional 8.182 g of *tert*-butanol was added. The mixture was returned to reflux for 120 min. This time upon cooling, a black tar-like resin formed on the lower layer of the flask while some particulate was still observed on the upper walls of the flask. A distillation head was installed between the reaction flask and condenser, then distillation was carried out with the oil bath set between 120 and 140 °C under positive nitrogen pressure. Heating of the reaction mixture was stopped ten min following the last observed drop of distillate.

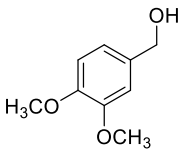
The mass of distillate (which crystallized on ice) was 11.275 g which equates to a recovery of 80% solvent! The powdery material coating the upper walls of the reaction flask was isolated from the bulk resin by rinsing it away with isopropyl alcohol (0.307 g). The bulk resin was slow

to dissolve in isopropanol and scraping the gooey mass of material was challenging, so the flask was charged with isopropanol then sonicated in a warm H_2O bath until the mixture had phase separated into brown powdery solid and dark brown solution.

The mixture was separated by suction filtration through a 1 cm Hirsch funnel with qualitative filter paper. The residue was rinsed copiously with isopropanol. The light tan solid was observed to weigh 2.174 g following vacuum drying. The theoretical yield was determined to be 4.843 g, if all 18 mmol of TBAA were incorporated as acetoacetic esters (mass addition equal to 1.819 g) into the original sample of Kraft lignin. The isolated yield of modified lignin was 45% of the theoretical maximum.

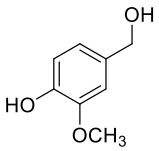
3.4.3. Preparation of Lignin Model Compounds

3.4.3.1. Veratryl Alcohol



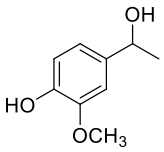
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88–6.68 (m, 3H), 4.48 (s, 2 H), 3.774 (s, 3H), 3.770 (s, 3H), 2.69 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 148.4, 133.7, 119.3, 111.0, 110.4, 64.93, 55.9, 55.8.

3.4.3.2. 4-(Hydroxymethyl)-2-methoxyphenol



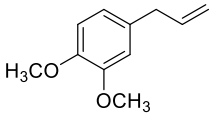
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J*=1.8 Hz, 1H), 6.86 (d, *J*=8.0 Hz, 1H), 6.81 (dd, *J*=1.8 Hz, 8.0 Hz, 1H), 5.59 (s, 1H), 4.57 (d, *J*=3.8 Hz, 2H), 3.87, (s, 3H), 1.58 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 145.5, 133.2, 120.4, 114.5, 110.2, 65.7, 56.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 6.88 (s, 1H), 6.75–6.65 (m, 2H), 4.98 (t, *J*=5.7 Hz, 1H), 4.37 (d, *J*=5.7 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.3, 145.3, 133.5, 119.1, 115.0, 111.0, 63.0, 55.5. Also known as vanillyl alcohol, supplied by Sigma Aldrich.

3.4.3.3. 4-(1-Hydroxyethyl)-2-methoxyphenol



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 6.90 (s, 1H), 6.79–6.73 (m, 2H), 4.95 (d, *J*=4.2 Hz, 1H), 4.67–4.56 (m, 1H), 3.75 (s, 3H), 1.29 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.2, 145.1, 138.5, 117.6, 114.9, 109.6, 68.0, 55.5, 26.0. Prepared by Catherine A. Sutton by reaction of vanillin with methyl magnesium bromide in THF solution. Yield unknown. Purified by flash column chromatography to afford a white crystalline solid.

3.4.3.4. 4-Allylveratrole or 3-(3,4-Dimethoxyphenyl)-1-propene[1]

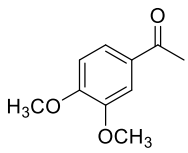


^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J*=8.64 Hz, 1H), 6.74–6.68 (m, 2H), 5.95 (dddd, *J*=6.68, 6.68, 10.08, 16.8 Hz, 1H), 5.13–5.02 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.32 (d, *J*=6.68 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 147.3, 137.6, 132.5, 120.3, 115.5, 111.8, 111.2, 55.76, 55.63, 39.7; FTIR (ATR) cm^{-1} 3017, 2935, 2833, 1637, 1591, 1511, 1464, 1258, 1233, 1139, 1027, 911, 849, 805, 766, 745, 644.

A 250 mL single neck round bottom flask was charged with eugenol (99%, Acros Organics, 16.788 g, 0.1022 mol, 1.0 eq.), anhydrous DMF (50 mL) and the light-yellow solution was warmed on an oil bath (40 °C preheated). Potassium carbonate (30.153 g, 0.218 mole, 2.13 eq.) was added to the stirring reaction mixture which took on a distinctive amber color and became green. Iodomethane (6.5 mL, 14.82 g, 0.104 mmol, 1.02 eq.) was added by syringe and the green color rapidly dissipated. The mixture was sealed with a yellow cap-plug and stirred on the warm bath for 17 h. The color of the reaction mixture darkened significantly upon standing. The heterogeneous slurry was poured over ice (400 mL). The mixture was stirred as the ice melted and was partitioned in a 1 L separatory funnel with diethyl ether.

The ethereal solution (250 mL light gold colored) was isolated, and the aqueous mixture (400 mL of brown colloidal mixture) was extracted with additional ether (2 × 100 mL). The golden yellow ethereal extracts were combined, backwashed with H_2O (2 × 100 mL), then once with saturated sodium chloride solution (100 mL). The organic solution (350 mL) was dried (sodium sulfate) and concentrated by rotary evaporation under reduced pressure. The mass of crude residue was 20.53 g of brown solution. The mixture was adsorbed onto silica gel and purified by flash chromatography. The very significant major eluate peak's fractions were combined and concentrated to afford 17.88 g (98%) of colorless oil.

3.4.3.5. 4-Acetylveratrole or 1-(3,4-dimethoxyphenyl)ethanone[1]



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J*=2.04, 8.32 Hz, 1H), 7.44 (d, *J*=1.96 Hz, 1H), 6.80 (d, *J*=8.36 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 148.9, 130.4, 123.2, 110.0, 109.9, 56.0, 55.9, 26.1; FTIR (ATR) cm^{-1} 3002, 2938, 1669, 1586, 1510, 1415, 1262, 1078, 1019, 876, 807, 766, 568.

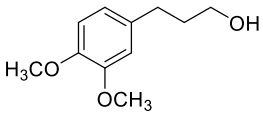
A 250 mL single neck round bottom flask was charged with apocynin (acetovanillone, 16.620 g, 100 mmol, 1 eq.) as a tan powder and anhydrous DMF (50 mL); the solution which formed was dark brown in color. The solution was capped with a yellow cap-plug and warmed on an oil bath (40 °C). Potassium carbonate (30.837 g, 228 mmol, 2.2 eq.) was added to the mixture but did not totally dissolve. The mixture was stirred for 40 min and iodomethane (6.5 mL, 14.82 g, 104 mmol, 1.04 eq.) was added to the warmed solution in a steady stream by syringe. The cap-plug was sealed into the neck of the flask. The reaction was stirred; within 10 min, the color of the solution had drastically lightened to a straw yellow. Within 2 min the mixture had thickened with

precipitate which continued to develop during the course of the reaction. The mixture was stirred on the warm oil bath for 17 h and was also observed to darken upon standing.

The reaction slurry was poured into a 400 mL beaker charged with ice. Upon contact with the ice, the color of the solution became tan. The contents of the flask were rinsed over with diethyl ether, and the mixture was stirred until the ice had melted then it was allowed to partition in a 1000 mL separatory funnel. The ethereal solution was isolated (300 mL), and the aqueous phase was extracted with additional ether (2 × 100 mL). The organic extracts were combined (500 mL), backwashed with distilled H_2O (2 × 100 mL) then saturated sodium chloride solution (100 mL) and the first wash took on a slightly pink color. The isolated organic solution (450 mL of amber color) was dried (sodium sulfate). TLC indicated predominately one motile spot with an orange residue at the baseline.

The combined extract solution was concentrated by rotary evaporation under reduced pressure. The residue was a brown oil with a mass of 15.48 g (85% crude yield). The residue was adsorbed onto silica gel and purified by flash chromatography. The very major eluate fractions were combined and concentrated to afford a clear and colorless viscous oil. The viscous oil was heated by heat gun to assist transfer to an Erlenmeyer flask. Upon cooling to room temperature, the residual material crystalized. The mass of the white crystalline material was 15.422 g: isolated yield of 85%. The melting point range of the white crystalline solid was 53.6–55.6 °C.

3.4.3.6. 3-(3,4-Dimethoxyphenyl)-1-propanol[1]



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82–6.67 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H) 3.65 (t, *J*=6.4 Hz, 2H), 2.64 (t, *J*=7.7, 2H), 1.93–1.77 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 147.3, 134.7, 120.3, 111.9, 111.4, 62.3, 56.1, 56.0, 34.5, 32.8; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (d, *J*=8.2 Hz, 1H), 6.78 (d, *J*=1.9 Hz, 1H), 6.68 (dd, *J*=2.0, 8.1

Hz, 1H), 4.43 (t, *J*=5.1 Hz, 1H) 3.73 (s, 3H), 3.70 (s, 3H) 3.4 (q, *J*=6.0 Hz, 2H), 2.53 (t, *J*=7.8, 2H), 1.69 (p, *J*=7.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 148.6, 146.8, 134.7, 120.0, 112.3, 111.9, 60.1, 55.5, 55.4, 34.5, 31.2; FTIR (ATR) cm^{-1} 3497, 3366, 2935, 1591, 1514, 1258, 1233, 1138, 1025, 807, 763.

A single neck round bottom flask was charged with 4-allylveratrole (17.88 g, 100.3 mmol, colorless oil) and was sealed with a white serum septum and flushed with nitrogen. To that oil was added THF (100 mL, HPLC grade), and the solution was stirred while chilling on an ice bath beneath an argon balloon. A disposable polypropylene syringe and 18 gauge stainless steel needle was used to draw up 50 mL of borane-THF complex (1 M solution in THF, stabilized with 5 mmol sodium borohydride), and that solution was added dropwise to the ice-cold 4-allylveratrole solution over 40 min. The mixture was stirred overnight as the ice bath thawed.

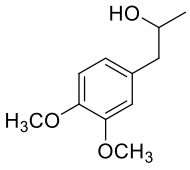
A solution of sodium hydroxide (2.49 g, 62.25 mmol, dissolved in 30 mL H_2O) was prepared. To the clear and colorless reaction mixture was added acetone (100 mL), and distilled H_2O (100 mL) followed by the alkaline solution; all additions were made by syringe under an argon balloon. The mixture was slightly turbid. Hydrogen peroxide (50 mL of 30% solution, EMD Scientific) was dispensed into a beaker, then drawn up into a syringe and added dropwise to the stirring reaction mixture. The reaction mixture became turbid during the addition of peroxide solution.

The oxidation was determined to be exothermic by observing the temperature of the outer wall of the flask with an infrared thermometer which rose from ambient to 33 °C. The H_2O was wiped from the flask which was transferred to an oil bath (preheated to 65 °C) and fitted with a tall West condenser. The mixture was refluxed for 1.66 h under atmosphere. The mixture was translucent, but upon resting partitioned to afford a clear upper layer. As the reaction mixture

stirred above the oil bath, a small amount of MnO_2 (~50 mg) was added bit by bit to destroy any residual hydrogen peroxide. The decomposition of hydrogen peroxide was exothermic, so the reflux condenser was reattached, and the mixture was stirred for 40 min. The silicone oil was cleaned from the flask with Hex, then the reaction mixture was concentrated by rotary evaporation under reduced pressure.

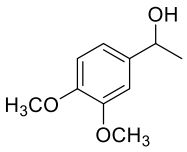
The concentrate was gravity filtered through a pad of Celite 545 filter aid into a 1000 mL separatory funnel. The filter was rinsed heavily with diethyl ether, then EtOAc. The filtrate was shaken then allowed to partition. The organic solution was isolated, the lower aqueous solution was extracted with 2 × 100 mL of EtOAc. The organic extracts were combined and backwashed with 100 mL of saturated sodium chloride solution in H_2O. The combined organic solution was isolated and dried (sodium sulfate) and concentrated by rotary evaporation under reduced pressure. Upon concentration, the clear colorless light oil had a mass of 18.60 g, or 95% crude yield. The mixture was purified by flash chromatography, and the major eluate fractions were combined and concentrated by rotary evaporation under reduced pressure to afford 15.84 g (81%) of clear, colorless oil which was characterized as a mixture of primary and secondary alcohol (10 mol%). The material was used as a mixture of regioisomers since preliminary experiment had indicated a similar reactivity between secondary and primary aliphatic alcohols under the conditions of neat acetoacetylation.

3.4.3.7. 1-(3,4-Dimethoxyphenyl)-2-propanol



1-(3,4-Dimethoxyphenyl)-2-propanol could be identified in the ^{1}H NMR spectrum but was not fully resolved while it was clearly resolved in the ^{13}C NMR spectrum; ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 147.9, 131.2, 121.5, 112.7, 111.5, 69.1, 56.1, 56.0, 45.5, 22.85.

3.4.3.8. 1-(3,4-Dimethoxyphenyl)ethan-1-ol[1]



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J*=1.9 Hz, 1H), 6.78 (dd, *J*=8.2, 1.7 Hz, 1H), 6.73 (d, *J*=8.2 Hz, 1H), 4.7 (q, *J*=6.4 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 2.68 (s, 1H), 1.38 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 148.2, 138.7, 114.5, 111.0, 108.7, 69.9, 55.9, 55.8, 25.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 (d, *J*=1.7 Hz, 1H), 6.87 (d, *J*=8.2 Hz, 1H), 6.83 (dd, *J*=1.7, 8.1 Hz, 1H), 5.02 (d, *J*=4.2 Hz, 1H), 4.71–4.59 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 1.30 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.0, 148.0, 140.6, 117.6, 112.0, 109.8, 68.3, 56.1, 55.9, 26.5; FTIR (ATR) cm^{-1} 3518, 2968, 2834, 1593, 1514, 1463, 1416, 1257, 1229, 1138, 1092, 1023, 860, 808, 764.

A 500 mL Erlenmeyer flask was charged with 4-acetylveratrole (14.421 g, 80 mmol, 1 eq.) with the aid of a heat gun, and the viscous oil began to crystalize on the inside of the flask upon cooling. Absolute EtOH was added, and the material was noted to fully crystalize (it lost all gooeyness) and resisted dissolution. The mixture was stirred for 5 min. The solid dissolve except for a few large chunks to afford a clear and colorless solution. Sodium borohydride (0.982 g 26 mmol, 32 mol%), was added as white granular solid without noticeable change. The flask was submerged in a room temperature H_2O bath and stirred under an argon balloon for 17 h.

Silica gel was added to the faintly hazy reaction solution while it stirred in a well-ventilated fume hood. As the silica gel was added, there was noticeable outgassing. When the slurry had stopped effervescing, it was transferred to a 500 mL single neck round bottom flask with the aid of 95% EtOH for concentration. The mixture was adsorbed onto silica gel by rotary evaporation under reduced pressure, then chromatographed by Combiflash: Hex/EtOAc. The very major fractions were combined and concentrated by rotary evaporation under reduced pressure to a

constant mass. The mass of the colorless oil which crystallized in the freezer but thawed at room temperature was 13.60 g, 74.62 mmol, 93% isolated yield.

3.4.4. Acetoacetylation of Lignin Model Compounds

3.4.4.1. General procedure for acetoacetylation of lignin model compounds[1]

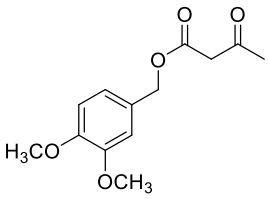
A 25 mL single neck conical flask was charged with substrate (4 mmol) and *tert*-butyl acetoacetate (4.4 mmol). The flask was fitted with a short path distillation apparatus built from a 75° side arm, Vigruex column (as an extension), a 105° vacuum take off adaptor, and a 100 mL single neck round bottom flask which was submerged in ice to freeze *tert*-butanol in the distillate. The top neck of the 75° side arm was sealed with a red rubber serum septum. Nitrogen was injected into the reaction mixture by modifying a nitrogen line (dried by passage through a column of indicated Drierite) with a disposable polypropylene syringe terminated by a long stainless-steel needle (20 gauge) which was inserted through the septum. The depth of the submerged needle below the surface of the reaction mixture was carefully set to avoid interference with the spinbar. The vacuum take-off was connected to an air-free bubbler. Nitrogen was bubbled through the reaction system as such for 20 min at a rate of circa 1 bubble/second.

An aliquot (~0.1 g, determined exactly by analytical balance) of the homogenous reaction solution was pulled and dispensed directly into a tared NMR tube (disposable polypropylene syringe and long stem stainless-steel needle: 20 gauge) for the initial (time =0 min) ^{1}H NMR. The stirring reaction mixture was lowered into a preheated (130 °C oil bath) and a stopwatch was started. Note: The reactions were completely thermally equilibrated with the oil bath (set to either 100 or 130°C) during the initial 5 min. Aliquots were pulled in similar fashion at regular intervals (with the spacing between increasing after the first h of the reaction) while the mixtures were heated, and *tert*-butanol was collected as white solid in the ice-chilled catch flask.

The aliquot charged NMR tubes were prepared for analysis by addition of ~30 µL of nitromethane (99% pure): actual mass determined by change in mass of the charged tube upon an Accuris Analytical Series Balance. To each tube was added roughly 0.6 mL of $CDCl_3$ (99.8 atom% D), the tubes were capped, and the mixtures were shaken to homogeneity. Initial experiments indicated that there was not a detectable change in a sample's mass during the course of the 3 h of the reaction.

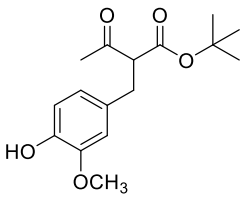
The standard proton experiment (Topspin command: rpar PROTON) was modified slightly (D1 =20 seconds, number of scans =8) to establish good agreement between the determined and known concentrations of the time =0 aliquots. As many species as possible were identified and quantified by relation to the internal standard: nitromethane to calculate weight percentages and molalities. Following 2 or 3 h of reaction, the mixtures were allowed to cool, and the products were isolated by flash chromatography for characterization (^{1}H and ^{13}C NMR, FTIR, HRMS).

3.4.4.2. 3,4-Dimethoxybenzyl 3-oxobutanoate



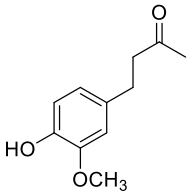
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J*=2.0, 8.0 Hz 1H), 6.87 (d, *J*=2.0 Hz, 1H), 6.82 (d, *J*=8.0 Hz, 1H), 5.09 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.46 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 167.2, 149.5, 149.2, 128.0, 121.6, 121.4, 112.0, 111.2, 67.4, 56.1, 50.3, 30.4.

3.4.4.3. Tert-butyl 2-(4-hydroxy-3-methoxybenzyl)-3-oxobutanoate



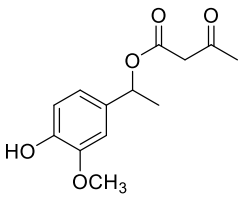
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J*=7.8 Hz, 1H), 6.69–6.59 (m, 2H), 5.46 (s, 1H), 3.83 (s, 3H), 3.61 (t, *J*=7.6 Hz, 1H), 3.01 (d, *J*=7.6 Hz, 2H), 2.15 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 168.6, 146.6, 144.4, 130.4, 121.7, 114.5, 111.7, 82.2, 62.8, 56.1, 33.9, 29.7, 28.1.

3.4.4.4. 4-(4-Hydroxy-3-methoxyphenyl)butan-2-one



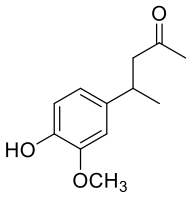
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J*=8.03 Hz, 1H), 6.67 (d, *J*=2.0 Hz, 1H), 6.64 (dd, *J*=2.0, 8.0 Hz, 1H), 5.48 (s, 1H), 3.85 (s, 3H), 2.80 (t, *J*=7.8 Hz, 2H), 2.71 (t, *J*=7.8 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 146.6, 144.1, 133.1, 121.0, 114.5, 111.2, 56.07, 45.75, 30.3, 29.7.

3.4.4.5. 1-(4-Hydroxy-3-methoxyphenyl)ethyl-3-oxobutanoate



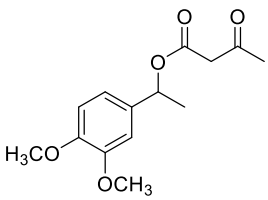
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92–6.79 (m, 3H), 8.85 (q, *J*=6.6 Hz, 1H), 5.61 (s, 1H), 3.88 (s, 3 H), 3.42 (s, 2H), 2.19 (s, 3H), 1.53 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 166.6, 146.7, 145.8, 133.0, 119.5, 114.5, 109.3, 73.7, 56.2, 50.6, 30.3, 22.0.

3.4.4.6. 4-(4-Hydroxy-3-methoxyphenyl)pentan-2-one



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J*=8.0 Hz, 1H), 6.71–6.65 (m, 2H), 5.57 (br s 1H), 3.85 (s, 3H), 3.21 (hex, *J*=7.0 Hz, 1 H), 2.70 (dd, *J*=7.0, 16.0 Hz, 1H), 2.60 (dd, *J*=7.7, 16.0 Hz, 1H), 2.04 (s, 3 H), 1.22 (d, *J*=6.9 Hz, 3H).

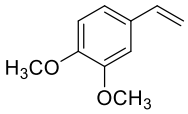
3.4.4.7. 1-Acetoacetoxy-1-(3,4-dimethoxyphenyl)ethane[1]



HRMS $[C_{14}H_{18}O_5Na]^+$ Calcd: 289.1052, Found: 289.1057; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, *J*=1.8, 8.2 Hz, 1H), 6.89 (d, *J*=1.9 Hz, 1H), 6.84 (d, *J*=8.2 Hz, 1H), 5.9 (q, *J*=6.6 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.45 (s, 2 H), 2.22 (s, 3 H), 1,56 (d, *J*=6.6 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 166.4, 149.0, 148.9, 133.4, 118.7, 111.0, 106.6, 73.4, 55.9, 50.4, 30.1, 21.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92–6.85 (m, 2H), 6.94 (d, *J*=1.6 Hz, 1H), 5.78 (q, *J*=6.6 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.60 (s, 2H), 2.15 (s, 3H), 1.46 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 202.0, 167.0,

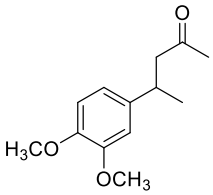
149.1, 148.9, 134.1, 118.7, 112.0, 110.4, 72.8, 56.0, 55.9, 50.2, 30.6, 22.3; FTIR (ATR) cm^{-1} 2935, 1736, 1712, 1517, 1256, 1233, 1141, 1064, 1024, 806, 765.

3.4.4.8. 1-(3,4-dimethoxyphenyl)ethene[1]



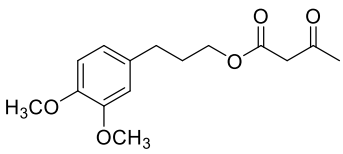
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0–6.9 (m, 2H), 6.82 (d, *J*=8.2 Hz, 1H), 6.65 (dd, *J*=10.9, 17.6 Hz, 1H), 5.61 (dd, *J*=0.8 17.6 Hz, 1H), 5.15 (dd, *J*=0.7, 10.9 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, *J*=1.8 Hz, 1H), 6.96 (dd, *J*=1.9, 8.3 Hz, 1H), 6.90 (d, *J*=8.2 Hz, 1H), 6.65 (dd, *J*=10.9, 17.6 Hz, 1H), 5.71 (dd, *J*=1.0, 17.6 Hz, 1H), 5.13 (dd, *J*=1.0, 10.9 Hz, 1H) 3.78 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.4, 149.3, 137.0, 130.6, 119.8, 112.36, 112.1, 109.5, 55.92, 55.89. Reportedly prepared and characterized by Mi *et al.* from 4-acetylveratrol by sodium borohydride reduction and acid catalyzed dehydration.[48]

3.4.4.9. 4-(3,4-Dimethoxyphenyl)-pentan-2-one[1]



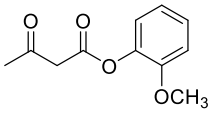
HRMS $[C_{13}H_{18}O_3Na]^+$ Calcd: 245.1154, found: 245.1164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J*=8.0 Hz, 1H), 6.8–6.7 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.26 (h, *J*=7.04 Hz, 1H), 2.73 (dd, J=6.6, 16.1 Hz, 1H), 2.63 (dd, *J*=7.8, 16.1 Hz, 1H), 2.06 (s, 1H), 1.25 (d, *J=7.0 Hz*, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 1149.0, 147.6, 139.0, 118.5, 111.4, 110.5, 56.03, 56.00, 52.4, 35.3, 30.8, 22.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.8–6.8 (m, 2H), 6.73 (dd, *J*=8.2,2.1 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.14 (h, *J*=7.0 Hz, 1H), 2.71 (dd, *J*=7.0, 14.2 Hz, 1H), 2.69 (dd, *J*=7.0, 14.5 Hz, 1H), 2.03 (s, 3H), 1.15 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 208.0, 149.1, 147.6, 139.4, 118.8, 112.3, 111.32, 56.0, 55.9, 51.5, 34.9, 30.6, 22.7; FTIR (ATR) cm^{-1} 2960, 1713, 1518, 1464, 1419, 1361, 1261, 1142, 1028, 809, 765.

3.4.4.10. 1-Acetoacetoxy-3-(3,4-dimethoxyphenyl)propane[1]



HRMS $[C_{15}H_{20}O_5Na]^+$ Calcd: 303.1208, Found: 303.1210; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72, (d, *J*=8.6 Hz, 1H), 6.72 (d, *J*=8.1 Hz, 1H), 6.71 (s, 1H), 4.16 (t, *J=6.7* Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.46 (s, 2H), 2.63 (t, *J*=7.6 Hz, 2H), 2.28 (s, 3H), 2.02–1.91 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6, 167.3, 149.0, 147.5, 133.7, 120.4, 111.9, 111.4, 64.8, 56.1, 56.0, 50.2, 31.7, 30.4, 30.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (d, *J*=8.1 Hz, 1H), 6.79 (d, *J*=2.0 Hz, 1H), 6.68 (dd, *J*=2.0, 8.0 Hz, 1H), 4.02 (t, *J*=6.5 Hz, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.60 (s, 2H), 2.55 (d, *J*=7.6 Hz, 2 H), 2.17 (s, 3H), 1.84 (p, *J*=7.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 202.1, 167.8, 149.1, 147.5, 134.0, 120.5, 112.4, 64.2, 56.0, 55.8, 50.0, 31.3, 30.6, 30.3; FTIR (ATR) cm^{-1} 2939, 1740, 1714, 1515, 1260, 1236, 1154, 1028, 809, 764, 542.

3.4.4.11. 2-Acetoacetoxyanisole[1]



HRMS $[C_{11}H_{12}O_4Na]^+$ Calcd: 231.0633, Found: 231.0646; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.19 (m, 1H), 7.07 (dd, *J*=1.6, 7.8 Hz, 1H), 7.01–6.93 (m, 2H), 3.83 (s, 3H), 3.69 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 165.33, 151.1, 139.5, 127.4, 122.8, 121.0, 112.6, 55.9, 50.0, 30.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (td, *J*=1.7, 7.8 Hz, 1H), 7.14 (dd, *J*=1.4, 8.3 Hz, 1H), 7.09 (dd, *J*=1.7, 7.9 Hz, 1H), 6.97 (td, *J*=1.4, 7.6 Hz, 1H), 3.85 (s, 2H), 3.77 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 201.3, 168.9, 151.2, 139.5, 127.7, 123.2, 121.1, 113.4, 56.2, 49.7, 30.4; FTIR (ATR) cm^{-1} 2946, 1760, 1717, 1606, 1500, 1309, 1255, 1196, 1134, 1109, 1042, 1024, 750, 511.

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4. ELABORATION OF CELLULOSE-DERIVED FURANICS

Lignocellulosic-biorefinery[1-3] has accelerated the development of sustainable materials science.[4-12] Investigations of renewable platform chemicals and their applications have a longstanding history with synthetic-organic chemists who seek simple and clear-cut preparations to facilitate the advancement of their work. Bio-sourced platform chemicals derived from cellulose offer exciting challenges due to their high oxygen content as compared to petroleum-sourced commodity chemicals. Consider the quintessential differences found in the comparison of furan and benzene. The evolution of industrial requirements necessitates exploitation of unique biomass-derived compounds which can be implemented in the creation of sustainable applications. The sustainability of such products can be realized especially when they are manufactured in an eco-friendly manner.

4.1. Furanic Platform Chemicals, Polymers and Furan-Dienes

Process challenges have throttled the scalable preparation and implementation of renewable furanics. Such challenges continue to stifle their contribution to the development of sustainable materials applications. The currently applied methods of scalable chemical processes sometimes lack the chemoselective precision necessary to further fuel strategic development. A diverse application-portfolio will be essential for the continued innovation and deployment of sustainable technologies. Those challenges additionally include disparities of feedstock contamination which are not adequately controlled by infant biorefineries but must be tolerated by nascent technologies to benefit from their fruition. Robust protocols are required which offer eco-friendly chemoselection[13] between multiple sites susceptible to competing transformations including oxidation, or reduction, or condensation.

4.1.1. Cellulose Derived Platform Chemicals

As discussed in chapter 1 of this dissertation, lignocellulosic biorefineries can offer various biobased feedstocks or platform chemicals to compete with or complement those derived from petroleum refineries.[14] Sustainable routes towards heteroatom containing materials with potential for biorenewability have been explored[15] as have *"chemical transformations of biomass-derived C6-furanic platform chemicals for sustainable energy research, materials science, and synthetic building blocks"*.[16] The following section will discuss promising furanic platform chemicals procurable through cellulosic biorefinery with great potential for continued development.

4.1.1.1. 5-(Chloromethyl)furfural

There are many valuable chemicals derivable from cellulosic biomass;[17] the importance of 5-(chloromethyl)-2-furancarboxaldehyde—*or 5-(chloromethyl)furfural (CMF)*—in preparing potentially profitable platform chemicals has been reviewed.[18] Among those are levulinic acid which is often a competitive byproduct of aromatic aldehyde synthesis from saccharide precursors; indeed, most of the significant obstacles to commercialization of cellulose biorefinery technologies can become unlocked by their chemoselective preparation in sustainable fashion. The main advantage of CMF over HMF lies in its hydrophobicity which facilitates preparation in highly selective fashion by partitioning away from an acidic aqueous reaction mixture.

Hydrophobic intermediates such as 5-(halogenomethyl)furfurals have been prepared from HMF,[19] directly from saccharides,[20-25] and from wood.[26, 27] Halogenomethylfurfurals have been investigated as high value intermediates in the preparation of sustainable biofuels.[28, 29] Mascal and Nikitin (2009) reported *"dramatic advancements in the saccharide to 5-(chloromethyl)furfural conversion reaction"*.[30] CMF has found application in the *"synthesis of natural herbicide δ-aminolevulinic acid"*,[31] conversion into the *"blockbuster antiulcer drug ranitidine (Zantac)"*,[32]

"synthesis of insecticide Prothrin and its analogues",[33] and in the preparation of bioderivable η^3-fufuryl complexes with palladium.[34] CMF has been developed as a sustainable source of the biofuel[35] and major biobased terephthalic acid precursor[36]—*2,5-dimethylfuran*.[37, 38] CMF can be transformed into 5-(chloromethyl)furan-2-carboxoyl chloride by reaction with *tert*-butyl hypochlorite.[39]

4.1.1.2. 5-(Hydroxymethyl)furfural

HMF has also been termed: (1) 5-(hydroxymethyl)furfural, (2) 5-(hydroxymethyl)-2-furancarboxaldehyde, and (3) 5-(hydroxymethyl)furan-2-carbaldehyde. Functionally rich HMF[40-44] has been prepared from tandem depolymerization/dehydration[45] of cellulosic-biomass[46-48] and also directly from monosaccharides.[49-60] The early history of HMF preparation appeared in the German language literature in the late 1890's–1900's and was clarified by Reichstein (1926) in combination with his preparation of 5-(hydroxymethyl)-2-furoic acid (HMFA).[61] Purified by vacuum distillation, Reichstein obtained 16 g of HMF from processing 200 g of cane sugar. The single greatest barrier to commercialization of HMF as a platform chemical is its preponderance for side reactions such as the formation of humins.[62]

Depolymerization of cellulose and isomerization of glucose into fructose is required prior to dehydration in the prevailing mechanism for HMF genesis. A mixture of glucose or starch in H_2O with weak acids and bases was found by Mednick (1961) to facilitate both the isomerization and dehydration reactions to greater overall effect than acid alone.[63] These combined phenomena indicate the disparate nature of the overall sequence which continually challenge the production of HMF directly from cellulosic biomass.

The greatest benefit afforded by CMF production *versus* HMF production lies in their relative partitioning behavior which has been investigated.[64] With the proper phase-modifiers, the

selectivity for aromatic aldehyde products following dehydrative-aromatization in HMF production can be significantly enhanced. Binder and Raines (2009) examined the use of the polar aprotic solvent *N*,*N*-dimethylacetamide modified with lithium chloride with a series of catalysts and additives in the *"transformation of lignocellulosic biomass into furans for fuels and chemicals"*.[45] Isolation of 5-(acetoxymethyl)furfural (AMF) transcends the matter of HMF's H_2O solubility and poor partitioning characteristics.[65]

HMF's H_2O solubility has created many process challenges leading to a relative dearth of commercialization in contrast to hemicellulose-derived furfural.[66] The greater H_2O solubility of HMF as compared with furfural can be attributed to its hydroxymethyl moiety. While both compounds have been investigated as toxic biproducts detected in lignocellulosic hydrolysate,[67] the presence of the hydroxymethyl moiety allows HMF to maintain H_2O solubility and provides a handle for biotransformation.

One company of note, AVA-Biochem of Switzerland, has commercialized a hydrothermal processing technology to convert hexoses to HMF.[68] Their process is conducted in aqueous solution, but the product can be refined into crystalline and even food grade material. This optimized technology has allowed scaleup and diversification of derivative chemistries as it exerted a stabilizing influence on the supply stream. As such it was important to adapt the transformations and activities described in this chapter from chromatographically pure laboratory preparations of HMF to tolerate commercially available supplies.

4.1.1.3. Working with Commercially Available HMF

The typical procedure for purification of 95% grade HMF included decolorization with activated carbon and took advantage of the differential solubility of HMF in diethyl ether as compared with a reddish goo which clung to anhydrous sodium sulfate and could thereby be

isolated from the refined HMF by filtration through a pad of filter aid. Concentration of the light yellow ethereal solution followed by crystallization in a freezer afforded purified HMF. HMF purified thusly was stable for a period of months when stored below room temperature.

The commercially available material could, of course, be purified by flash column chromatography.[69] In fact when it was, the recovered mass of HMF was 94% of the input mass which closely matched the HPLC trace reported for the 95% purity assay of HMF supplied by AVA Biochem. The only isolated eluate besides the very major HMF was identified as 2-furfuryl alcohol by ^{1}H NMR and equated to 2% of the total input mass. When the purified HMF was stored on the bench under argon but not protected from light, the yellow crystalline solid developed a red oil on its surface in a matter of weeks. The HMF purified by decolorization and treatment with sodium sulfate could be stabilized by storage of the solution in HPLC grade THF or HPLC grade acetone beneath inert atmosphere and protected from light. In this way, convenient stock solutions could be prepared for working with the deliquescent HMF during humid summer months. Complete descriptions of these practices have been included in the experimental section of this chapter.

4.1.1.4. 2,5-Bis(hydroxymethyl)furan

Strangely, Finan (1963) noted the *"convenient preparation"* of 2,5-bis(hydroxymethyl)furan (BHMF) from 5-(acetoxymethyl)-2-furoate or its methyl ester by lithium aluminum hydride reduction, followed by *in situ* acetylation to provide 2,5-bis(acetoxymethyl)furan (BAMF). Finally by a deacetylation step, BHMF was procured in high purity and that was deemed superior to the previously reported syntheses of BHMF from HMF;[70] accessing methyl 5-(acetoxymethyl)-2-furoate required the synthesis of methyl 5-(chloromethyl)-2-furoate and its use in the alkylation of sodium acetate in acetic acid. The author's preference for

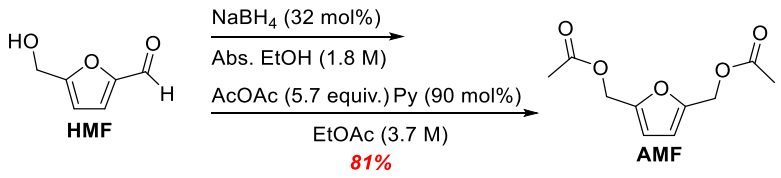
this seemingly convoluted method can be understood when considering the process challenges encountered while working with the (hydroxymethyl)furan moiety and in general when working with biomass derived compounds of suspect origin or purity. The well-defined stepwise approach offered multiple check-points wherein recrystallization or vacuum distillation could be readily employed while many of the intermediate steps were close to quantitative in conversion.

Timko and Cram (1974) prepared 2,5-bis(hydroxymethyl)furan from HMF—*presumably in EtOH*—by sodium borohydride reduction in 92% yield; the note is lacking in detail although HMF was prepared from sucrose in 41% isolated yield.[71] They went on to prepare 2,5-bis(chloromethyl)furan and from there to prepare cyclic oligoethers. Their HMF was prepared from sucrose and oxalic acid in aqueous solution and resulted in a 41% yield which compared favorably with the optimal yield (54% based only on fructose present in sucrose) reported by Haworth and Jones (1944).[72]

Cottier, Descotes, and Soro (2003) utilized BHMF derived diallyl ethers to prepare heteromacrocycles by ring-closing methathesis;[73] that chemistry required reaction of BHMF with sodium hydride and subsequent reaction with allyl bromide by a Williamson ether synthesis in a mixture of THF and dimethyl sulfoxide as solvent. Ring-closure was affected by exposure of olefin containing furanic-diethers to a benzylidene ruthenium complex under high dilution. Their preparation of BHMF began with HMF derived from dehydration of fructose or inulin and was carried out in MeOH (1 M) with a large excess of sodium borohydride (two molar equivalents). The reaction was reportedly complete in 15 min at 4 °C, and the resulting mixture was neutralized by addition of hydrochloric acid (2 M) to destroy polyborate species generated during the reduction. Following extraction (EtOAc) and flash column chromatography (DCM and EtOAc as eluents), a 97% isolated yield of white solid BHMF was achieved.

4.1.1.5. Improvements in the Preparation of BHMF and Derivatives

Several modifications were made by EMS during investigations into the reactivity of 2,5-bis(acetoxymethyl)furan (BAMF) as a furan-diene—*see chapter 5 of this document for details of those experiments*—and in the preparation of biobased poly(silyl ether)s. In the course of those studies,[74, 75] improvements to the sustainability and convenience of BHMF preparation from HMF were made without sacrificing yield and can be summarized as: (1) substitution of EtOH for MeOH as the reduction solvent, (2) limiting the amount of excess sodium borohydride from two molar equivalents to 30 mol%, and (3) replacing the acidification by hydrochloric acid and concomitant liquid-liquid extraction with adsorption onto amorphous silica gel followed by solid phase extraction.

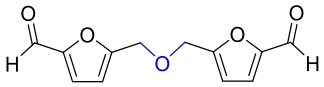


Scheme 4.1. Preparation of BAMF from HMF

Taking a leaf from the book of Finan[70] as illustrated in Scheme 4.1 and detailed in the experimental section of this chapter, HMF was reduced by action of sodium borohydride (32 mol%) in absolute EtOH (1.8 M). The reaction mixture was concentrated, diluted with EtOAc (3.7 M), acetic anhydride (5.7 eq.) and pyridine (90 mol%) at ambient temperature. BAMF was isolated by pouring the acylation mixture over H_2O ice with vigorous hand stirring. Creamy yellow solid was isolated (81% over two steps) which was NMR pure and suitable for use in the Diels-Alder reactions with benzyne. This preparation required no flash column chromatography or solid phase extraction.

4.1.1.6. 5,5'-[Oxybis(methylene)]di(2-furaldehyde)

Chundury and Szmant (1981) described the use of HMF and CMF in the preparation of polymer building blocks.[76] These two materials were themselves considered to be relatively unstable despite their high yielding synthetic preparation, but were effectively stabilized by dimerization in various fashions to afford suitable monomers of practical importance. OBMF was prepared from sucrose, fructose and HMF with isolated yields ranging from 17–76%; reactions occurred in dimethyl sulfoxide mediated with boron trifluoride etherate and were worked up by continuous liquid-liquid extraction (cyclohexane for eight days).



5,5'-[Oxybis(methylene)]di(2-furaldehyde)

OBMF

Fig. 4.1. 5,5'-[Oxybis(methylene)]di(2-furaldehyde) (OBMF)

Musau and Munavu (1987) described the preparation HMF (92%) and OBMF (1%) using fructose with a highly acidic ion-exchange resin in the presence of dimethyl sulfoxide.[77] The yield of OBMF was substantially increased (to 30%) by substituting toluene for DMSO and boron trifluoride etherate. Alkylation by nucleophilic solvent presents a significant challenge when working with acidic ion-exchange resins and benzylic or furylic alcohols.[78] Amarasekara, Nguyen, Okorie, and Jamal (2017) described the preparation of a FDCA analog derived from OBMF.[79] Beginning with fructose, and avoiding the isolation of HMF, their method employed DMSO and a highly acidic ion-exchange resin at 110 °C for 24 h to afford OBMF in 76% yield following aqueous workup with methyl *tert*-butyl ether as extraction solvent.

In our studies,[75] we have achieved yields consistently near 50% while we explored non-alkylating solvents such as chloroform and DCM. We have examined both the action of tosic acid and Amberlyst 15. While the methods explored—*see the experimental section of this chapter for*

full details—failed to increase the yield or sustainability of OBMF production, they were somewhat comparable to literature and did allow us access to this interesting substrate. Probably the greatest advantages to working with OBMF compared with HMF lie in masking the hydroxy functionality as an ether and in its crystallinity thereby making purification methods such as recrystallizing very effective; isopropyl alcohol was the preferred solvent for OBMF recrystallization.

4.1.1.7. Coupling of Diacyl Chlorides with HMF

Chundury and Szmant (1981) produced terephthalate- and isophthalate-linked dialdehydes by alkylation with *in situ* prepared 5-(iodomethyl)-2-furancarboxaldehyde in 85% yield.[76] That process capitalized on the advantageous preparation of CMF, however given a steady commercial supply of clean and dry HMF such as exists today, procedures for the acylation of HMF with activated dicarboxylic acid derivatives could prove fortuitous. While thionyl chloride confers multiple sustainability challenges when utilized in superstoichiometric amounts, the recycling of excess reagent for subsequent reuse has been established.[80]

There were no issues inherent to the reactivity of (hydroxymethyl)furan or furfuryl moieties with acid anhydrides as observed in the cases of 2,5-bis(acetoxymethyl)furan (*vide supra*) and 5-(acetoxymethyl)furfural (*vide infra*). The acyl transfer catalyst[81] DMAP was added to facilitate the reaction between furylic alcohols and acetic anhydride to wonderful effect; no inhibition of the catalyst was observed when acid anhydrides were the acylating agents employed. When acid chlorides were the acylating agent, triethyl amine was added to absorb the hydrochloric acid generated during the reaction which served to drive it to completion and to protect the furanic-products from degradation induced by strongly acidic conditions. Modular ester-linked dialdehyde

derivatives were prepared from condensation with biobased diacid chlorides and also with terephthaloyl dichloride—*see experimental section of this chapter for full details*.

Commercial HMF, freshly prepared adipoyl dichloride, DMAP, and triethyl amine when combined in diethyl ether (ambient temperature to reflux) afforded a tan powder slurry. Bis((5-formylfuran-2-yl)methyl) adipate (32 g, melting point of 97 °C) was expediently isolated from that slurry by diluting the reaction mixture with H_2O ice followed by concentration by rotary evaporation under reduced pressure, suction filtration with cold H_2O washing, and air drying. The material isolated accounted for 78% of the theoretical yield and was identified as the product by infrared spectroscopy, as well as ^{1}H and ^{13}C NMR spectroscopy. Purification of the product by flash column chromatography indicated that it was at least 96% pure and only slightly improved the melting point range: 98–101°C.

A few modifications were made to the procedure and bis((5-formylfuran-2-yl)methyl) glutarate was obtained (85% yield, melting point range of 93–95 °C). The modifications entailed: (1) use of purified HMF, (2) use of commercially available glutaryl chloride, (3) use of HPLC grade acetone as the reaction solvent, (4) the latent heat of the reaction was sufficient to complete it so no additional heating was supplied, (5) the reaction time was shortened to two h, and (6) use of 3 mol% DMAP as acyl transfer catalyst. Following those modifications, bis((5-formylfuran-2-yl)methyl) terephthalate was isolated in 94% yield, although the reaction mixture had to be diluted and heated to keep the intermediate products dissolved during the reaction.

4.1.1.8. 5-(Hydroxymethyl)-2-furancarboxylic Acid

In no small part due to the interest in an aromatic upgrade strategy,[82] there exists a growing movement towards bio-renewable AB type monomers[74] such as ethyl 5-(acetoxymethyl)-2-furancarboxylate.[83] Thus far, there have been few practical improvements to the facile laboratory

scale preparation of hydroxyacid platform chemicals since 5-(hydroxymethyl)-2-furancarboxylic acid (HMFA) was prepared from HMF by Reichstein (1926).[61] That protocol proceeded with good yield (84%) on a 100 mmol scale with vacuum distilled HMF as substrate. It required freshly prepared super-stoichiometric silver oxide in aqueous suspension with potential for silver recovery. The simple environmental factor (sEF) corresponding with that protocol has been calculated to be 5.2 which is not a bad score today for an emerging technology. That sEF indicates more than 5 g of waste would be produced for each 1 g of HMFA prepared by that method not counting solvents or H_2O. A reaction displaying similar results but requiring no coinage metals would be advantageous to the continued exploitation of biorenewable resources.

The base-mediated disproportionation of HMF into (BHMF) and (HMFA) provides a brilliant example of the Cannizzaro reaction which affords two highly desirable and separable products.[84, 85] Recent advancements include refined techniques to avoid discoloration endemic of alkaline treatment of HMF, and improvements to the sustainability of the process by excluding solvents during the disproportionation.[86] However, if only the hydroxyacid is considered as a desired product, then the maximum yield afforded by a dismutation strategy is severely limited to a theoretical 50%.

Alternatively, benign bio-enzymatic transformations have been investigated to afford sustainable, efficient and ecofriendly routes to HMFA.[87, 88] Yet, there are significant hurdles to the widespread adoption of bio-transformative technologies. Most laboratories currently outfitted for applications of novel biobased monomers lack capacity for the substantial investments of time, training, and infrastructure required to maintain a living-reactor. This limiting function excludes those labs from contributing to desirable innovation in sustainable materials science. The scalability of bio-reactors along with challenges associated with product isolation and treatment of

wastes from such technologies must be considered non-trivial. In addition, the many sensitivities of enzymes may include concentration (relative and absolute), denaturation by organic solvents, and substrate-specificities which can act in concert to preclude robust performance with a wide array of feedstocks.

Similar obstacles have been encountered in the development of chemo-catalytic routes to HMFA, which is often reported as a minor side product detected as an intermediate in the preparation of FDCA.[89, 90] Catalytic methodologies both *bio*- and *chemo*- will certainly contribute to sustainable industrial-scale productions once optimized product streams and consistent substrate quality have been realized. Development of those avenues must continue to be pursued. Meanwhile, immediate utilization of renewable furanics would benefit from a simple and benign process to procure high quality materials. The envisioned process tolerates a range of substrates while destroying their variable impurities and will be described in a later section (*vide infra*).

4.1.1.9. 2,5-Diformylfuran

The symmetric dialdehyde prepared from chemoselective oxidation at HMF's furylic hydroxyl functionality is known as 2,5-furandicarbaldehyde, or 2,5-furandicarboxaldehyde, or 5-formylfurfural or 2,5-diformylfuran (DFF). While both aldehyde moieties are equal in terms of reactivity as Lewis bases or as electrophiles, they are cross conjugated to the furan ring and exert a modest stabilizing effect on the lowest unoccupied molecular orbital. This translates to an enhanced electrophilic character overall with correspondingly greater reactivity towards nucleophiles as compared with the aldehyde of parent furfural or HMF. However, since the reactivity enhancement is an artifact of the mesomeric effect exerted independently upon the furanic nucleus and transmitted to the crossed aldehyde only by induction from the ring, reaction

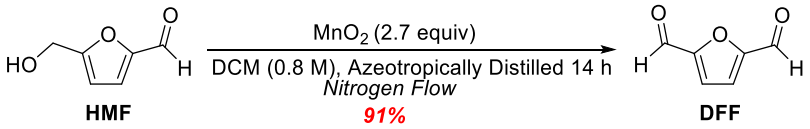
at one aldehyde immediately reverts the reactivity of the remaining aldehyde to essentially the same level as HMF.

The reactivity difference between the first and second aldehyde to react in DFF primes the system for desymmetrization reactions with greater selectivity for mono-reaction than could be described by a statistical distribution of products. This phenomenon was noted and capitalized upon when 5-(diethoxymethyl)furfural (68% isolated yield) from DFF was prepared by tosic acid catalyzed reaction with triethyl orthoformate in dry acetonitrile.[91] The extent of differential aldehyde reactivity in DFF was probed by combination of DFF with stoichiometric equivalents of stabilized phosphonium ylides.[92] Not surprisingly, the greatest selectivity was observed when the most stabilized phosphonium ylides—*those containing electron deficient substituents or extensive conjugation to an aromatic system*—were employed; all the phosphonium ylides investigated were quite stabilized as indicated by a complete preference for *E* alkylidene products: substantiated by ^{1}H NMR coupling constant analysis. The reactions were carried out in refluxing THF for one h and yields between 70–90% were observed.

Having discussed the curious chemistry conferred by DFF,[93] let us explore some potentially sustainable methods of its generation using the abundant metal manganese. HMF has been selectively oxidized to afford DFF by sodium hypochlorite catalyzed by manganese (III) salen catalysts.[94] The experiments were completed using an aqueous phosphate buffer (pH~11) and DCM to create a biphasic system at room temperature. The Mn(III)-salen with the best performance under the above stated conditions contained a rigid phenylene diamine linker in the backbone and afforded DFF in 89% yield as determined by gas chromatographic analysis.

The chemoselective oxidation of HMF to DFF (89% and 84% isolated yields) using MnO_2 (4 molar equivalents) in azeotropically distilling DCM or toluene under positive nitrogen pressure

has been reported by Vijjamarri, Streed, Serum, Sibi, and Du (2018).[75] Serum, Selvakumar, Zimmermann, and Sibi (2018) reported refinements to that technology as illustrated in Scheme 4.2.[95] Specifically, the stoichiometric excess of MnO_2 could be reduced without sacrificing the yield (91% isolated). The major challenges facing further development of MnO_2 oxidation technologies with biobased furanic substrates include: (1) use of superstoichiometric oxidant, (2) proper mixing of the heterogeneous reaction mixture upon scaleup, (3) reactions utilized hazardous[96] DCM as solvent which has been recommended for replacement,[97] (4) toluene is capable of alkylating the furylic-oxymethylene moiety while also capable of undergoing oxidation, and (5) the tedium and specialty glassware required for continuous delivery of solid oxidant.



Scheme 4.2. Preparation of DFF with minimal MnO_2

Manganese-iron mixed oxides (Mn_6FeO_x) have been developed as robust, reusable, and selective oxidants for.[12] This technology may address many of the stated issues to MnO_2 oxidation techniques: (1) Mn_6FeO_x is a catalyst which is regenerated by atmospheric oxygen, (2) scalability of the heterogenous system remains a challenge (typical scale reported was 126 mg HMF), (3) proscribed solvent, DMF, was used (0.2 M [substrate]), (4) DMF is hydrolytically unstable at high temperature which limits the potential for solvent recycling, and (5) the reactor employed must stand heating above 100 °C, while maintaining a positive pressure oxygen atmosphere, and vigorously mixing the heterogenous reaction.

4.1.1.10. 2,5-Furandicarboxylic Acid

Mucic acid also known as galactaric acid and 2,3,4,5-tetrahydroxyhexandioic acid can be dehydrated by action of hot hydrobromic acid to afford 2,5-furandicarboxylic acid (FDCA) or

dehydromucic acid as it was referred to by Hill (1901);[98] therein he related—*in English*—the early triumphs of FDCA production during the preceding 25 years from the German language literature. The dipotassium salt of saccharic acid, also known as glucaric acid, was deemed more accessible by Phelps and Hale (1901); its reaction in concentrated hydrobromic acid took less time and led to dehydromucic acid with greater purity and in higher yields.[99] Hill and Wheeler (1901) conducted early experiments in the reduction of dehydromucic acid.[100]

Oxidation of biorenewable HMF, either directly or through a variety of steps, is the chief strategy for preparing FDCA. The first "s*imple, clear cut, synthetic procedure for it"* transformed methyl 5-(acetoxymethyl)furan-2-carboxylate into FDCA in aqueous solution *via* nitric acid oxidation and was described by Gonis and Amstutz (1962) while they also related the state of FDCA art at that time.[101] Out of 100 g substrate, circa 55 g crude acid was obtained, and underwent Fisher esterification in MeOH mediated by sulfuric acid. Dimethyl 2,5-furandicarboxylate was purified by vacuum distillation, and upon saponification (10% aqueous sodium hydroxide) afforded a 35 g or 45% isolated yield of pure FDCA.

Moore and Bunting (1985) prepared a treatise on the preparation of isomeric furandicarboxylic acids and their implementation into polymeric materials such as polyamides and polyesters; highlights included descriptions of the earliest reports of poly(ethylene furandicarboxylate)s as well as a compendium of synthetic techniques for prepared monomers and polymers.[102] The large scale preparation of FDCA began with mucic acid (130 g, 0.62 moles) was accomplished by reaction with aqueous hydrobromic acid (48%, 330 mL) at reflux for two days. The black solid residue was isolated and ground with solid calcium carbonate, digested in boiling H_2O, then isolated *via* suction filtration. Following decolorization of the aqueous filtrate, the mixture was acidified by addition of concentrated hydrochloric acid, thus affording white solid

precipitate. The material was air dried, weighed 44 g (45% yield) and characterized by melting point analysis (325 °C), as well as IR and ^{1}H NMR spectroscopy.

There has been much recent activity in the field of HMF conversion to FDCA or a derivative thereof using advanced catalysis and atmospheric oxygen.[103-111] Another interesting technology has built a bridge between hemicellulose derived 2-furoic acid and cellulose derivable FDCA.[112] The method lacks optimization for sustainability, but nonetheless serves to strengthen the potential supply chain of FDCA; first 2-furoic acid is brominated in a mixture of carbon tetrachloride and acetic acid, then esterified prior to a palladium mediated carbonylation reaction which affords dimethyl 2,5-furandicarboxylate good overall yield.

FDCA has been conveniently prepared on the laboratory scale by potassium permanganate oxidation in alkaline aqueous media. On a 100 mmol scale, FDCA was prepared from commercially available HMF as received in 70% isolated yield with a simple environmental factor of 5.8 and a complete environmental factor of 252. The details of this preparation method have been included in the experimental section of this document while discussion of the result has been made in relation to chlorous acid oxidation—*vide infra.* FDCA (assayed greater than 80% pure) has also been acquired from AVA Biochem.

4.1.2. Biorenewable Furanic Polymers

Sustainable polymeric materials have defined modern technological development from prehistory and provided a great many societal benefits; prior to the petroleum revolution all plastics were biorenewable.[113] It seems like myriad routes to sustainable polymers derived from biorenewable materials not only exist but are readily accessed. In truth, a boggling degree of intricate study is required for what feels like the smallest of gain. As discussed by Zhang, del Rio-Chanona, and Shah (2017),[114] evaluation the productive and economic potentials connoted by

adoption of these technologies can only begin by considering a comprehensive reaction network covering polymeric material synthesis.

The general utilization of furans in polymer chemistry has been reviewed by Gandini and Belgacem (1997).[115] Goussé, Gandini, and Hodge (1998) related the prevalent application of Diels-Alder and *retro*Diels-Alder reactions in polymers containing furan-dienes in their backbone and as side chains.[116] Moreau, Begacem and Gandini (2004) detailed catalytic advances in the chemistry of biorenewable furans and their ensuing polymers.[117] Gandini (2010) updated the narration of sugar and polysaccharide derived furans and their antecedence to remarkable polymers.[118] A compilation of monomers and polymers from renewable resources was prepared by Gandini, and Lacerda (2015).[119]

Diacid substituted norbornenes have been used to prepare amorphous-unsaturated polyester resins which afforded degradable elastomeric thermosets upon treatment with radical initiators by Brown and Sheares (2007).[120] The low solids content of those thermosets could potentially be remedied by using newly developed benzyne and biorenewable furan-diene Diels-Alder adducts[74, 95] such as 7-oxabenzonorbornadienes due to the enhanced ring-strain imparted by fusion to a benzene ring.[121]

4.1.2.1. Polymers from HMF

Biobased furanic-diols derived from HMF—*including 2,5-bis(hydroxymethyl)furan, 5,5'-bihydroxymethyl furil, 5,5'-dihydroxymethyl furoin, and bis[5-(hydroxymethyl)furan-2-yl)methyl]adipate*—have been investigated in the preparation of linear and cross-linkable poly(ester)s as well as poly(ester-urethane)s by Mou and Chen (2016).[122] The simplest diol monomer—*2,5-bis(hydroxymethyl)furan*—was prepared by sodium borohydride reduction of HMF. The polyesters derived from fumaryl chloride and 2,5-bis(hydroxymethyl)furan underwent

self-curing by Diels-Alder cycloaddition between the electron deficient dienophilic olefin contained in the fumarate moiety and the electron rich furan-diene. Furil diol-monomers were prepared from furoin triol-monomers by chemoselective oxidation with MnO_2. Furoin monomers were in turn prepared directly from HMF in a self-coupling reaction mediated by an *N*-heterocyclic amine organocatalyst as described by Liu, Zhang, and Chen (2012).[123]

Described as a rigid diol building block, BHMF was incorporated it into the preparation of a series of biobased polyesters in an enzymatic synthesis.[124] Lipase acrylic resin from *Candida antarctica* Lipase B is commercially available under the trade name Novozyme 435 and required activation by drying under reduced pressure over phosphorous pentoxide for satisfactory polymerizations. A series of renewable diethyl esters were combined with lipase and diol monomer in diphenyl ether by a three stage method. Stage one included heating under nitrogen stream to 80 °C for two h. Stage two was executed by lowering the pressure inside the reactor to about 360 torr while maintaining the reaction temperature at 80 °C for four h. Stage three was accomplished by lowering the vacuum to 2 torr while maintaining the reaction temperature at 80 °C for sixty six h. The polymerization reaction was quenched by the addition of chloroform. The immobilized catalyst was isolated by filtration and rinsed heavily with chloroform, and the polyesters were precipitated by concentration *in vacuo* and infusion of MeOH. All the polyesters prepared thusly appeared as slightly yellow semi-crystalline powders. The modular nature of the diacid precursors not surprisingly were found to modulate the thermomechanical properties of the polyesters prepared thereof; most notably, the thermal stability of BHMF derived polyesters increased with increasing methylene linker spacing between carboxylate moieties.

Poly(silylether)s with potential for incorporation into biomedical applications have been prepared directly from HMF and several of its derivatives.[75] Such poly(silylether)s were prepared

using a benign manganese salen catalyst and shown to be degraded in predictable fashion relating to lowering the pH of the solutions. Incorporation into poly(silylether)s significantly increased the thermal stability of the furanic moiety.

Due to their electron rich character, these poly(silylether)s could be formulated into thermally remendable resins with maleimide crosslinkers by a Diels-Alder mechanism.[125] Diels-Alder and *retro*-Diels-Alder reactions of substituted maleimides and furan-dienes have been explored.[126] The reaction between simple maleimide and BHMF provided an *"efficient route for the construction of polycyclic systems"*.[127]

4.1.2.2. Polymers from HMFA

Moore and Kelly (1975) prepared 2-oxo-3,8-dioxabicyclo[3.2.1]octane and its corresponding polyester in the first ring-opening polymerization of a bicyclic lactone containing the THF nucleus.[128] Their preparation began with catalytic hydrogenation of HMFA over a 5% rhodium on carbon at room temperature and 3 atmospheres of hydrogen for 5–6 h. The isolate from hydrogenation was treated abundantly with strongly acidic ion exchange resin in benzene and dioxane before azeotropic distillation. A clear liquid was obtained following concentration and vacuum distillation, which was purified by solid phase extraction through a Florisil pad with benzene-EtOAc eluent.

The white low melting solid (42–43 °C) was thusly procured in 20% yield and was characterized by FTIR and ^{1}H NMR. Their anionic lactone-ring-opening polymerization employed the tetra(*tert*-butoxy)titanate—*also known as Tyzor TBT*—under dry nitrogen stream with two relatively low temperature regimes: 100 °C and 170 °C. Following dissolution in chloroform with precipitation into light petroleum ether, 33% yield of sticky solid was obtained and analyzed by FTIR and NMR. To confirm the likely lactone-ring-opening mechanism *versus* an implausible

cyclic-ether-ring-opening mechanism, the glassy solid polymer was hydrolyzed by treatment with aqueous sodium hydroxide (0.2 M). Isolation of a clear colorless oil and esterification thereof by the action of diazomethane afforded methyl 5-(hydroxymethyl)tetrahydrofuran-2-carboxylate as characterized by FTIR and NMR. The same product was isolated from neutral hydrolysis of 2-oxo-3,8-dioxabicyclo[3.2.1]octane and subsequent reaction with diazomethane.

Moore and Kelly (1984) reported the preparation of poly(hydroxymethylfuroate) or poly(2,5-furandiylcarbonyloxymethylene) from methyl 5-(hydroxymethyl)-2-furoate utilizing melt-poly(transesterification) with calcium acetate and antimony oxide catalyst at 240 °C.[129] In contrast to patent literature, the polymeric material prepared was of poor appearance—*brown solid with no film forming or fibrous properties*—it revealed no glass transition below 250 °C at which point thermal degradation was apparent. Their report was spurred by those disclosures of related oligomers in the patent literature. It seems curious that they did not report on the use of titanate catalysts at lower temperatures. The question of thermal stability comes to mind, perhaps a lower temperature solution polymerization would prove effective. Indeed, the conclusion made by Moore and Kelly was that incorporation of this particular moiety into polymeric materials would remain limited to *"polymerization techniques utilizing mild catalysts and moderate to low temperature"*.

Certainly, the unique challenges presented by an AB type monomer such as 5-(hydroxymethyl)-2-furoic acid preclude discrete formation of an acid chloride for activation. Perhaps biocatalytic approaches could be employed. One of the chief features presented in this report details a protocol for preparing methyl 5-(hydroxymethyl)-2-furoate directly from 5-(hydroxymethyl)-2-furoic acid in 85% isolated yield on the 100 mmol scale. This chemoselective transformation provided a highly reproducible starting point for the optimization of said transformation detailed later in this chapter.

4.1.2.3. Polymers derived from FDCA

Isohexides and FDCA are considered the premier rigid monomers derived from sachharides by van Es (2013).[130] In *"a tribute to furan excellency"*, Sousa, Vilela, Fonseca, Matos, Freire, Gruter, Coelho, and Silvestre (2015) reviewed biobased polyesters with a special focus on FDCA.[131] Highlights included recent advancements in the synthesis, polymerization, catalysis, and application of FDCA. Characteristic innovations in this field have been made while investigators strive for high performance thermomechanical properties; these include polymeric materials synthesis and processing, as well as development of commercializable products.

Moore and Kelly (1979) reported the preparation of poly(2,5-furandiylcarbonyloxy-1,4-phenylenedimethylmethylene-1,4-phenyleneoxycarbonyl) from 2,5-furandicarbonyl chloride and bisphenol A in four distinct systems.[132] Those systems were: (1) aluminum trichloride or (2) zinc dust catalyzed polymerizations in tetrachloroethane solution at 155 °C, (3) uncatalyzed reaction in chloroform at ambient temperature mediated by triethylamine, and (4) interfacial polymerization in benzene. Both catalyzed solution polymerizations afforded products of similar intrinsic viscosity and yields. Both uncatalyzed solution and interfacial polymerizations afforded materials with significantly greater intrinsic viscosities compared to the catalyzed processes. The yield of the uncatalyzed solution polymerization was superior to every other method studied while the interfacial polymerization was greatly inferior to the alternate methods. Thermal decomposition of the polymers was observed above 225 °C. The appearance of polyesters prepared from both catalyzed methods was negatively affected and resulted in brown materials likely due to inherent acid instability of the furanic core structure; both base mediated methods resulted in white film-forming polymers.

Biobased FDCA can be prepared from oxidation of HMF or from acid mediated dehydration of saccharic acid. Moore and Kelly (1978) were motivated by *"the constraints placed upon the limited petrochemical resources of the world"* to investigate polyesters derived from FDCA, 2,5-bis(hydroxymethyl)furan and 1,6-hexanediol.[133] In that vein, they also investigated *cis*- and *trans*-tetrahydrofuran-2,5-dicarboxylic acid copolyesters with ethylene glycol as well as *cis* and *trans*-bis(hydroxymethyl)tetrahydrofuran. Due to the oxygen sensitivity of the heterocyclic monomers described, solution polymerization provided the most expeditious route toward polymers of this type as compared with melt-poly(transesterification). They found that the polyesters with the lowest glass transition temperatures were prepared from a combination of *cis*-2,5-tetrahydrofurandicarboxylate and *cis*-2,5-bis(oxymethyl)tetrahydrofuran subunits.

Their investigation into melt-poly(transesterification) of dimethyl 2,5-furandicarboxylate with 1,6-hexandiol included examination of lead dioxide and antimony oxide mixed with calcium acetate while the results of intrinsic viscosity determinations were used to evaluate effectiveness. Intrinsic viscosity measurements are a poor representation of number average molecular weight but decently relatable to weight average molecular weight.[134] Extension of the antimony oxide with calcium acetate protocol led to blackening when 1,6-hexanediol was replaced with BHMF. It is curious that while a titanate catalyst as described in their lactone-ring-opening polymerization (*vide supra*),[128] facilitated the preparation of 2,5-furandicarboxylate containing polymers, but when 2,5-tetrahydrofurandicarboxylate monomers were employed it resulted in blackening with low intrinsic viscosities.

When a solution of diol and triethyl amine in chloroform was added to diacid chloride in chloroform slowly below 0 °C, the typical yellowing of the polymerization reaction mixture could be avoided. While THF containing polyesters could be prepared by solution polymerization, they

were H_2O soluble and had a high affinity for triethyl amine hydrochloride which made purification and analysis difficult. Additionally, the tetrahydrofuranic diols were comparatively unreactive under the conditions of solution polymerization and gave polymers with low intrinsic viscosities. Could an acyl transfer catalyst such as DMAP have benefited this protocol?[135]

Multiple polycondensation techniques were applied to FDCA by Gomes, Gandini, Silvestre, and Reis (2011) and "study provided ample evidence in favor of the exploitation of furan monomers as renewable alternatives to fossil-based aromatic homologs".[136] Poly(ethylene 2,5-furandicarboxylate) was prepared—mediated by antimony oxide (Sb_2O_3)—from bis(hydroxyethyl)-2,5-furandicarboxylate which was in turn prepared from Fisher esterification of ethylene glycol and FDCA. DMF mediated reaction between thionyl chloride and FDCA afforded 2,5-furandicarbonyl chloride in high purity and yield as a white powder while avoiding formation of insoluble polyanhydride species. The diacid chloride prepared thusly was very suitable for application in interfacial polycondensation with hydroquinone.

Direct polycondensation combines carboxylic acid monomers with hydroxyl monomers. The current industrial technology employed for the production of terephthalic acid—*a component in poly(ethylene terephthalate) of beverage and food packaging fame*—is currently produced by direct polycondensation. FDCA underwent direct polycondensation with an array of terminally disubstituted diols as reported by Jiang, Liu, Zhang, Ye, and Zhou (2012).[137] Astonishingly, they claim to have employed tetrabutyl titanate in this direct polycondensation; typically the titanate catalysts—*considered anionic catalysts by some and essentially neutral by others*—are employed in relatively low temperature (less than 280 °C) polytransesterification reactions. Exposure of the titanate catalysts to H_2O is the typical protocol for quenching their reactions and leads to the release of hydroxylic residues while precipitating titanium dioxide.[135]

In a similar study, polyesters were prepared by a direct polycondensation method from FDCA and simple aliphatic diols (ethylene glycol and 1,4-butanediol) mediated by antimony oxide (Sb_2O_3).[138] The direct polycondensation was also extended to vanillic acid to make comparison between multiple biobased aromatic polyesters possible. While the poly(ethylene 2,5-furandicarboxylate) contained semi crystalline morphology (T_m=71 °C and T_g=212 °C, poly(vanillate) was amorphous. While the poly(ethylene 2,5-furandicarboxylate) prepared from the direct polycondensation method began to decompose at 355 °C, poly(vanillate) prepared in similar fashion began to decompose at 200 °C.

Poly(ethylene 2,5-furandicarboxylate) was synthesized, compared and contrasted with a commercial polyester juggernaut, poly(ethylene terephthalate) as well as its high-performance analog poly(ethylene 2,6-naphthalenedicarboxylate).[139] Amorphous samples of poly(ethylene 2,5-furandicarboxylate, poly(ethylene terephthalate), and poly(ethylene 2,6-naphthalenedicarboxylate) all displayed characteristic glass transition temperatures—*87 °C, 80 °C, and 123 °C respectively*—and melting temperatures—*215 °C, 246 °C, and 267 °C respectively*. The melting point of poly(ethylene 2,5-furandicarboxylate) could be increased to 231 °C by high temperature crystallization. The heat of fusion for poly(ethylene 2,5-furandicarboxylate, poly(ethylene terephthalate), and poly(ethylene 2,6-naphthalenedicarboxylate) was estimated to be 137 J/g, 140 J/g, and 103 J/g respectively. Poly(ethylene 2,5-furandicarboxylate) displayed flexibility intermediate between the more flexible poly(ethylene terephthalate) and less flexible poly(ethylene 2,6-naphthalenedicarboxylate). The onset of thermal degradation for poly(ethylene 2,5-furandicarboxylate) occurred at 325 °C which was approximately 20 °C lower than poly(ethylene terephthalate and 40 °C lower than poly(ethylene 2,6-naphthalenedicarboxylate).

A ring-opening poly(transesterification) strategy—*mediated by tin(II) ethylhexanoate*—was employed to prepare poly(butylene 2,5-furanoate-co-terephthalate) from cyclic oligomers[140, 141] derived from 1,4-butanediol and diacid chlorides at great dilution.[142] Advantages in formation-rates of random copolyesters were afforded by the ring opening strategy in comparison to a traditional melt-polycondensation technique to achieve similar molecular weights; weight-average molecular weights above 55,000 $g \cdot mol^{-1}$ were achieved. Incorporation of furanic subunits repressed the crystallinity of copolyesters despite the highly crystalline nature of poly(butylene 2,5-furanoate); substitution of the furanoate moiety for the terephthalate moiety depressed the crystallizability.

Poly(2,2-dimethyl-1,3-propylene furanoate) or poly(neopentylene 2,5-furandicarboxylate) with a melting point of 198 °C and glass transition temperature of 68 °C was prepared from a mixture of 2,2-dimethyl-1,3-propandiol and dimethyl 2,5-furandicarboxylate following a two-stage melt polycondensation method.[143] Thermal decomposition was observed at 356 °C with a maximum rate of decomposition at 444 °C. The mechanism of thermal decomposition was probed by pyrolyzer-gas chromatography-mass spectrometry and determined to occur *via* radical scission and not β-scission in contrast to most polyesters.

The first stage of the polyester synthesis—*poly(transesterification)*—began with a diol/diester ratio of 1.0/2.2 at 160–190 °C over five h under inert atmosphere (ambient pressure) and was mediated by tetrabutyl titanate (400 ppm). The second stage—*polycondensation*—occurred when a vacuum was applied (5.0 Pa) slowly over thirty min. This slow application of vacuum is critical to remove the excess diol (1.2 molar equivalents) and to avoid excessive foaming or oligomer sublimation. Under reduced pressure, the polycondensation mixture was slowly heated

190–235 °C in steps over three h. Purification was simple *i.e.* samples were milled and washed in MeOH.

FDCA was combined with bioderivable-long-chain-diols in an asymmetric monomer strategy which provided facile preparation of high purity polymers. In this strategy, 5-(methoxycarbonyl)furan-2-carboxylic acid was prepared by partial hydrolysis of dimethyl 2,5-furandicarboxylate, followed by activation by reaction of the carboxylate with thionyl chloride and quenching with a suitable diol.[144] In this fashion, FDCA which could be considered an AA type monomer, can be converted into an AB type monomer, which would expansively simplify the preparation of polymeric materials derived thereof. This process so facilitated the titanate catalyzed poly(transesterification) reaction as to avoid the usual formation of colored impurities within the melt. The effects of varying titanate concentration, reaction temperature, and reaction time were detailed.

Biodegradable and biorenewable polyesters have been prepared from 1,20-eicosanediol and dimethyl 2,5-furandicarboxylate.[145] Although it was a rather hydrophobic polyester with close to zero H_2O uptake— H_2O *contact angle (96°)*—it degraded in neutral aqueous phosphate buffer in the presence of *porcine pancreas* enzyme. The thermally stable polyester—*5% weight loss at 358 °C*—displayed a melting point (107 °C) and glass transition (7 °C) which the authors deemed comparable to polyolefins in thermomechanical behavior.

Isomeric substitution effects in poly(ethylene furanoate) have been investigated by Thiyagarajan *et al* (2014).[146] Polymers derived from 2,4-furandicarboxylic acid and 3,4-furandicarboxylic acid were prepared with molecular weights in the range of 34,000–65,000 Daltons. Titanate catalysts were used in a melt poly(transesterification) strategy with dimethyl FDCA esters. The series of isomeric diacids were themselves procured from hemicellulosic

biorefinery through the oxidation and disproportionation of furfural which also afforded furan in a Henkel reaction.[147, 148]

4.1.3. Aromatic Upgrading of Furan-Dienes

The ability to efficiently diversify renewable platform chemicals as they are discovered is critical to increasing the velocity of molecular innovations. Investigation of nonedible biomass as a sustainable alternative to petroleum continues to expand as a field of research. From the standpoint of renewable feedstocks, these expansions require the development of biorefinery technologies along with the diversification and concomitant valorization of platform chemicals.

Often, investigators choose a petroleum commodity chemical and attempt to create a sustainable alternative either through production of a facsimile or an analogous structure readily obtained from biorefinery products. An aromatic upgrade strategy could offer benzenoids from furans through the Diels-Alder reaction followed by either elimination of H_2O or *via* deoxy-aromatization.[149] The conversion of poly(ethylene terephthalate) into benzene-rich oils provides a complementary pathway approaching sustainability and expanding the use then reuse cycle even further.[150] For example, biobased benzoic acid has been prepared from the Diels-Alder reaction of methyl acrylate—*dienophile*—and furan—*the quintessential furan-diene*.[151]

4.1.3.1. Furan-Dienes and the Diels-Alder Cycloaddition Strategy for Biomass Valorization

Moore and Kelly (1978) reported "*thermally initiated crosslinking of an unsaturated heterocyclic polyester*" derived from 2,5-furandicarboxoyl chloride along with a mixture of *cis*- and *trans*—2,5-2*H*,5*H*-bis(hydroxymethyl)dihydrofuran *via* solution polymerization in chloroform with triethyl amine (90% yield).[152] Their discovery was made serendipitously while attempting to obtain a melting point for the soluble copolymer around 100 °C; a reaction occurred which rendered the material totally insoluble. The phenomenon was clearly attributed to the

dihydrofuran moiety since analogous polymers derived from either 2,5-bis(hydroxymethyl)furan or 2,5-bis(hydroxymethyl)THF remained soluble upon similar treatment. According to a reference to J. E. Kelly's Ph. D. dissertation, while being reactive materials, furanic polymers are typically thermally stable in the absence of acid below 160 °C.

Upon closer inspection by differential scanning calorimetry, the anomalous polymer exhibited an exothermic transition between 105–110 °C which was not accompanied by any weight loss. When a sample was heated to 150 °C, it became partially insoluble and upon secondary inspection no longer displayed the 105–110 °C exothermic transition. When heated to 250 °C the insoluble polymeric material underwent an additional exothermic transition accompanied by 70% loss of weight.

The strange thermosetting polymer could also be prepared—albeit in 1% yield—by heating a solution in tetrachloroethane to 155 °C for three days and isolating the precipitate which exactly matched the infrared spectrum obtained from heating the neat polymer. The infrared spectral comparison of the soluble and insoluble polymers matched with two exceptions; absorbance in the aromatic region (1580 cm^{-1}) lost intensity for the insoluble material while absorbance in the olefinic region (1650 cm^{-1}) intensified for the insoluble material. The fact that decreasing concentration—*solution phase compared with liquid phase*—inhibits the formation of the insoluble or crosslinked polymer combined with alterations observed in the infrared spectra led the authors to consider a Diels-Alder crosslinking mechanism.

This would be the earliest example of such a reaction with 2,5-furandicarboxylate moieties which have been investigated in the following chapter of this dissertation. Additionally, this report validates the paradigm of biorenewable materials research for the discovery of novel crosslinking mechanisms not offered by petroleum derived feedstocks. The ability to prepare thermosetting

resins from recycled furanic polyesters could serve to further incentivize their industrial adoption by creation of secondary product streams.

Five-membered heterocycles including pyrroles, furans, and thiophenes, have been identified as *"latent functional group equivalents"*.[153] Furans have historically been the most widely exploited monocyclic aromatic dienes. An example of highly substituted anthranilate derivatives was given which illustrates latent potential for valorization of furanics by aromatic upgrading; a concept of paramount importance to the following chapters.

The electronics of substituents at the C2 and C5 positions greatly influence the reactivity of furan-dienes in concerted [4+2] cycloaddition reactions: the Diels-Alder reaction. An overpowering activation imparted by amino- and methyl- substitutions at C2 and C5 in the presence of cyano-substitution at position C3 was demonstrated during the preparation of anthranilate derivatives by normal electron demand Diels-Alder cycloaddition. Carboxylate substitution at C3 has been tolerated, and even capitalized upon as a directing group in *ortho*-lithiation strategies for the synthetic installation of vinyl moieties containing electron withdrawing substituents in an exquisite example of dianion chemistry.[154] Normal electron demand intramolecular Diels-Alder reactions catalyzed with methylaluminum dichloride were reported which serve to demonstrate the utility and proclivities of furan-dienes.

Synthetic applications of furan Diels-Alder chemistry have been reviewed.[155] Two categories were delineated by molecularity: bimolecular and intramolecular Diels-Alder reactions. There were many more examples of intramolecular Diels-Alder reactions with furan-dienes. The pervasiveness of furan Diels-Alder chemistry was attributed to its elegance in the synthesis of six-membered rings and for its great efficiency. Cycloadducts with furan (7-oxabicyclo[2.2.1]hep*tert*-5-enes or 7-oxanorbornenes) *"can be manipulated with impressive selectivity"*.[155]

4.1.3.2. Biobased Terephthalic Acid

The synthesis of biomass derived terephthalic acid has garnered interest as a potential renewable feedstock for the polymeric materials industry.[156] While the sustainability of the industrial production has been scrutinized in the context of improving the current production stream,[157] other research has gone into swelling the production stream with renewable routes[158, 159] to access terephthalic acid. Alternative technologies under development entail the substitution of terephthalic acid in polymeric materials with renewable analogs such as FDCA.[160-162]

The decreased aromaticity of the furan-ring relative to the benzene-ring,[163] combined with the introduction of hemicellulose- and cellulose-derived furanics has resulted in their employment as furan-dienes[164] in the Diels-Alder strategy for renewable terephthalic acid. The cycloaddition strategies for renewable terephthalic acid can thereby be delineated into two distinct camps derived from polysaccharide precursors: the hemicellulose and the cellulose route. Both components of poly(ethylene terephthalate), ethylene glycol and terephthalic acid have been targeted for production from biomass.[165]

The traditional barrier thwarting previous investigators attempting cycloaddition with cellulose-derived diethyl 2,5-furandicarboxylate has been broken.[166] A solvent-free protocol for 100% bioderivable poly(ethylene terephthalate) *"via a one-pot heterogeneous Lewis acid catalyzed Diels−Alder addition and dehydration of 2,5-furandicarboxylic acid diethyl ester with ethylene"* was described. The selectivity for diethyl terephthalate was high (88%) and the yield moderate (59%) in the cycloaddition step. A thoughtful article succinctly reviewed the state of the art and made extensive use of green chemistry metrics and systems thinking as they targeted then optimized the Diels-Alder cycloaddition of diethyl 2,5-furandicarboxylate with ethylene at high pressure (60 bar) and temperature (250 °C) on a variety of zeolite catalysts.

4.1.3.3. Biobased Xylene

The highly oxidized nature of cellulose derived six-carbon furanics as a class seem uniquely suited to redox-efficient transformation into difunctional benzenoids by a cycloaddition and aromatization strategy. One such technology utilizes a Sn-β catalyst to prepare methoxymethyl substituted arenes with pressurized ethylene gas which could then be oxidized to dimethyl terephthalate, but this reaction failed to yield any product with dimethyl 2,5-furandicarboxylate as the substrate.[36, 82] The electronic demands of the Diels-Alder reaction have led to an impasse which has been met mainly by the employment of reduced derivatives such as alkyl-substituted furans and activated dienophiles such as acrolein[167] or pressurized ethylene gas.[168-170] Those adducts must be protected from the *retro*Diels-Alder reaction by immediate, often *in situ*, aromatization (by either dehydration or decarbonylation) to afford *p*-xylene or related compounds such as biorenewable toluene.[171] Once renewable xylene[172, 173] has been secured it may be dropped into the current industrial production of terephthalic acid. The proclivity towards the *retro*Diels-Alder reactions in both strategies severely hinders access to the synthetically interesting [2.2.1] bicyclic 7-oxanorbornene intermediates.

"The Diels-Alder and dehydration reactions of furan derivatives with ethylene catalysed by liquid Brønsted acids and Lewis acids" was reported.[174] The experimental evidence combining ethylene and furan-dienes in the presence of catalytic difluorochloroacetic acid provided a clear demonstration of a normal electron demand Diels-Alder mechanism and of the acid sensitivity of furanic systems with open C2 or C5 positions; 2,5-dimethylfuran: 50% yield, 2-methylfuran: 23% yield, furan: 5% yield, methyl 5-methyl-2-furoate: 18% yield, FDCA: 0% yield, and dimethyl 2,5-furandicarboxylate: 0% yield. The yields reported were of the benzenoid derivative prepared in

situ under the reaction conditions: 0.2 M concentration of substrate in 1,4-dioxane under 3.5 Mpa ethylene pressure at 200 °C for 24 h reaction time.

4.1.3.4. Biobased Phthalic Anhydride

Biobased terephthalic acid was synthesized from furfural and verified as 100% biobased carbon using the technique of accelerator mass spectrometry.[175] Furfural was oxidized to a mixture of fumaric and maleic acids by sodium chlorate mediated by vanadium pentoxide in moderate yield (58%) after 10 h reaction time which compared a bit unfavorably with the example of 78% at 12.5 h reaction time set by Milas (1927).[176] The mixture of olefinic diacids was converted to maleic anhydride in high yield (95%) by the action of hot (155 °C) phosphorous pentoxide under reduced pressure (10 Pa, 2 h). Furan is produced on an industrial scale primarily by the palladium catalyzed decarbonylation of furfural.[177]

The reaction of maleic anhydride with 2,5-dimethylfuran has been studied by implementing density functional theory electronic structure calculations to explore the mechanistic details of the Diels-Alder cycloaddition.[178] The Diels-Alder adduct from furan and maleic anhydride was prepared at room temperature in ethoxyethane over twelve h (98% yield of the thermodynamically more stable exo product).[175] A mixed-anhydride method was used to prepare phthalic anhydride in 84% yield.[179] Dipotassium phthalate was isolated practically quantitatively following reaction with aqueous potassium hydroxide at 80 °C for two h. Biorenewable terephthalic acid was prepared (44% yield) by thermal rearrangement (420 °C, 2 h) mediated by cadmium iodide, followed by acidification with 1 M aqueous hydrogen chloride.

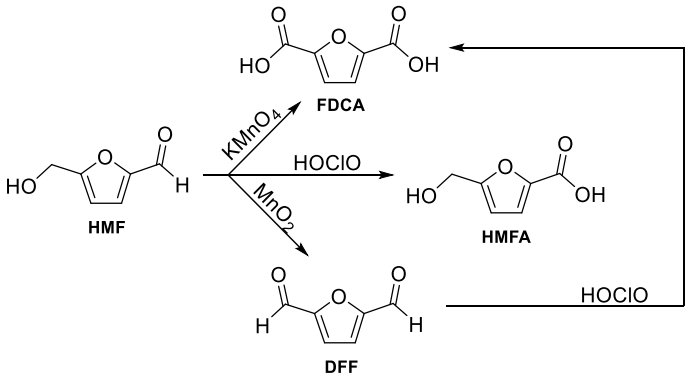
4.1.3.5. Potential for Biobased Anthranilic Acid

Modified cycloadducts of hemicellulose derivatives—*substituted furans and maleic anhydride*—may be prepared at low temperature. Following a process of hydrolytic aromatization,

the first benzenoid accessed will be phthalic anhydride derivatives, themselves valuable commodities. Substituted phthalic anhydrides may be thermally rearranged in an anachronistic process known as the Henkel method to finally yield terephthalic acid derivatives.[180] Extension of this approach could pave the route to biorenewable anthranilic acids: themselves laudable heterocycle precursors.[181]

4.2. Heterogeneous Manganese Dioxide Oxidations

Amidst avid interest, many renewable furanics have not achieved platform chemical status. These include 5-(hydroxymethyl)-2-furoic acid (HMFA) (Scheme 4.1), and DFF (Scheme 4.1). While those remain under-utilized, FDCA, (Scheme 4.1),[182, 183] has been identified as a top value added renewable feedstock.[184] Importantly, FDCA has been evaluated as a terephthalic acid analog for applications in polymer chemistry.[185, 186] Akin to both DFF and FDCA, 5-formyl-2-furoic acid (FFA) (Scheme 4.1) is potentially an intermediate in the conversion between those structures with scanty mention in chemical literature. All of these renewable furanics are linked by their common antecedent: HMF.



Scheme 4.3. Synthetic relationships and interesting derivatives of HMF: FDCA, HMFA, DFF

To expand upon the utility of diacid production such as in the preparation of FDCA from DFF, improvements to the sustainable preparation of the dialdehyde were required. Manganese dioxide (MnO_2) is a well-known and mild-oxidant with great potential for use in chemoselective

transformations.[187-189] Previously we have reported the replacement of DCM with toluene during this heterogeneous oxidation.[75] However, at the outset of this investigation there existed several challenges associated with the sustainable use of this comparatively benign oxidant.

4.2.1. Manganese Dioxide and Sustainable Chemistry

Ball, Goodwin, and Morton (1948), faced the challenging issue of chemoselective oxidation in the preparation of a conjugated aldehyde in the synthesis of retinene or vitamin A aldehyde, which contains five olefins.[190] While surveying the literature, and probing the applicability of potassium permanganate modified with sulfuric acid, *"the one consistent tendency seemed to be an improved yield when hydrated manganese dioxide was formed, i.e. when the sulphuric acid used was insufficient to give a clear solution"*. Their study culminated in the *"smooth conversion to retinene at room temperature when vitamin A in light petroleum was allowed to stand over manganese dioxide"* and resulted from screening three types: (1) *"ordinary granular laboratory reagent"*, (2) *"a much finer grade of the commercial product"* with smaller granules, and (3) freshly *"prepared by mixing aqueous solutions of equivalent amounts of manganous sulfate and potassium permanganate, filtering, washing until free from sulphate ions and drying on a porous plate in a desiccator"*.

Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker (1952) reported the synthesis of vitamin A from cyclohexanone which included an elegant alternative oxidation to Oppenauer reaction, and which utilized a highly active suspension of MnO_2 in light petroleum. The results of five successful oxidations including simpler alcohols—allylic alcohol, cinnamyl alcohol, oc*tert*-3-yn-2-ol, and 3-dehydro-β-ionol—were reported.[191] As stated by those authors: *"it therefore appears that the method may be general for alcohols of the allylic type, whether they are primary or secondary and possibly when the unsaturation is acetylenic"*. That report also

addressed the lower reactivity of commercially available MnO_2 by including an improved procedure for freshly preparing highly active MnO_2 which led to substantial citation in the chemical literature; key features of their protocol include precipitation of MnO_2 in the presence of alkali and avoidance of under- or over- drying. Although the Attenburrow method affords highly active MnO_2 capable of completely transforming cinnamyl alcohol to cinnamaldehyde in 30 min at ambient temperature, conversion of 5 g cinnamyl alcohol required 50 g of MnO_2!

Sondheimer, Amendolla, and Rosenkranz (1953) described the *"oxidation of steroidal allylic alcohols with* MnO_2*"*, and related the series of MnO_2 reports found in academic literature since 1948.[192] While commercially available materials were wholly unsatisfactory in their screenings, freshly prepared MnO_2 from combination of manganous sulfate and potassium permanganate[193] was quite effective. However, these authors did not find it necessary to treat their precipitated MnO_2 with alkali, dried their materials between 120–130 °C, and found that such material could be stored in a stoppered jar for several months without losing activity. Their study expanded the solvent scope from light petroleum to include benzene, chloroform, ethylene chloride, and even acetone. In an extension of that research, the ability of MnO_2 to mediate dehydrogenation reactions between carbon–carbon σ-bonds was also investigated.[194]

Harfenist, Bavley and Lazier (1954) reported the oxidation of vitamin A alcohol to its aldehyde by action of MnO_2 suspended in petroleum ether.[195] They cited reports of facile oxidation reaction performed by mild shaking of slurried reaction mixtures or elution through MnO_2 containing columns as instigating their methodological development and application of the technology to *"determine and to extend its scope"*. Their study included an array of commercially available reagents and a key observation: *"since all of the compounds previously reported as oxidizable have had two or more double bonds in a position to conjugate with the carbonyl group*

which is formed, it was thought of interest to test the utility of this method as a means of preparing substituted acroleins, vinyl ketones, and aromatic aldehydes". Although the conditions have been deemed *"mild"*, suspensions in ether of highly active MnO_2 prepared from manganous sulfate and potassium permanganate could result in spontaneous combustion once and was *"narrowly averted in a third trial"*. As such, these investigators avoided further application of highly active MnO_2 and instead focused on preparations from thermal decomposition of manganous oxalate or carbonate with and without nitric acid treatment oven dried at 220–250 °C.

While increasing the relative amounts of MnO_2 beyond a certain point, did not increase the yields of aldehyde products, the purity of the isolates increased supposedly through a mechanism of preferential chemical adsorption of the substrate upon the solid oxidant. A study was made specifically of benzylic alcohol conversion to aromatic aldehydes with a four to one oxidant to substrate weight to weight ratio. An enhancement in the reaction was noted when diethyl ether was the solvent as compared to hexane and electron rich aldehydes could typically be prepared in greater yield. Importantly, the conditions which served effective for preparation of aromatic aldehydes were woefully inadequate for the preparation of allylic alcohols unless the MnO_2 was treated with nitric acid prior to drying. Neither preparation demonstrated much conversion of saturated alcohols.

A study of *"solid manganese dioxide as an oxidizing agent"* was made by Highet and Wildman (1955) as they further explored the oxidizing power of the purportedly reliable and selective reagent.[196] Examples of two benzaldehydes, Schiff bases, a lactam, and two lactones were provided with spectral evidence. Solvents such as chloroform, diethyl ether, and hexane were screened. Results were tabulated as isolated % yields as calculated from the weight of 2,4-dinitrophenylhydrozone derivatives. The implication of a lactone formation mechanism which

operated upon aliphatic 2-hydroxytetrahydropyran could indicate one heretofore ignored substrate degradation pathway; oligoesters may form from transient hemiacetals derived from reaction of alcohol-substrate and aldehyde product. Pyridine additive (5%) was found to poison the activity of MnO_2. In the provided protocol for preparation of benzaldehyde from benzyl alcohol, 1 g MnO_2 was used in dilute suspension (40 mL solvent) for conversion of 1 mmol substrate.

Evans (1959) reviewed *"oxidations by manganese dioxide in neutral media*" wherein descriptions of various sources and a brief history of the material was provided.[197] Evans also credits Ball, Goodwin, and Morton (1948)[190] for discovering the facility of heterogenous oxidation chemistry in neutral or non-aqueous media and the high selectivity characteristic of MnO_2 reactions. That chemistry was referred to as dehydrogenation which covers both the oxidation of activated hydroxyls in terms of an oxygen-carbon or carbon–carbon σ-bond. A lack of standardization in early experiments was blamed for creating divergent viewpoints regarding the utility of these oxidations within the organic chemistry community. Evans attributes the erratic observations reported in the literature to widespread variations in the MnO_2 either supplied or prepared; a compendium of active MnO_2 preparations was provided with citations. The necessity of an empirical approach in any application of MnO_2 chemistry was highlighted and *"the selectivity and efficiency of the reactions often justify the necessary exploration*".

In the same year, Gritter and Wallace (1959) experimentally surveyed dependencies of reaction-rate and specificity on variables such as quantity of oxidant, reaction temperature, solvent, and method of preparation in their study of MnO_2 oxidations.[198] An innovative technology employed in the Gritter and Wallace study was magnetic stirring with a PTFE coated magnetic spinbar which afforded constant change in the surface of MnO_2 available for substrate adsorption. The occlusion of higher oxides of manganese or chromium was invoked to explain the obviously

faster oxidation rates when the preparation of MnO_2 began with potassium permanganate. Additionally Gritter and Wallace repudiate the claim of Attenburrow *et al.*[191] regarding the necessity of alkali washing precipitated MnO_2 for maximum activity, and indicate that any oxidation mediated by atmospheric oxygen is negligible.

Pratt and van de Castle (1961) exploited the azeotropic distillation of H_2O produced as byproduct in the oxidation of activated alcohols by MnO_2—*prepared by the Attenburrow procedure*—in benzene to actively track the extent of reaction.[199] They proposed a free radical intermediate based on *"the effects of changes in structure of the alcohols on their rates of oxidation"*; specifically, the relatively minor rate changes correlated to varying electron withdrawing substituents in the *para* position to the benzylic alcohol were interpreted as support for a radical intermediate. Their focus on benzyl alcohols—*or phenylcarbinols as they were dubbed in the manuscript*—and reproducible collection of moisture in a Dean-Stark trap made the determination of relative rates of reaction possible and relevant.

An alternate explanation for the relatively insensitive reaction-rates could be the balance of multiple phenomena: (1) actual substrate-oxidation-rate on the solid surface, (2) the adsorption rates of the product and substrate, and (3) the desorption rates of the product and substrate. Since the adsorption rate of substrate would likely be modulated mostly by steric influences and secondary interactions. Such interactions were implicated in the case of 4-methoxy substituted phenylcarbinols which were slower to convert to benzaldehydes. The real balance would be between oxidation-rate—*retarded by electron withdrawing substituents*—and desorption of the product—*accelerated by decreasing the affinity for the solid surface and thereby accelerated by decreasing the Lewis basicity of the product as in the case of electron withdrawing substituents.*

Gritter, Dupre, and Wallace (1964) investigated the relationships between rate changes—*and (1) solvent, (2) temperature, (3) type of manganese dioxide employed*—in the oxidation of benzyl alcohols.[200] Their experiments were standardized at 10 : 1 weight ratio between MnO_2 and benzyl alcohol at 2 wt% concentration in various solvents at various temperatures. While screening various sources and preparations of MnO_2, they found "*no direct correlation between active oxygen and the oxidizing power of the solid"* but rather *"the oxidizing power of the manganese dioxide increases with a decrease in purity of the manganese dioxide*". These investigators adapted the methods of Pratt and van de Castle[199] while following their experiments with infrared spectroscopy. The results of their study could not refute the intermediacy of free radicals; however, a polar mechanism was presented which relied on the coordination of hydroxylic oxygen with surface bound metal cation coordinated with two discreet MnO_2 molecules.

Goldman (1969) reported the *"activation of manganese dioxide by azeotropic removal of* H_2O*"* and described the colloquial view of MnO_2 as shifting from a *"relatively selective oxidant of allylic alcohols"* to *"a less discriminate, condition-dependent oxidizing agent"*.[201] Following the preparation of MnO_2 by Attenburrow procedure,[191] a wet filter cake (40–60% H_2O) could be stored for more than a year and conveniently activated at any time by activation through a process of azeotropic distillation with benzene. The benzene azeotroping procedure was credited for removal of occluded and not tightly bound H_2O, which makes it likely that the actual hydration of the MnO_2 prepared thusly is within the ideal range for oxidation chemistry—*not too dry*—while freeing up active binding sites for substrate. The substrate: MnO_2 weight: weight ratios for their experiments were all 1: 10 with products typically isolated as the 2,4-dinitrophenylhydrazone.

Goldman (1969) also reported the *"observation of a large isotope effect in the manganese dioxide oxidation of benzyl alcohol"*.[188] That primary kinetic isotope effect was between 13.3 and

15.1, which indicated the role of carbon-hydrogen bond cleavage in the rate limiting step. In competition experiments, the observed kinetic isotope effect was determined to be 18.2 and was *"presumably resulting from the combined primary and secondary*" effects. These results were taken as evidence for the reversibility of the prerequisite adsorption of substrate to MnO_2 active surfaces.

Kimura, Fujita, and Ando (1988) investigated the *"sonochemical activation of manganese dioxide*" to avoid the *"experimentally so tedious"* preparations of activated oxidant.[202] Even very poor oxidants such as 99% crystalline MnO_2—*which is typically inert towards cinnamyl alcohol*—became effective in acetonitrile solvent following irradiation in a sonic cleaning bath. The reactions could be carried out under sonication or the material could be preactivated as such then simply stirred. One drawback to their study was a reliance on yields calculated by gas chromatography and a distinct lack of isolated yield data.

For the first time in academic literature, Tsuboi, Ishii, Sakai, Tari, and Utaka (1990) described the *"oxidation of alcohols with electrolytic manganese dioxide*" which is a cheap commercially available, reliable source of MnO_2 which *"does not need to be purified"*.[203] In a set of experiments comparing the rates of 1-pheynyl-1-propanol oxidation, electrolytic MnO_2 proceeded at a faster rate than the so called activated MnO_2 in hexane solution under nitrogen atmosphere. Their generalized experiment utilized a MnO_2 : substrate weight ratio of 11 : 1.

There have been efforts to limit the solvent and reaction time required for the oxidation of activated alcohol such as the *"active manganese dioxide on silica*" reported by Varma, Saini, and Dahiya (1997),[204] or the *"solvent free oxidation of alcohols with manganese dioxide"* reported by Lou and Xu (2002).[205] In both of those instances, yields were not significantly improved over conventional methods, and the risk of run-away oxidation was significantly increased; both teams

worked exclusively below the gram scale. I would have to say this may not be the best trend in terms of worker safety since on one occasion in our lab, a fire was only narrowly averted by dilution with sand when electrolytically precipitated MnO_2 was combined with a stoichiometric mixture of *N*,*N*-dimethylacetamide and HMF (~30 g). It would probably be safer and more scalable to identify safer alternative solvents or decrease the amount of excess oxidant required.

Towards that end, Kamimura, Komatsu, Moriyama, and Nozaki (2013) have developed a *"sub-stoichiometric oxidation of benzylic alcohols with commercially available activated MnO_2 under oxygen atmosphere"*.[206] The key to this technology was higher temperatures—*refluxing toluene*—and exposure of the reaction mixture to dioxygen atmosphere. Notably no over oxidation to benzoic acids was observed. It seems likely that these conditions also benefited from the azeotroping conferred by refluxing aromatic solvents. In the case of hemicellulose derived 2-fufuryl alcohol, only 70 mg/mmol MnO_2 was loaded; the yield for the biobased substrate was lackluster (34%) with a significant amount of substrate recovered (23%). The poor mass balance could have been caused by secondary oxidative processes which were only accessible to the furan-ring as opposed to the benzene- and naphthalene-rings of other substrates screened. This method could significantly improve the sustainability of robust benzaldehyde substrates, but only to a certain degree as the MnO_2 could not be satisfactorily reused in multiple runs.

4.2.2. Survey of Reaction Conditions for Heterogenous MnO_2 Oxidations

First of the barriers to sustainable application of MnO_2 oxidation technology to be addressed by our efforts, the stochiometric excess of oxidizer required for complete conversion of starting materials is wildly inconsistent. While freshly prepared MnO_2 is much more reliable, commercial sources are typically suitable if azeotropic distillation is used to dry the reaction mixture. Unfortunately, such strongly dehydrating conditions may favor oligo-acetal formation.

Secondly, the scalable preparation of DFF from HMF[75, 95] has heretofore utilized either halogenated or high-boiling aromatic solvents such as DCM or toluene respectively—*see experimental section for details of preparations*

4.2.2.1. General Protocol for MnO_2 Oxidation (Table 4.1)

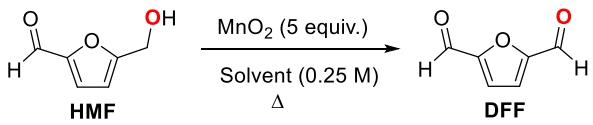
To establish an internally consistent baseline excluding batch inconsistencies, an experiment was devised which utilized 0.25 M concentration of aldehyde substrate (10 mmol) in the specified solvent, with 5 molar equivalents of MnO_2—*added in a lump sum*. The mixtures were stirred under inert atmosphere and distilled over a moisture trap for specified time as determined by solvent boiling point (Table 4.1). The mixtures were diluted with MeOH while still warm and separated by suction filtration through Celite. The filtrate was concentrated to afford solid products of useable purity, but commonly contaminated with paramagnetic manganese impurities. The crude products were dissolved in DCM then purified by elution through a two stage microcolumn of silica gel and Celite. Upon concentration, highly pure DFF was obtained and those are the yields reported in Table 4.1.

4.2.2.2. Discussion of Results (Table 4.1)

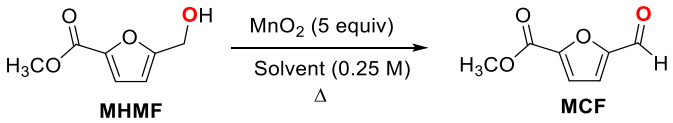
The halogenated solvent, DCM, performed well (76% and 75%, Table 4.1, entries 1 and 2) following 3 h and 6 h of distillation respectively. Remarkably, with this excess of oxidant, the azeotropic distillation did not seem to matter. To escape the negative impact of halogenated solvent usage, EtOAc was targeted as a DCM replacement (Table 4.1, entries 3, 4, and 5) to good effect (yields of 73%, 82% and 68%) with little variation observed upon altering the general workup procedure to circumvent DCM microcolumn chromatography (Table 4.1, entry 5). Surprisingly, refluxing in EtOAc without a moisture trap actually resulted in significantly higher yields (82%, Table 4.1, entry 4); this boost in yield was not observed in DCM (Table 4.1, entry 2). Toluene was

effectively replaced by a preferable process solvent—cyclopentyl methyl ether (CPME)[207]—which gave similar yield to EtOAc (72%, Table 4.1, entry 6) but CPME required only 30 min of distillation to achieve that yield.

Table 4.1. Heterogeneous MnO_2 oxidation



Entry	Reaction Solvent	Time (h)	Yield (%)[a]
1[b]	CH_2Cl_2	3	76
2		6[c]	75
3[b]	EtOAc	1.5	73
4		2.5[c]	82
5[b]		1.5[e]	68
6[b]	CPME	0.5	72



Entry	Reaction Solvent	Time (h)	Yield [a]
7	CH_2Cl_2	10[e]	87
8		3	82
9	EtOAc	1.5	82
10	CPME	0.5	79

a: isolated; b: purified HMF; c: HMF as received with no moisture trap and the reaction mixture was adsorbed onto silica gel immediately following the reaction then purified by flash column chromatography; d: H_2O replaced MeOH in the workup followed by liquid-liquid extraction; e: acetone replaced MeOH in the workup.

To our delight, carboxy substitution presented no inherent challenges to the conversion of methyl 5-(hydroxymethyl)-2-furoate (MHMF) to methyl 5-formyl-2-furoate (MFF) in consistently greater yield (Table 4.1, entries 7–10, yields 79–87%) than was observed for DFF. This trend in the results likely stems from degradation of the furfuryl moiety during the reaction conditions which explains why DFF should suffer disproportionately compared to MFF. A related compound,

methyl 3-(*E*)-(5-(hydroxymethyl)furan-2-yl)propenoate, has been reportedly converted to methyl 3-(*E*)-(5-formylfuran-2-yl)propenoate by shaking with MnO_2 (10: 1 mass ratio MnO_2: substrate) in DCM (90% isolated yield).[208] Also, Methyl 3-(*E*)-(5-(hydroxymethyl)furan-2-yl)propenoate underwent heterogeneous MnO_2 oxidation to methyl 3-(*E*)-(5-formylfuran-2-yl)propenoate (5: 1 mass ratio MnO_2: substrate) by stirring overnight in chloroform (88% isolated yield).[209]

4.2.3. Scaleup of Heterogenous MnO_2 Oxidations

MnO_2 can provide practical access to 2,5-diformyl furan (DFF), but the conditions for each substrate should be optimized experimentally to account for MnO_2 reactivity, substrate sensitivity, and sustainability considerations. The reaction with methyl 5-(hydroxymethyl)-2-furoate (MHMF) was scaled up (circa 25 g, 157 mmol) and MnO_2 superstoichiometry was attenuated (3.3 molar equivalents, circa 2 weight equivalents). Silica gel (circa 25 g) was ground by a large pestle with the MnO_2 in a large mortar for two reasons: (1) to increase the surface area of the MnO_2, and (2) to provide an internal drying agent which could contain H_2O typically removed by azeotropically distilling the reaction mixture. The mixture of silica and MnO_2 was added continuously to a distilling solution of MHMF (0.13 M in EtOAc) over 80 min during which time no H_2O was observed collecting in the moisture trap. Lack of distillate indicated that silica gel was an adequate drying agent capable of maintaining the H_2O concentration of the reaction medium below the saturation point of H_2O in EtOAc.

Following typical workup procedure detailed in the experimental section of this chapter, 77% of the theoretical maximum product, methyl 5-formyl-2-furoate (MFF), was isolated in highly pure crystalline form. An additional 4% of the theoretical maximum yield was separated cleanly from 5% recovered substrate by flash column chromatographic purification of the recrystallization liquor. No substrate or product could be detected in solution following methanolic digestion of the

reaction filter pad: a clear indication that the combination of silica gel in the reaction mixture and H_2O addition at the close of the reaction defeated the usually encountered phenomenon of substrate or product capture in adsorption to the heterogenous oxidant.

The ramifications of mixing silica gel with MnO_2 prior to addition was investigated further. One of the more serious barriers to large scale MnO_2 oxidations is the formation of a muddy mixture of hydrated MnO, $Mn(OH)_2$ and MnO_2. One of the serious conclusions drawn from reaction screening (Table 4.1) implicates oligoacetal formation which could disproportionately affect the yields of DFF with its two aldehydic functionalities over MCF which contains only one aldehyde moiety. Since mixing MnO_2 with circa half its weight of amorphous silica gel led to no H_2O separating from reaction solvent (EtOAc *vide supra*) without seriously impacting the yield (77% of MCF), a domain of hydrated silica gel (relatively acidic when compared with the basic oxides of manganese) could play a dual role in defeating oligoacetal formation *via* hydrolysis while precluding manganous mud by acting as a filter aid.

This was approach combined with several modifications in the preparation of pure DFF in good yield with no flash column chromatography (88 mmol from 100 mmol HMF). Using the lump sum approach (3.3 eq. MnO_2, 2: 1 mass ratio with silica gel) in EtOAc (0.17 M) with a brief reaction time (90 min) with no distillation trap, the reaction was halted by the addition of saturated sodium chloride solution to displace any furanics adsorbed on manganese surfaces. Following suction filtration through a pad of silica gel with copious EtOAc washing, the filtrate was partitioned in a separatory funnel. Notably, all the black color (finely divided manganese species) had agglomerated upon addition of brine and were neatly retained by the silica gel filter pad. Following two washings of the EtOAc phase (800 mL) with saturated aqueous sodium chloride (250 mL total volume of washings), the organic solution was dried (Na_2SO_4), concentrated, and

digested in a minimal amount of hot sonicating IPA (65 mL) for 90 min. Following chilling and subsequent suction filtration, pure DFF was isolated in 88% yield. To determine the extent of DFF loss to the brine washings, those solutions were combined and exhaustively back extracted with EtOAc ultimately affording 410 mg (3% of the input mass) of light crystalline solid.

DFF (81 mmol) was prepared beginning with HMF (100 mmol) in EtOAc (0.25 M) while consuming much less MnO_2 (260 mmol) than was employed in the general screening (Table 4.1). The MnO_2 was added bit by bit (at 20 min intervals in six portions) to the distilling reaction mixture over two h with the aid of a pressure equalizing solid addition auger under positive nitrogen pressure. Rather than a Dean-Stark trap for drying the distilling EtOAc, a Soxhlet extractor was charged with oven dried 4 Å molecular sieves. Aliquots of the reaction mixture were subjected to micro workup and NMR spectroscopic analysis at reaction time of 4 h and 10 h. Relative integrations of the aldehyde region associated with DFF and HMF were misleading, which was perhaps indicative of oligoacetal formation. Initial separation of the heterogenous reaction mixture was by suction filtration through a pad of filter aid accompanied by copious washing by EtOAc. The filtrate was adsorbed onto silica gel then purified by flash column chromatography.

It had been presupposed that a serious loss of product was occurring due to product adsorption upon the heterogeneous mixed manganese oxide surface upon completion and cooling of the reaction. Additionally, DFF presented the possibility of crystallizing from concentrated reaction mixtures which could lead to agglomerations and further occlusion of product. For those reasons, MeOH was added as the reactions (Table 4.1) cooled to increase the solubility of DFF while also theoretically displacing it on the mixed manganese oxide surfaces. Upon scaleup (300 mmol of HMF) employing the lump sum approach (MnO_2, 3.7 eq.) in DCM (0.5 M) with distillation over a moisture trap (6 h), the advantages and limitations of this approach were

encountered. While affording 97% recovery of the expected mass following suction filtration through Celite, ^{1}H NMR analysis appeared to indicate that the material was relatively pure (roughly 85% DFF) and contaminated primarily with HMF. Following trituration under IPA modified with a bit of acetone and chilling, 78% yield of DFF was isolated. The product was NMR pure but held onto a brown color not observed in other preparations.

4.3. Chlorous Acid Oxidation of Biobased Furanics

Chemoselective oxidation contextually refers to a process of reagent discrimination between multiple reducing sites within a given substrate. Examples of such reducing sites include furan-substituted primary alcohols or aldehydes as well as the furan ring itself. The transformation of HMF to HMFA was initially targeted, due to chemoselectivity challenges inherent in the electron-rich-furan system containing both furanyl alcohol and furfuryl moieties. A review of large scale oxidations, considered useful to the pharmaceutical industry,[210] quickly revealed a promising chemoselective oxidant for consideration: chlorous acid. Chlorous acid is widely encountered in the form of acidified sodium chlorite for the purpose of food processing.[211-215]

4.3.1. Development of Chlorous Acid Oxidations

The earliest reported success of chlorite mediated chemoselective oxidation reactions was made by Lindgren and Nilsson (1973).[216] That protocol employed *in situ* generated chlorous acid from reaction of sodium chlorite and sulfamic acid in aqueous solution. The sulfamic acid served a dual role wherein it mediated the equilibrium concentration of chlorous acid while sulfamate acted as a benign and carbon-neutral chlorine scavenger. The work outlined alternative stoichiometric chlorine scavengers such as resorcinol as well as the use of inert cosolvents such as *tert*-butanol for substrates with sparing H_2O solubility. Chlorine scavengers specifically reactive with hypochlorous acid produced during the reaction are required to avoid oxidation of chlorite to

form chlorine dioxide.[217, 218] Importantly, it also established the reactivity enhancement of electron withdrawing substitution on the aromatic nucleus which defines chlorite/chlorous acid as a nucleophilic oxidant.

Chlorous acid is a rare type of oxidant due to its nucleophilic reactivity. It was popularized by Bal, Childers and Pinnick (1981) since it resulted in a more eco-friendly methodology compared with many potentially competitive oxidation strategies described therein.[219] Pinnick *et al.* determined chlorous acid was a viable alternative to silver oxide protocols for such sensitive substrates as α,β-unsaturated aldehydes including cinnamaldehyde. However, protocols of this type generally have been optimized for substrates with even greater sensitivity than may be required for the bulk preparation of renewable platform chemicals. As such, those procedures rely on large stoichiometric excesses of oxidant and hypochlorite scavenger—*specifically 2-methyl-2-butene*—which leaves the scalability, sustainability and therefore the direct applicability of such oxidations for the preparation of renewable furanics (Scheme 4.1) in question.

Serendipitously, flavorful and potentially bio-renewable[220] vanillin was oxidized to electron rich vanillic acid with a low environmental factors (sEF=1.7 and cEF=156) by Lindgren and Nilsson.[216] For preparation of vanillic acid, substrate concentrations were maintained between 0.049–0.046 M and the product was isolated by suction filtration; for preparation of *o*-vanillic acid, substrate concentrations were maintained between 0.019–0.020 M and the product was isolated by liquid-liquid extraction. The use of excess H_2O and liquid-liquid extraction in the case of less H_2O soluble *o*-vanillic acid significantly worsened the environmental factors (sEF=2.1 and cEF=401) if 500 mL of diethyl ether was used in the extractive workup.

The chemoselectivity challenges inherent in vanillin are like many of those encountered in the oxidation of HMF. While the protocol of Lindgren and Nilsson (1973)[216] required almost

exactly stoichiometric amounts of oxidizer and activator/chlorine scavenger, it may be favorably and directly compared with the silver oxide protocol reported by Reichstein (1926)[61] since both afforded an 84% isolated yield of product (vanillic acid (VA) and HMFA respectively). A key difference between the reactions of vanillin and HMF is exemplified by the action of unmediated chlorous acid on furan rings which may affect oxidative-ring opening to such products as 4-oxoalkenoic acids[221, 222] whereas vanillin undergoes chlorination.

The clean conversion of 5-(acetoxymethyl)furfural (AMF) into 5-(acetoxymethyl)-2-furancarboxylic acid (AMFA) was reported by Moore and Partain (1985)[223] and strongly indicated that a carbonyl substitution on the furan core is sufficient to inhibit oxidative ring-opening while employing a modified Lindgren/Nilsson[216] protocol. The use of stoichiometric sodium chlorite and sulfamic acid was especially well suited to AMF's transformation as it was the only oxidation—*found by Moore and Partain*—which avoided undesired hydrolysis of furylic acetate ester to afford HMFA from AMF. The associated environmental factors to AMF's oxidation with chlorous acid compared favorably to that of vanillin by: (1) employing a more concentrated reaction medium (from 0.166 to 0.138 M), and (2) by improving the isolation of product by continuous liquid-liquid extraction (sEF=0.9 and cEF=40). The difference between a s*E*F and a c*E*F or *complete*-Environmental factor is the accounting for H_2O and solvents in the latter. c*E*F calculation is more difficult from the literature at large since the fine details such as exact amounts of H_2O or solvent utilized in reaction workup are not uniformly reported.

Given the favorable environmental factors (*E*Fs) associated with chlorous acid oxidations mediated by sulfamic acid, an excellent technology was identified for advancing the development of sustainable strategies towards bio-renewable furanics (Scheme 4.1). The widespread use of acidified sodium chlorite for food processing,[211, 212, 214, 215] in conjunction with the many uses of

sulfamic acid,[224, 225] and the role of chlorinated sulfamate derivatives as safer chlorine vehicles act to further support this direction of inquiry into a facile and eco-friendly oxidation technology. The rare trait of nucleophilic oxidation makes substrates such as DFF promising precursors to renewable diacids: FDCA.

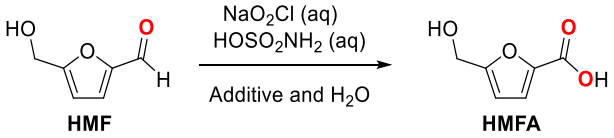
4.3.2. Reaction Optimization for HMFA

Conditions were sought which would effectively transform HMF to HMF while identifying important factors capable of modulating the types and amounts of waste generated. Ideally conditions with a wide range of applicability or general facility would be identified.

4.3.2.1. Preliminary Reaction Optimization for HMFA

Beginning with intermediate-low substrate concentration (0.03 M and 1.3 molar equivalents of oxidant and hypochlorous acid scavenger), this facile and economic protocol[216, 223] underwent multivariate optimization while considering yield of HMFA, reagent stoichiometry, additives, reaction time, environmental factors,[226] as well as solvent selection (Table 4.2, entry 1). Hydroxyacid product was isolated from ethereal extract after less than two h reaction time. Initially product HMFA appeared as a white crystalline hydrate which was dried by dissolution in EtOAc followed by subsequent rotary evaporation under vacuum. The desired product was finally isolated in 48% yield (s*E*F=5.0 and c*E*F=1347). If scaling this protocol, over a kilogram of waste would be produced per gram of isolated product. The degree of interpretation offered by a single sustainability metric usually is inversely proportional to the complexity of its execution. environmental factors lack a weighting system to penalize the generation of hazardous wastes, but their calculation is extremely straight forward. Herein is presented a composite picture of this process by considering multiple variables and their interplay.

Table 4.2 Optimization of HMF oxidation by chlorous acid.



HMF HMFA

Entry	[HMF][a]	Additive	$NaClO_2$ (eq)	H_3NO_3S (eq)	s*E*F	c*E*F	Time (h)	Yield (%)[b]
1	0.03	--	1.3	1.3	5.0	1347	1.7	48
2	0.22	--	1.1	1.4	2.6	163	2.0	77
3	0.93	--	1.0	1.3	2.9	75[c]	24	67
4[d]	0.12	EtOH[e,f]	1.1	1.2	2.1	162[c]	2.0	82
5[f]	0.08	Acetone[e]	2.0	2.3	4.2	384[g]	0.3	82
6[d]	0.10	Acetone[e]	1.0	1.1	2.0	264	0.5	83
7[d]	0.10	Acetone[e]	1.1	1.1	1.6	272	0.5	99
8[d]	0.10	Acetone[e]	1.1	1.1	1.7	276	0.5	97
9	0.10	Acetone[e]	1.1	1.1	1.6	269	2.0	99
10	0.10	--	1.2	1.2	2.0	319	2.0	88
11[h]	0.33	Acetone[e]	1.1	1.1	2.7	84[c]	1.5	70
12	0.33	DMSO[i]	1.1	1.1	2.5	109[c]	1.5	72
13	0.33	H_2O_2[j]	1.1	1.1	1.7	142	2.6	94

a: molarity; b: isolated yield; c: workup by continuous liquid-liquid extraction; d: ascorbic acid quench (0.2 eq); e:(1:1 vol:vol with H_2O); f: isolate was roughly 90% pure contaminated with ethyl ester of HMFA; g: ascorbic acid quench (1.4 eq); h: ascorbic acid quench (1.1 eq) ; i: (1 eq) and product was contaminated with dimethyl sulfone; j: 1.4 (eq) added as 3% solution. *Please refer to the experimental section of this chapter for complete reaction details.*

The waste from this reaction (Table 4.2, entries 1–13) was primarily composed of H2O contaminated with active chlorine species such as chlorine dioxide as well as N-chlorosulfamates. While the remediation of H2O contaminated thusly is rather straightforward, it would clearly be desirable to limit the generation of such waste. An important observation was made during the course of this oxidation; a decrease in the yellow-amber color typical of commercial HMF with concomitant development of a yellow-green color associated with the generation of chlorine dioxide was noted. These phenomena were rationalized as the bleaching of colored impurities as would be desirable in the process of paper pulping, and as competitive side reactions between

hypochlorous acid and chlorite. Notably the color of chlorinated H2O could be destroyed by addition of saturated ascorbic acid solution.

Simply put, the low yield and high *E* factors from entry 1 (Table 4.2) can both arise from low substrate concentration (0.03 M) during the oxidation. The concentration of HMF in aqueous solution was increased to 0.22 molar (Table 4.2, entry 2) and the reaction time was two h. The desired product was isolated in 77% crude yield but smelled faintly of acetic acid; upon recrystallization in IPA a 75% isolated yield of pure HMFA was obtained over two crops. *e*Factors were calculated based on the crude yield; this excluded the recrystallization solvent from the equation which preserved the value of comparing entries 1 and 2 (Table 4.2). The s*E*F was calculated to be 2.6; this result compared favorably with the preparation of HMFA by Reichstein (1926)[61] albeit with an unacceptably low yield. The c*E*F from entry 2 (Table 4.2) was 163 which compared very favorably to a c*E*F of 1347 from entry 1 (Table 4.2). From these initial reactions, several critical sectors were identified which required further optimization: (1) chlorite/sulfamate excesses, (2) concentration/cosolvent, and (3) reaction neutralization/workup. These were addressed in clusters.

The preparation of vanillic acid reportedly proceeded in more concentrated solution than *o*-vanillic acid likely due to the greater H_2O solubility of vanillin compared with *o*-vanillin; as such, vanillic acid could be isolated by suction filtration with any residual vanillin remaining soluble and thereby resulting in less waste produced per reaction.[216] The isolation procedure of precipitation was non-viable in the case of HMFA since it is H_2O soluble. When liquid-liquid extraction with EtOAc—*as opposed to diethyl ether*—was employed it led to a greater isolated yield (77% Table 4.2, entry 2) with corresponding improvement to the s*E*F (2.6). The limited usage of H_2O led to a significant improvement in c*E*F (163). However, an exotherm during the addition

of oxidizer was made apparent by this concentration and must be countered as further scaling or concentration changes in the reaction mixture were to be considered. Considering the principles of green chemistry, the handling of hazardous chemicals such as chlorine dioxide must be limited to maintain worker safety.[227]

Ascorbic acid was chosen as a completely benign reagent for destroying the active oxyhalides in solution. Other common reducing agents were considered but excluded due to their alkaline nature and potential side products generated upon reacidification. Sulfite solutions could have produced sulfurous acid and thereby evolved noxious sulfur dioxide gas. Neutralization of the oxidizing reaction mixture by sodium thiosulfate could have generated colloidal sulfur under the acidic conditions which is totally unacceptable for monomer production. Mere substoichiometric amounts of ascorbic acid (typically around 0.2 molar equivalents) were required since most of the hypochlorous acid produced during the reaction was locked up in nonvolatile *N*-chlorosulfamates.

A much more concentrated reaction mixture was investigated and required a greater reaction time to attenuate the exotherm of oxidizer addition; this obligatory tedium decreased the facility of employing concentrated chlorous acid reaction mixtures. However, when proper care was taken the reaction proceeded in fair yield (67%, Table 4.2, entry 3) with the addition of oxidizer taking four h and the mixture stirred for another twenty h as its surrounding ice bath thawed. The s*E*F for entry 3 actually worsened (2.7) due to the lowered yield while the c*E*F was significantly improved from entry 2 (Table 4.2) by reduction in H_2O consumption (75). Had the theoretical maximum yield of product been isolated, the s*E*F would have been 1.6 and the c*E*F would have been 50. The crude product isolated smelled faintly of acetic acid, so an attempt to purify it without recrystallization was made by triturating the solid beneath a mixture of DCM and

a bit of EtOAc followed by suction filtration. Sadly, while this process refined the product (7.51 g) was only 45% of the overall theoretical yield; better isolation techniques were required.

While the chlorous acid oxidation provided extreme chemoselection between furylic hydroxyls and furylic aldehydes, the lackluster yields (Table 4.2, entries 1–3) could perchance be attributed to the formation of sulfamate esters with HMF or HMFA which would lead to loss of product. Esterification reactions of this type would likely be exacerbated by higher temperatures and higher concentrations such as in Table 4.2, entry 3. EtOH was considered as a compatible cosolvent which could act as a sacrificial hydroxyl group in the formation of sulfamate esters. EtOH provided an additional benefit as it could be easily removed by rotary evaporation under reduced pressure following the oxidation but prior to the isolation of HMFA; this was expected to increase the extraction efficiency in the final workup.

4.3.2.2. Cosolvent Additive Investigation in Reaction Optimization for HMFA

The role of EtOH as cosolvent was explored at lower concentration (0.12 M) which allowed for a return to a two h reaction time while the temperature of the reaction was monitored internally and controlled by periodic addition of H_2O ice to the stirring reaction. Additional features of this experiment included concurrent addition of aqueous sulfamic acid and aqueous sodium chlorite since there was a fear that too high an acid concentration could be degrading HMF substrate; these modifications resulted in a higher yield (82%, Table 4.2, entry 4) but with unforeseen consequence. The product isolated from this reaction was contaminated with ethyl 5-(hydroxymethyl)-2-furancarboxylate. This interesting outcome provided another plausible mechanism by which condensation products from HMFA and hydroxylic species in solution (itself or HMF) could be limiting the efficiency of this reaction. Such features must be considered when employing higher concentrations of substrate in the reaction mixture.

At this stage of the investigation due to considerations of worker safety, active chlorine in the reaction medium (Table 4.2, entry 4) was quenched with ascorbic acid (0.15 molar equivalents) at the two h mark; this addition extirpated the greenish-yellow color associated with chlorine dioxide. These practices led to an improved s*E*F (1.8) and c*E*F (145) without significantly sacrificing the isolated yield despite contamination with ethyl ester. The cosolvent strategy seemed promising, but a cosolvent was required which would not engage in esterification of HMFA.

Acetone was then tentatively considered as a benign alternative to EtOH. Acetone could act as a suitable cosolvent despite the potential formation of chloroform and acetic acid by the haloform reaction with hypochlorous acid.[228, 229] That reaction is typically carried out under basic conditions wherein the initial addition of halogen is the rate limiting step. In the acidified media employed during chlorous acid oxidation, formation of chloroacetone was of greater concern[230] although that side reaction should not be observed if sulfamic acid acts as an active chlorine scavenger as envisioned. Even if formed, chloroacetone undergoes photolysis to afford hydrogen chloride and not chlorine radicals so the danger to the upper atmospheric ozone layer is not heightened. However, if generated, the negative ramifications of human exposure to this historical chemical weapon would not be tolerable.

The scale of these reactions was decreased, relative volumes of EtOAc utilized in the extraction was increased and reaction times were kept short (20–30 min) with no ill effect upon the isolated yields of HMFA (82% and 83%, Table 4.2, entries 5 and 6). Sodium chlorite solutions could be added in as little as three min since the exotherm was negligible at this scale and concentration. In entry 5, twice the usual amount of oxidant, sulfamic acid and subsequent ascorbic acid were employed with negligible impact other than to the s*E*F (4.1 *versus* 1.8). The c*E*F (384 and 475 respectively) were fairly consistent to each other which implies that variations between

substrate, reagent, and quench stoichiometry were minor players in the determination of c*E*Fs. The use of equal and seemingly excessive amounts of extraction solvent (EtOAc) in both reactions greatly increased the c*E*Fs. The results indicated that similar isolation of extractables was achieved by the large excess of EtOAc employed in the workup while providing clear indication that oxidant was not getting consumed by side reactions fast enough to confound creation of HMFA.

If exhaustive extraction is required to completely isolate H_2O soluble HMFA, then the use of continuous liquid-liquid extraction should be implemented to reduce solvent consumption; while this paradigm shift could negate the utility of cosolvent employment in the preparation of HMFA by chlorous acid oxidation, the use of acetone was foreseen as a fortuitous route to a widely applicable transformation; such a protocol wherein typical cosolvents such as *tert*-butanol would be insufficient to solvate some substrates or might unduly complicate the purification process. Since drastic concentration of the reaction mixture leads to larger exotherms and potential degradative esterification of substrate and product, there is an upper limit on the feasible reaction concentration in aqueous solution. Even while employing continuous liquid-liquid extraction there are limitations to how much aqueous phase can be worked up as constrained by apparatus capacity. Unless you have access to a skilled glass blower, the apparatus size is limited to circa 100 mL in the commercially available Gregor extractor.

Prior to final optimization of HMF's transformation into HMFA, the conditions of entry 6 (Table 4.2) were modified slightly to create a general protocol designed to tolerate a wide range of furanic substrates: (1) the stoichiometric excess of sulfamic acid was set to 1.1 molar equivalents) while it was added directly to the aqueous acetone reaction mixture prior to chlorite addition, (2) sodium chlorite (1.1 molar equivalents) was added as an aqueous solution (roughly 10% by weight), (3) the reaction time was kept at 30 min, and (4) the ratio of EtOAc employed in

the workup was increased (30 mL per 1 mmol substrate); this protocol afforded HMFA in very high yield (99%, Table 4.2, entry 7) and was very reproducible (97%, Table 4.2, entry 8). The s*E*Fs were very good (1.6 and 1.7 respectively) while c*E*Fs (272 and 276 respectively) were inflated by the exhaustive extraction. Comparing the c*E*Fs of entries 6–8 (Table 4.2) indicates how closely the impact of extraction solvent and yield have been balanced in this general protocol.

A set of experiments (Table 4.2, entries 9 and 10) probed the impact of the acetone cosolvent strategy under the generalized reaction conditions and without ascorbic acid quench. The difference between entries 9 and 10 (Table 4.2) was the use of acetone cosolvent which entry 10 was lacking. Not employing acetone cosolvent meant there was a greater ratio of H_2O to HMFA during the standardized extraction workup (30 mL/1 mmol substrate) and resulted in a lower isolated yield (88%) which correspondingly inflated the s*E*F (from 1.6 to 2.0) and the c*E*F (from 269 to 319).

Instead of the ascorbic acid quench upon completion of the typical 30 min reaction time, the reaction mixtures were sparged with air in a well ventilated fume hood for 90 min. The consequence of this sparging was loss of yellow-color associated with chlorine dioxide. Later it was discovered that an aqueous solution of ascorbic acid charged into the rotary evaporator's catch flask was even more effective in removing the chlorine dioxide from the reaction mixture in so far as it contained and destroyed the chlorine dioxide and required no lengthy sparging time. If scaling this type of reaction, the chlorine dioxide containing effluent from the sparging mixture should be forced into a gas trap containing reducing agent or reducing solution should be charged into the rotary evaporator's catch flask.

The effects conferred by different additives and workup procedures was evaluated with a series of experiments summarized in entries 11–13 (Table 4.2). The experiments were carried out

at with initial substrate concentrations of 0.33 M. When acetone cosolvent was employed on the 200 mmol scale (Table 4.2, entry 11), the reaction temperature was monitored internally and controlled (10–19 °C) by submersion of the reaction mixture in an ice bath and modulating the dropping rate of sodium chlorite solution (10% by weight). The reaction mixture was stirred for an additional h as it warmed to ambient temperature with no notable latent exotherm. The mixture was quenched with stoichiometric ascorbic acid (220 mmol) to lure out any extreme complications from adding so much additional material to the reaction mixture. The mixture was continuously extracted with EtOAc (700 mL) for nearly 9 h under argon, by which time the extract solution was dark amber and contained black flecks. The extract was gravity filtered and concentrated to afford light solid stained with dark amber solution.

Sonication of the crude residue in EtOAc (150 mL) afforded light colored solid beneath dark amber solution. Upon isolation, the resulting yield of pure but somewhat discolored HMFA was 70%. The s*E*F was moderate (2.7) due to the lower yield while the c*E*F was good (84) for this series thanks to the use of continuous liquid-liquid extraction. Comparing the coloration of the reaction mixtures from entries 3 and 11 (Table 4.2), extended exposure to chlorine dioxide did not damage the appearance at all, whereas an equivalent of ascorbic acid created numerous obstacles to the isolation of pure material. Upon considering the results in relation to multiple other experiments (Table 4.2, entries 6–10), it can thereby be concluded that while the addition of ascorbic acid in substoichiometric amount to small scale reactions which are subsequently extracted at ambient temperature is a useful tactic; but the reactivity of chlorine dioxide[231] may not warrant its post-reaction destruction upon scaleup. Could an effectively selective noncarbonaceous hypochlorous acid scavenger system be identified such that chlorine dioxide generation might be totally prevented?

4.3.2.3. Hypochlorous Acid Preventing Additives in Reaction Optimization for HMFA

In that vein, consideration was given to a report made by Dalcanale, and Montanari (1985). Therein dimethyl sulfoxide (DMSO) or alternatively hydrogen peroxide (H_2O_2) could be added to acidified mixtures of sodium chlorite which achieved selective aldehyde oxidation into carboxylic acids.[232] These additives were particularly useful for aldehyde substrates and acid products which are incompatible with hypochlorous acid. Their preferred reaction medium for preparation of cinnamic acid was cinnamaldehyde (50 mmol) in acetonitrile (50 mL) with sodium dihydrogen phosphate (20 mL of 8% by wt. aqueous solution) and H_2O_2 (52 mmol of 35% by wt.). The temperature of their reaction was controlled (10 °C) as sodium chlorite (70 mmol in 1 M aqueous solution) was added dropwise. The reaction was quenched after about an h by addition of sodium thiosulfate (3 mmol) with subsequent reacidification to afford cinnamic acid (95% yield) as crystalline solid.

The protocol described for cinnamic acid[232] was adjusted to speed up the reactions by adding additional H_2O_2 (250 mmol for 50 mmol substrate). Also, pH of the reaction mixture was lowered (to approximately 2) by careful addition of concentrated hydrochloric acid to the sodium dihydrogen phosphate buffer. Furfural was converted by this modified procedure into furoic acid (82% isolated yield) and maleic acid (15% isolated yield)! When applied to *p*-hydroxybenzaldehyde, the accelerated procedure afforded only 7% isolated yield of *p*-hydroxybenzoic acid with quinone and chlorinated tars as the major products.

An insightful replacement of acetonitrile as reaction solvent with DMSO—*1 M substrate concentration while sodium dihydrogen phosphate (20 mL of 8% by wt. aqueous solution)*—led to an 86% isolated yield of *p*-hydroxybenzoic acid when sodium chlorite (70 mmol in 1 M aqueous solution) was added dropwise over two h and the reaction was stirred overnight; the reaction was

stirred overnight then made alkaline by addition of saturated aqueous sodium hydrogen carbonate. The aqueous mixture was washed three times with DCM to remove much of the DMSO and dimethyl sulfone. Subsequent reacidification with 10 M hydrochloric acid then afforded crystalline product.

Based on the Dalcanale and Montanari protocols,[232] several questions were raised which if answered could provide insight in the further development of sustainable technologies focused on HMFA production: (1) What would be the effectiveness of these additives (H_2O_2 or DMSO) in the presence of sulfamic acid (molecular wt.=97 g/mol) as opposed to sodium dihydrogen phosphate (120 g/mol)? (2) If reactions were kept constrained to aqueous solution as in the case of HMFA production, is there any reason to handle concentrated (35%) H_2O_2 when 3% USP grade is so widespread and benign? (3) Given the alacrity of chlorous acid's reaction with aromatic aldehydes, is more than one molar equivalent of DMSO necessary?

The effectiveness of DMSO as a masking agent was characterized for aqueous chlorine, hypochlorous acid, and *N*-chlorosulfamic acid in spectroscopic determination of oxychlorines: chlorine dioxide, chlorate, and chlorite.[233] DMSO and aqueous chlorine react to yield two equivalents of chloride and one of dimethyl sulfone. The rate of reaction is accelerated at lower pH, and dependent not on chlorine concentration but on that of hypochlorous acid. The redox-potential of DMSO was elevated by lowering the pH of aqueous solution such that only hypochlorous acid could oxidize it under acid conditions.

DMSO utilized in tandem with sulfamic acid should preclude the formation of chlorine dioxide by destroying hypochlorous acid directly. It could also lead to waste streams which contain no active chlorine by reverting *N*-chlorosulfamic acid to benign sulfamic acid *via* intermediate hypochlorous acid; sulfamic acid and dimethyl sulfone have both been found rather benign in

rats.[234, 235] With these thoughts in mind, an experiment was carried out with one equivalent of dimethyl sulfoxide, one molar equivalent of sodium chlorite, and one molar equivalent of sulfamic acid at 0.3 M substrate concentration in H_2O (Table 4.2, entry 12). Some notes on the peculiarities of this protocol: (1) the exotherm observed by internal thermal probe upon contact of the chlorite solution with the reaction mixture containing DMSO was much greater than in any other previous experiment, (2) the yellow color of the reaction mixture dissipated significantly from the initial amber color, never developed the sickly green color associated with chlorine dioxide, but nevertheless was much more yellow than other chlorous acid oxidation mixtures, (3) the reaction mixture retained a degree of turbidity.

Following gravity filtration, the reaction mixture was subjected to continuous liquid-liquid extraction (EtOAc) under atmosphere for 9.5 h. Amazingly, the color of the aqueous phase and the boiling solvent phase never developed the amber color, much less the black flakes encountered in entry 11 (Table 4.2) but the extract solution was orange. The progress of the extraction was tracked by periodic sampling of the extract returning to the boiling flask; following concentration of the aliquots to determine a %solids content, ^{1}H NMR was employed to analyze the relative composition of the solids. Upon concentration of the extract solution, a wet looking cream colored solid developed which was digested in a sonicating mixture of Hex and EtOAc (75:25 vol:vol). The digestion was cooled, the solid isolated by suction filtration, rinsed with Hex to afford a solid phase mixture of HMFA (61%) and dimethyl sulfone (39%) characterized by ^{1}H NMR.

This worked out to a 72% yield of HMFA if it could be isolated from the sulfone. It also worked out to 69% of dimethyl sulfone predicted by the theoretical yield. Subsequent esterification reactions (*vide infra*) could discern no ill effect imparted by the dimethyl sulfone contamination which was partially removed during that purification. Depending on the source of HMF (which is

often synthesized in DMSO and carries contaminants therefrom),[77] as well as the designs upon HMFA produced, this variant of chlorous acid oxidation could prove to be a very effective in scalable preparations.

Finally, a chlorous acid oxidation was carried out in an aqueous solution (0.3 M) containing H_2O_2 (1.4 eq) from dilution of a 3% USP grade solution. Amalgamation of HMF, sulfamic acid, H_2O and H_2O_2 led to a slow dissipation in the reaction's color as it was stirred cold (10 °C). A 1 M solution of aqueous sodium chlorite was added dropwise while the internally monitored temperature was controlled (10–15 °C) over 15 min. The union of chlorite with reaction solution was very obviously not as exothermic as the addition to aqueous DMSO (entry 12, Table 4.2). After two h of stirring as the ice bath thawed, the reaction was exhaustively extracted, first with diethyl ether, then with EtOAc. The extracts were all colorless but a little turbid with dispersed H_2O. The extracts were kept separated and stored capped over anhydrous sodium sulfate for 48 h. The extracts were individually tested with starch iodide peroxide indicator strips; all tested negative while the aqueous phase which had been stored open to the atmosphere turned the indicator strip black! The aqueous phase was diluted, iced, and neutralized by addition of sodium thiosulfate solution.

The organic extracts were combined and upon concentration and drying, afforded strikingly white HMFA (94%). The s*E*F for this reaction was very good (1.7) and the c*E*F (142) suffered a bit due to the iterative extraction employed to avoid heating the oxidizing reaction mixture. These experimental conditions (Table 4.2, entry 13) have substantial potential for further optimization into a scalable platform technology since if the stoichiometric ratios of the reaction were completely balance, the role of sulfamic acid would be catalytic while the only side products would be sodium chloride and oxygen. A combined system of catalytic sulfamic acid with

hydrogen peroxide as hypochlorite scavenger has been explored in the oxidation of dialdehyde cellulose.[236]

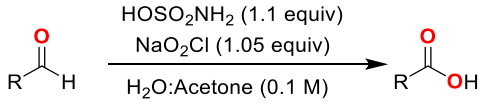
4.3.3. Investigation of Substrate Scope: Chlorous Acid Oxidations

A variety of substrates were screened (Table 4.3) by employing the conditions from entries 7 and 8 (Table 4.2). The method was very robust and largely independent to varying oxidations states present in substitutions on the furanic core (entries 1–15, Table 4.3). In addition to effective aromatic aldehyde transformation,[216, 223] aqueous chlorous acid oxidation in the presence of acetone cosolvent demonstrated phenomenal tolerance for labile side groups including furoate ester moieties as well as oxidatively unstable groups such as furylic methyl groups and electron rich aromatic systems. A significant advantage to the isolation of some products was afforded by the acetone cosolvent system when its removal resulted in precipitation of those carboxylic acids (entries 1, 2, and 10–15, Table 4.3).

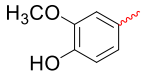
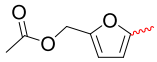
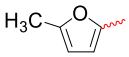
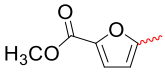
4.3.3.1. General Protocol for Chlorous Acid Oxidation (Table 4.3)

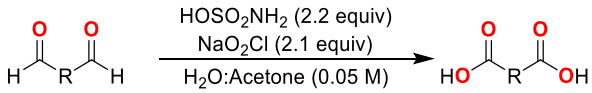
A solution of substrate (10 mmol, 0.2 M) in acetone was prepared then diluted with DI H_2O forming a roughly 0.1 M solution in aqueous acetone (50:50 vol:vol). An approximately 1 M solution of technical grade sodium chlorite in H_2O (10.5 mmol, in 10 mL) was prepared. Sulfamic acid (11 mmol) was added to the aqueous acetone substrate solution as a granular solid while the mixture stirred. The sodium chlorite solution was added dropwise over 10 min to the stirring aqueous acetone reaction solution. On this small scale, the exotherm was negligible and not controlled. The mixture was stirred following completion of aqueous chlorite addition for 20 min, then quenched by adding solid ascorbic acid (1.5 mmol). The reaction solution was liberated of acetone by concentration with rotary evaporation under reduced pressure. Products were isolated from the concentrated reaction mixture by either extraction or precipitation.

Table 4.3. Substrate scope of optimized oxidation by chlorous acid

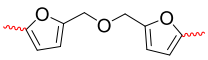
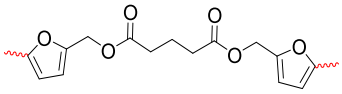
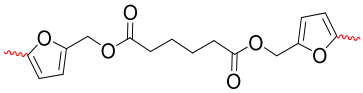
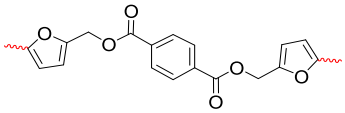


General Reaction for Monoaldehyde Substrates

Entry	R	Substrate	Product	Purification	Yield [a]
1		**V**	**VA**	Precipitation	88
2[b]					45
3		**AMF**	**AMFA**	Extraction	99
4[b]					97
5[c]					93
6		**MF**	**MFA**	Extraction	75
7[b]					22
8[d]					51
9		**MCF**	**MCFA**	Extraction	97
10				Precipitation	77



General Reaction for Dialdehyde Substrates

Entry	R	Substrate	Product	Purification	Yield [a]
11		**DFF**	**FDCA**	Precipitation	87
12		**OBMF**	**OBMFA**	Precipitation	87
13		**(HMF)G**	**(HMFA)G**	Precipitation	91
14		**(HMF)A**	**(HMFA)A**	Precipitation	92
15		**(HMF)T**	**(HMFA)T**	Precipitation	95

a: isolated (%); b: acetone cosolvent was replaced with EtOH; c: solid NaO_2Cl was added to 1:1 vol:vol mixture of acetone: H_2O where the substrate concentration was 0.5 M; d: the substrate was dispersed in H_2O (0.1 M) and a solution was formed only after addition of MeOH (10 vol% relative to H_2O)

Isolation by extraction: the concentrated reaction mixture was extracted with 100 mL EtOAc three times. The extracts were combined, backwashed with saturated aqueous sodium

chloride (10–20 mL), dried (Na_2SO_4), isolated and concentrated *in vacuo* to afford solid products. If the material smelled strongly of acetic acid or was gummy when scraped, Hex or heptane was added (10 mL) as the residue was triturated by metal spatula with just enough EtOAc added to make the solid free. The washing solution was carefully removed by pipette and the washing was repeated if necessary. Residual washing solution was removed *in vacuo*, affording pure carboxylic acid products.

Isolation by precipitation: the concentrated reaction mixture containing solid precipitate was chilled in an ice bath then separated by suction filtration over a 1 cm Hirsch funnel (qualitative filter paper). The filter cake was pressed, rinsed with ice-cold DI H_2O (total volume of filtrate was 100 mL), dried on the filter over suction, chopped, then spread on paper to air dry affording pure dicarboxylic acids.

4.3.3.2. Chlorous Acid Oxidation: Vanillin

The method was also comparable in effectiveness to the original substrate of Lindgren and Nilsson (88% *versus* the reported 84%, Table 4.3, entry 1).[216] When EtOH replaced acetone in the oxidation (Table 4.3, entry 2) not only was the yield by precipitation depressed, ethyl vanillate was detected in the NMR spectrum of the isolated white solid product. The transformation of vanillin (V) cleanly to vanillic acid (VA) was observed in high yield when the general reaction conditions employing EtOH as cosolvent were followed.

These results showcased the development of a protocol more robust than the original since it also worked well with HMFA (Table 4.2) without sacrificing the technology's original performance. In every case wherein colored impurities were apparent in the furanic substrate, there was significant bleaching and improvement to the color of the isolated products. This reaction

thereby achieved ancillary benefit to the desired chemoselective transformation by capitalizing on the otherwise wasted oxyhalide side-products to enhance the appearance and purity of products.

4.3.3.3. Chlorous Acid Oxidation: 5-(Acetoxymethyl)furfural

The substrate of Moore and Partain (1985), 5-(acetoxymethyl)furfural (AMF), was the closest electronic analog to HMF investigated and underwent transformation with very high yield to afford 5-(acetoxymethyl)-2-furancarboxylic acid (AMFA, 99%, Table 4.3, entry 3).[223] Capping of the hydroxymethyl moiety with an acetate ester significantly reduced the H_2O solubility of the aldehyde-substrate and acid-product while precluding the consumption of those materials in esterification side reactions. As indicated by this result, the generalized reaction conditions did not suffer from decomposition of oxidizer or from side reactions with the C2,C5-furan ring. This made the transformation of AMF to AMFA the perfect candidate for elaboration. Surprisingly, when EtOH replaced acetone as the cosolvent under the standardized conditions, AMFA (97%, entry 4, Table 4.3) was isolated free of any ethyl esters. When the standardized conditions were harshly modified in terms of substrate concentration (from 0.1 M to 0.5 M) and sodium chlorite delivery method (instead of as a 10% by wt. solution, as solid flakes), there was hardly any negative consequence (93%, entry 5, Table 4.3).

4.3.3.4. Chlorous Acid Oxidation: 5-Methylfurfural

The oxidatively susceptible 5-methylfurfural (MF) was converted to 5-methyl-2-furancarboxylic acid (MFA) with moderate yield (75%, entry 6, Table 4.3). Notably, the crude acid product was always contaminated with some residual aldehyde which was not observed with other substrates. This was attributed to the electronic effect upon relative reactivities initially commented on by Lindgren and Nilsson;[216] MF was the least electrophilic substrate investigated, so the competing reaction between chlorite and hypochlorous acid contributed more significantly

to the consumption of chlorite thus making it the limiting reagent. When EtOH replaced acetone in the general procedure the crude product isolated by extraction contained ethyl 5-methylfuroate. Digestion in Hex with a bit of EtOAc—*a typical method for removing residual acetic acid*—resulted in isolating a low yield of MFA (22%, entry 7, Table 4.3). When a bit of MeOH (10% by volume) was used to supplement the reaction mixture, a better yield of MFA was obtained (51%, entry 8, Table 4.3) and the concentrated washings contained methyl 5-methylfuraote.

An interesting and robust method for aerobic oxidation of furanic aldehydes utilizing *N*-heterocyclic carbenes was recently developed and performed best for substrates lacking electron withdrawing substitution at C5 such as: (1) hemicellulose derived furfural, (2) flavorant MF, and (3) HMF.[237] The efficient metal-free methodology overlapped and complemented the strategy disclosed herein by affording outstanding yields of their title compound: 2-furancarboxylic acid. That oxidation displayed an opposite electronic trend in reactivity as compared with chlorous acid. That protocol can effectively transform those substrates not well-tolerated by chlorous acid technologies but would likely fail in transformation of highly oxidized furans such as in conversion of DFF into FDCA.

4.3.3.5. Chlorous Acid Oxidation: 5-(Methoxycarbonyl)furfural

Desymmeterized FDCA (5-(methoxycarbonyl)furan-2-carboxylic acid, MCFA) has been prepared from dimethyl 2,5-furandicarboxylate in 50% *via* statistical mono-deprotection in methanolic sodium hydroxide by Shen *et al.* as the basis of their "asymmetric monomer strategy".[144] MCFA was prepared from 5-(methoxycarbonyl)furfural (MCF) by applying the general protocol for chlorous acid oxidation in fantastic yield (97%, entry 9, Table 4.3) with extractive workup. This substrate was tricky, in that copious white solid would precipitate as the acetone cosolvent was removed prior to final isolation; small amounts of residual acetone

drastically altered the final isolated yield by precipitation strategy (77% average of three trials, 72%, 77%, 82%, entry 10, Table 4.3.). Successful oxidation of MCF (entries 9 and 10, Table 4.3) provided a strong indication that there would be no electronic barriers precluding the preparation of FDCA directly from DFF by chlorous acid in aqueous acetone.

4.3.3.6. Chlorous Acid Oxidation: Dialdehyde Substrates

FDCA was prepared from DFF reliably and in good yield (87%, entry 11, Table 4.3) by applying the general protocol for chlorous acid oxidations with minor modification; the concentration of substrate was decreased to 0.05 M to maintain a similar concentration (0.1 M) of functionality in dialdehyde substrates. The FDCA prepared by chlorous acid oxidation was imbued with refined status and provided a scalable route from HMF with multiple opportunities to purify the intermediates while avoiding column chromatography. This method tolerated a range of impurity profiles while providing colorless FDCA suitable for applications in polymer chemistry.

Condensation reactions provide additional avenues for redox-efficient diversification of bio-renewable platform chemicals. Investigations into condensation products from HMF have included development of novel monomers such as 5,5'-[oxybis(methylene)]bis[2-furancarboxaldehyde]. However, the condensation route is often plagued by similar issues as the oxidation products. Nonetheless, a route to dialdehydes and diacids from HMF has been recently described along with investigation into the promising properties of polyesters derived thereof.[79] The hydrolytically unstable difurylic ether linked 5,5'-[oxybis(methylene)]bis[2-furancarboxylic acid] was prepared by the same method as FDCA (87%, entry 11, Table 4.3) with identical result (87%, Scheme 4.7). The ether-linked diacid, 5,5'-[oxybis(methylene)]bis[2-furancarboxylic acid], has also been prepared by Chundry and Smantz (1981) in 93% isolated yield by silver oxide suspended in aqueous acetone.[76]

Ester-linked dialdehyde substrates were prepared in greater than 90% yield (*vide supra*); their purification by precipitation and filtration was simple. These tan solids all underwent smooth conversion to modular diacids in greater than 90% yield by application of the general protocol for chlorous acid oxidation in aqueous acetone (entries 13–15, Table 4.3); facile isolation by precipitation provided renewable diacids which would be very difficult to selectively procure by other methods. Exquisite control was offered by the chemoselective chlorous acid oxidation reaction described herein. Notably, the reluctance of this protocol to induce hydrolysis or over-oxidation has greatly expanded the number of renewable furanics now available. The development of modular polyester precursors with tunable properties demonstrates the viability of this strategy for valorization of biobased platform chemicals through a strategy of diversification.

4.4. Preparation of Furan-Dienes for Benzyne Diels-Alder Reactions

Valorization of cellulose derived furan-dienes by cycloaddition with potentially biorenewable strain-driven super dienophile benzyne has been explored in the following chapter of this dissertation. The chemoselective oxidation protocols discussed earlier in this chapter provided a suite of symmetrically and differentially C2,C5-disubstituted furanic platform chemicals with established applications in sustainable polymeric materials science. In order to determine the stereoelectronic influences of various substituents upon the furan-diene core, multiple masking strategies were employed to protect hydroxylic moieties from side reactions with benzyne. Whether considering the surgical chemoselectivity challenges presented in esterification of HMFA, the conjugate reduction of furan diacrylate esters, or purification of commercially available FDCA subsequent to esterification, many of the adapted protocols presented herein provided significant advances in accessing biobased furanic polyester precursors while paving the way for their transformation into novel benzofuzed-heterobicylces.

4.4.1. Chemoselective Esterification of HMFA

Moore and Kelly reported preparation of AB type polyester precursor methyl 5-(hydroxymethyl)-2-furoate in high yield despite the competitive processes of acid mediated chlorodehydration—*to afford methyl 5-(chloromethyl)-2-furoate*—and etherification—*to afford methyl 5-(methoxymethyl)-2-furoate.*[129] No optimization details were provided, and the only specifications regarding concentration of acid mediator were as follows: HMFA "*(0.106 mol), was dissolved in 200 mL of a methyl alcohol solution containing 2% hydrogen chloride by weight and refluxed for 6 h*"; a bit arcane when considering the requisite balance of factors necessary to afford predominantly the methyl ester. Was that enigmatically specific phrasing crafted to be esoteric? There are a few ways to interpret "*2% hydrogen chloride by weight*" for anyone familiar with recondite methods of hydrogen chloride generation or delivery. Was anhydrous hydrogen chloride generated by combination of potassium chloride and sulfuric acid, then bubbled into MeOH until the weight of the solution increased by 2%? Did they mean to imply they added concentrated hydrochloric acid such that the MeOH would contain 2% hydrogen chloride by weight? Were they even dealing with a weight by weight percentage, or was that a reference to some weight by volume percentage?

Deliberation ensued. Given the parameters of concentrated hydrochloric acid including molecular weight (36.5 g/mol), density (1.2 g/mL at 25 °C), weight percentage of hydrogen chloride (35–37%) and molarity (12 mol/L) combined with knowledge of the substrate scale (106 mmol), the phrasing was dissected; it seems likely they were employing 1 molar equivalent of hydrogen chloride delivered in the form of ubiquitously available 12 molar hydrochloric acid (8.83 mL) which would weigh 10.6 g wherein 37% of that mass would be hydrogen chloride (3.9 g). When considering the mixed percentage defined as the fraction from weight of hydrogen chloride

divided by volume of MeOH then multiply by 100, it equates to 1.96% weight/volume! So perhaps they dissolved HMFA in MeOH (0.5 M) then added very nearly 1 molar equivalent of HCl in the form of concentrated hydrochloric acid?

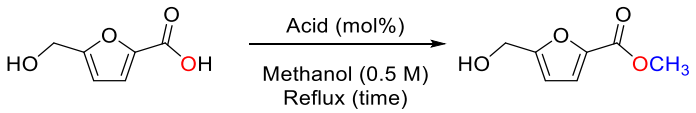
That became the starting point for optimizing the chemoselective Fisher esterification of HMFA in MeOH (Table 4.4). Initially the suspected conditions for the literature report were replicated (entry 1, Table 4.4); the yield of methyl 5-(hydroxymethyl)-2-furoate was 87% isolated following flash column chromatography. The reaction was very reliable on both the 10 and 50 mmol scale while coming in close agreement to the 85% isolated yield by vacuum distillation reported by Moore and Kelly.[129]

4.4.1.1. General Procedure

A flask was charged with HMFA (1 eq.), and HPLC grade MeOH. Acid (0.1 or 1 eq.) was added dropwise to the stirring solution. The flask's headspace was flushed with argon and sealed beneath a reflux condenser. The mixture was warmed to a gentle reflux (oil bath typically set to 80 °C) under argon for the specified reaction time (usually 6 or 29.5 h). The reaction mixture was neutralized by addition of concentrated sodium hydrogen carbonate(aq) (1 eq.), concentrated under reduced pressure, and partitioned with EtOAc. The EtOAc solution was washed with saturated sodium chloride(aq), isolated, dried (Na_2SO_4) and adsorbed onto silica gel prior to purification by flash column chromatography.

Next, the utility of anhydrous hydrogen chloride in MeOH was tested (73%, entry 2, Table 4.4). It makes sense that the lack of a MeOH-H2O azeotrope combined with the H2O delivered with HCl would confer some chemoprotection to the furylic hydroxyl moiety. It also seems very unlikely that a specialty of hydrogen chloride in MeOH was utilized in the initial report without specific mention.

Table 4.4. Chemoselective esterification: methyl 5-(hydroxymethyl)-2-furoate



Entry	Acid	Acid (mol%)	Reaction Time (h)	Isolated Yield (%)
1	Conc. HCl	100	6	87
2	0.2 M Methanolic HCl	100	6	73
3	H_2SO_4	100	6	94
4	Conc. HCl	10	<29.5	89
5	Conc. HCl	10	29.5	97
6	H_2SO_4	10	29.5	97

Complete details have been included in the experimental section of this chapter.

In both entries (1 and 2, Table 4.4), small amounts of methyl 5-(chloromethyl)-2-furoate and methyl 5-(methoxymethyl)-2-furoate were isolated. One must ponder the extent to which hydrogen chloride is required for this Fisher esterification. Would not a less nucleophilic conjugate base to the acid mediator of the reaction led to greater selectivity for the desired 5-(hydroxymethyl)-2-furoate? Concentrated sulfuric acid (1 molar equivalent) was substituted for concentrated hydrochloric acid and resulted in significantly greater yield of 5-(hydroxymethyl)-2-furoate (94%, entry 3, Table 4.4).

The outcome of entries 1–3 (Table 4.4) can be rationalized by implicating the intermediacy of 5-(chloromethyl)-2-furoate in the formation of methyl 5-(methoxymethyl)-2-furoate. The rate of chlorodehydration would depend on the concentration of protonated (hydroxymethyl) moieties and the concentration of chloride (same in both entries 1 and 2 while it was zero in entry 3). A subsequent reaction (either solvolysis or hydrolysis) leads to the formation of either methyl 5-(methoxymethyl)-2-furoate or regeneration of methyl 5-(hydroxymethyl)-2-furoate respectively. The balance of these reactions is reflected in entry 1, while the balance is shifted by the lower H_2O

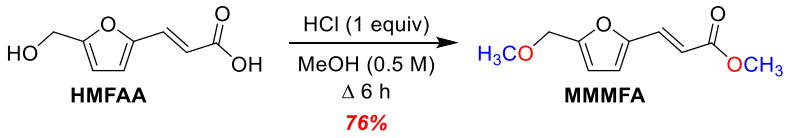
content of entry 2; in entry 3, there was no chloride, so there was no 5-(chloromethyl)-2-furoate so there was a much greater yield of 5-(hydroxymethyl)-2-furoate.

The formation of methyl 5-(methoxymethyl)-2-furoate directly from solvolysis of protonated methyl 5-(hydroxymethyl)-2-furoate could also be in play since the hydroxymethyl moiety could be undergoing replacement with sulfonate. The use of substoichiometric amounts of acid was explored (10 mol%) in entries 4–6 (Table 4.4). Since the acid concentration would also determine the rate of esterification, reaction times were extended to nearly 30 h of reflux in these side by side experiments. Serendipitously at 29.5 h the mixtures were checked and one of the duplicated 10% HCl in MeOH experiments (89%, entry 4, Table 4) had stopped heating sometime since the 18 h observation. The reactions were pulled and worked up at that point. Both reactions utilizing 10 mol% acid (conc. HCl or conc. H_2SO_4) afforded 97% isolated yields of methyl 5-(hydroxymethyl)-2-furoate (entries 5 and 6, Table 4.4).

4.4.1.2. Extension of the Moore and Kelly[129] Esterification Conditions

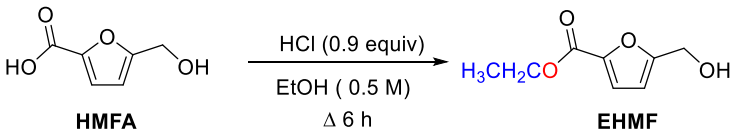
An analog of 5-(hydroxymethyl)-2-furoic acid, 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid was prepared crude from HMF by Knoevenagel condensation then subjected to 3% sulfuric acid in refluxing MeOH (40 mL for 6.3 g initial HMF) for 15 h to afford methyl 3-(5-(hydroxymethyl)furan-2-yl)acrylate in 30% isolated yield.[208] In another case, very similar Knoevenagel condensation conditions afforded 2.5 g of 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid from 6.3 g of HMF; in that case methyl 3-(5-(hydroxymethyl)furan-2-yl)acrylate (2.2 g) was prepared by reaction of the acrylic acid with diazomethane. Dyuti Dawn, a high school researcher in the Sibi group has prepared 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid in 92% isolated yield from HMF following modifications of a report made by Serum *et. al.*[95]

When 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid was subjected to the conditions of Moore and Kelly (Scheme 4.9),[129] the extent of their amazing chemoselective oxidation was revealed: carboxy substitution at C2 significantly hinders acid mediated substitution at a C5 hydroxymethyl substituent on a furan ring. Rather than isolating methyl 3-(5-(hydroxymethyl)furan-2-yl)acrylate, the major product (76%) was methyl 3-(5-(methoxymethyl)furan-2-yl)acrylate (Scheme 4.4).



Scheme 4.4. Nonselective esterification of 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid

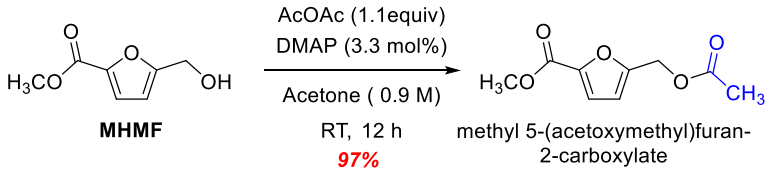
The outcome of Fisher esterification using 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid as substrate was illustrative of the enhanced chemoselectivity embodied in the HMFA. The carboxylic acid acts as a deterrent to the possible formation of resonance stabilized furylic carbocations by elimination of H_2O from the hydroxymethyl moiety under acidic conditions. Since 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid includes a two-carbon conjugated spacer, the stabilization due to resonance overpowers the destabilizing influence of the carboxylic acid moiety and destroys the previously observed chemoprotection which afforded ready access to AB type monomers from HMFA under a wide range of conditions. Perhaps the milder alternative reaction conditions employed later in Table 4.4 could capitalize on the revenant chemoprotective influence of the C2-furyl acrylate moiety.



Scheme 4.5. Fisher esterification: ethyl 5-(hydroxymethyl)-2-furoate

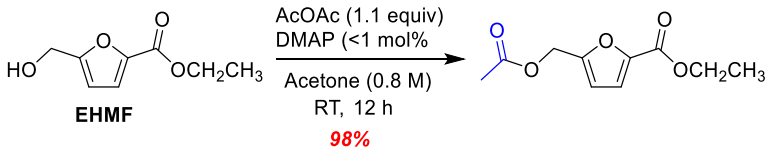
The chemoprotective effect inherent to HMFA was finely matched in the methanolic esterification medium. When ethyl 5-(hydroxymethyl)-2-furoate was prepared in similar fashion (Scheme 4.5), only a 60% isolated yield was obtained. This was likely due to the greater reaction temperature of boiling EtOH *versus* MeOH (78 °C *vs.* 65 °C), and the dehydrating influence created by the well-known H_2O-EtOH azeotrope.

4.4.2. Masking the Hydroxymethyl Functionality



Scheme 4.6. Acylation: methyl 5-(acetoxymethyl)-2-furoate

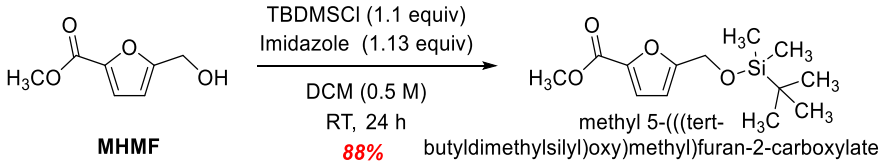
Acylation with acetic anhydride, catalyzed with DMAP in acetone, was found to facilitate the preparation of methyl 5-(Acetoxymethyl)-2-furoate which could be isolated by liquid-liquid extraction in pure form (97% isolated yield, Scheme 4.6). The use of acetic anhydride in minor excess (1.1 molar equivalents), low loading of the organocatalyst (3.3 mol%), and benign solvent (acetone) at room temperature combined to form a protocol with great potential for application in sustainble materials science. The preparation of ethyl 5-(acetoxymethyl)-2-furoate used less than a third of acyl transfer catalyst with no negative consequences (98% isolated yield, Scheme 4.7).



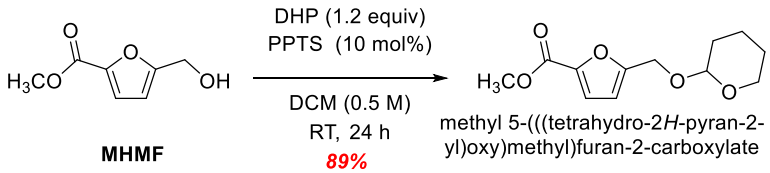
Scheme 4.7. Acylation: ethyl 5-(acetoxymethyl)-2-furoate

While the acetate group is bioderived and fairly labile, there existed a concern that its removal to prepare hydroxy ester AB type monomers derived from cycloaddition with benzyne could present obstacles not worth surmounting. As such, alkoxyalkyl ether and silylether

protecting groups were considered,[238] investigated and prepared by Anna Renner—*a senior undergraduate researcher in the Sibi group*.[74] An imidazole coupling at room temperature in DCM was employed to prepare 5-(((*tert*-dimethylsilyl)oxy)methyl)-2-furoate from methyl 5-(hydroxymethyl)-2-furoate and *tert*-dimethylsilyl chloride (Scheme 4.8). Thusly, the C5-hydroxymethyl moiety was protected in orthogonal fashion with a robust and bulky silylether in good yield (88%). Methyl 5-(((*tert*-dimethylsilyl)oxy)methyl)-2-furoate did require flash column chromatography for its isolation. This furan-diene was later integral in determining a degradation pathway of biobased 7-oxabenzonorbornenes during their dehydrative-aromatization reactions—*see chapter 5 for further details.*



Scheme 4.8. Preparation of methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)furan-2-carboxylate from methyl 5-(hydroxymethyl)furan-2-carboxylate



Scheme 4.9. Preparation of methyl 5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)furan-2-carboxylate from methyl 5-(hydroxymethyl)furan-2-carboxylate

Pyridinium *p*-toluenesulfonate catalyzed the reaction between methyl 5-(hydroxymethyl)-2-furoate and bioderivable 3,4-dihydro-2*H*-pyran[239] to afford methyl 5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-2-furoate in good yield (89 %, Scheme 4.9). This compound also required flash chromatography for isolation. The tetrahydropyranyl protection strategy proved to be uniquely suitable in the masking of hydroxylic functionality from reaction with benzyne while readily

cleaving to afford a novel AB type hydroxyester with C1,C4-disubstitution on a 7-oxabenzonorbornene core—*see chapter 5 for more details.*

4.4.1. Esterification of FDCA

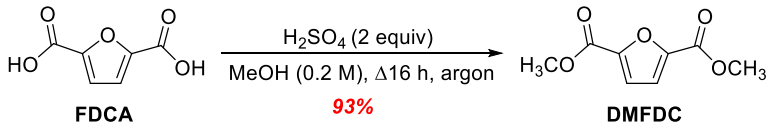
Preparation and processing parameters of both succinate and 2,5-furandicarboxylate from mimicked and actual bioreactor broths have been described.[185] The furanic dicarboxylate was found to be less sensitive to influences of competing inorganic and organic ions in anionic exchange sorption processes which allowed facile purification of residual HMF by its elution. Esters were prepared by alkylation with dimethyl carbonate. Fermentation impurities dramatically dropped the yield of esterified succinate from 0.98 mole ester per mole carboxylate in the authentic sample to 0.66 mole ester per mole carboxylate; fermentation impurities made negligible differences in the case of 2,5-furandicarboxylate (0.75–0.77 mole ester per mole carboxylate).

Dimethyl 2,5-furandicarboxylate has been prepared from FDCA (100 mmol) in refluxing MeOH (0.5 M, 5 h) mediated by sulfuric acid (108 mmol).[143] The isolation entailed concentration by rotary evaporation, filtration through a disposable Teflon membrane, precipitation with H_2O (100 mL), partial neutralization with sodium bicarbonate, suction filtration with H_2O washing, and air drying. The purification of crude product was achieved by recrystallization in a mixture of MeOH and H_2O (50/50 v/v) and afforded white needles (83% yield).

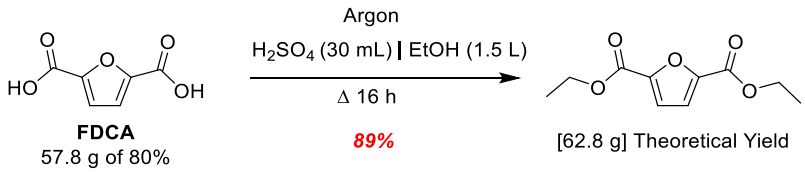
Through much trial and error over the past seven years, a reliable method was devised for isolating pure diesters of FDCA from 80% pure commercially available FDCA (Schemes 4.15 and 4.16). Preparation of simple esters provided polyester precursors in high yield while affording the opportunity for refining the purity of differentially contaminated diacid substrate. One exciting adventure entailed multiple sources of FDCA including one kilogram batch which turned out to

be almost completely FDCA monopotassium salt. That story arc was only resolved by, and I kid you not, a flame test; long story shortened to a phrase: the flame was violet.

Curiosity might be the fundamental requisite personality trait which defines a good scientist, but inarguably observation must be the fundamental skill. Certainly, observation has proven tantamount to success as it bred ingenuity while engaging the process challenges of dealing with biobased furanics. A direct access strategy for biorenewable terephthalic acid by cycloaddition and aromatic upgrade strategy could be made or broken based upon the successful application of oxidation methods at the furanic stage. Therefore, a pure and scalable method for esterified FDCA derivatives, independent of their source material, was required for the investigations of benzyne cycloaddition with electron deficient furan-dienes—*see chapter 5*.



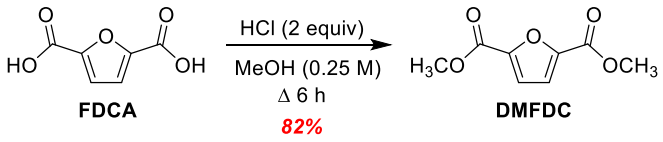
Scheme 4.10. Fisher esterification: dimethyl 2,5-furandicarboxylate



Scheme 4.11. Fisher esterification: diethyl 2,5-furandicarboxylate

Treatment of commercially available FDCA in alcoholic mixtures with stoichiometric concentrated sulfuric acid (related to functionality), afforded dark solid isolates which appeared amazingly pure to ^{1}H and ^{13}C (Schemes 4.10 and 4.11). EtOH or MeOH made no real difference; The dispersion of brown particulate was so fine and dark, that the NMR samples did not appear to contain solid. Upon standing in the queue for tube washing, it was observed that a clear and yellow $CDCl_3$ solution had developed with a thin layer of separated dark solid. Purification of the large

scale crude reaction isolates proceeded by dissolution in a minimal volume of DCM, followed by solid phase extraction through silica gel. Products of practically useful purity were obtained. Further refinements in purity could be made by recrystallization from isopropyl alcohol.

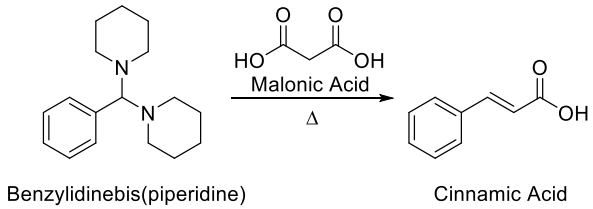


Scheme 4.12. Fisher esterification of FDCA from chlorous acid oxidation of DFF

The conditions of Moore and Kelly investigated in Table 4.4,[129] were adapted for diacid substrates and applied to the very pure FDCA procured from chlorous acid oxidation of DFF as explored in Table 4.3). Two equivalents of HCl were selected rather than sulfuric acid since there was no danger of chlorodehydration reactions. The methanolic concentration of FDCA was 0.25 M to keep the concentration of furoic acid moieties consistent with Table 4.4. Following six h of reflux beneath argon, the reaction was quenched in typical fashion an afforded pure dimethyl 2,5-furandicarboxylate upon concentration of the extract solution with no need for chromatographic purification (82% isolated yield, Scheme 4.12).

4.4.2. Knoevenagel Condensation as an Alternative to Oxidation

Knoevenagel (1898) innovated the reaction between active methylene moieties and reactive carbonyls.[240] After considering the reaction between malonate esters with similar substrates, he devised the reaction between benzylindinebis(piperidine) and malonic acid which resulted in the formation of cinnamic acid (Scheme 4.13). The results of his student's experiments indicated a general reaction of malonic acid condensation with aromatic aldehydes in ammoniacal alcohol, including biorenewable substrates such as furfural and cinnamaldehyde.



Scheme 4.13. Knoevenagel's initial synthesis of cinnamic acid

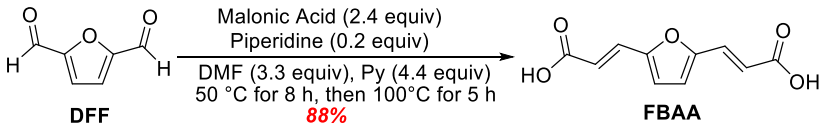
The order of addition was further investigated, and it was determined to be inconsequential whether or not aminals were preformed prior to combination of aldehyde and malonic acid. Ammoniacal alcohol and aniline were investigated as basic and or iminium activation agents; generally, the ammonia process afforded greater yields of acrylic acid derivatives. In the aniline mediated process, furfural did not proceed as expected while benzaldehyde reacted smoothly (80% cinnamic acid). Following the ammoniacal protocol, furfural (40% 3-(furan-2-yl)acrylic acid) performed about half as well as benzaldehyde (85% cinnamic acid).[240]

Doebner (1902) modified the Knoevenagel condensation protocol by running the reaction in pyridine as the solvent which facilitated the decarboxylation and the formation of α,β-unsaturated acids from aldehydes upon acidification.[241] Alternatively, biobased aldehydes undergo uncatalyzed reaction with Meldrum's acid,[242-247] followed by iron catalyzed hydrolysis and decarboxylation in nitromethane to afford C3-substituted acrylic acids.[247] Such methods have even been effective with HMF in the synthesis of 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid precursors.[248-250]

4.4.2.1. Synthesis of 2,5-Furanbis(acrylic Acid)

Also known as (2*E*,2'*E*)-3,3'-(furan-2,5-diyl)diacrylic acid or (2*E*,2'*E*)-3,3'-(furan-2,5-diyl)dipropenoic acid, 2,5-furanbis(acrylic acid) (FBAA) was prepared in 88% isolated yield on the 80 g scale (of product) by adapting the Doebner modification of the Knoevenagel condensation for the preparation of cinnamic acids to the biorenewable dialdehyde substrate DFF. (Scheme

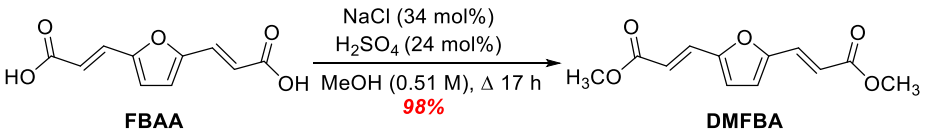
4.14). The method was later refined, and the periods of heating were shortened to two h each for the preparation of 3-(5-(hydroxymethyl)furan-2-yl)acrylic acid by Dyuti Dawn in 92% isolated yield. Key features of this reaction included the use of: piperidine catalyst (10 mol% per reaction functional group), minimal excess malonic acid (1.2 molar equivalents per reacting functional group), and a concentrated reaction medium (3.3 molar equivalents DMF and 4.4 molar equivalents of pyridine). Drawbacks to this protocol include the use of proscribed (DMF) or toxic (pyridine) cosolvents. While their relative amounts have been minimized, future work should be directed towards their replacement with benign alternatives.



Scheme 4.14. Preparation of (2*E*,2'*E*)-3,3'-(furan-2,5-diyl)diacrylic acid (FBAA) from DFF

4.4.2.2. Esterification of 2,5-Furanbis(acrylic Acid)

The Fisher esterification of 2,5-furanbis(acrylic acid) (FBAA) was extremely efficient and resulted in highly pure dimethyl 2,5-furanbis(acrylate) (DMFBA) in 98% isolated yield (Scheme 4.15. Differences between this esterification protocol and others included the use of: (1) a more concentrated reaction medium (0.51 M in MeOH which was 1 M of transforming functionality), (2) a mixture of sulfuric acid catalyst (24 mol%) in combination with sodium chloride additive (34 mol%), (3) use of a drying tube rather than argon atmosphere, and (4) the method of isolation (crystallization from the reaction mixture). Since the methanolic reaction medium likely exhibited a leveling effect upon sulfuric acid, the addition of sodium chloride merely served to increase the ionicity of the reaction medium without increasing the acidity (by decreasing the pH). This was expected to decrease the solubility of the neutral diester product and devised as a strategy to improve recovery of pure product while simplifying the reaction workup.



Scheme 4.15. Preparation of dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate (DMFBA) from FBAA

4.4.2.3. Conjugate Reduction via Cuprous Hydride

Narisada, Horibe, Watanabe, and Takeda (1989) developed the use of sodium borohydride ($NaBH_4$) in the presence of a methanolic suspension of cuprous chloride (Cu_2Cl_2) at 0 °C for 30 min as a method for chemoselective reduction of aryl halides and α,β-unsaturated esters.[251] Hypothetically, solubilized Cu_2Cl_2 forms a transient species of copper hydride (CuH)[252] upon contact with $NaBH_4$. The method was particularly applicable in the field of deuterium labeling. Cuprous chloride was screened against cupric chloride and nickel chloride hexahydrate in a variety of reductions thereby establishing the extent of selectivity imparted by each transition metal additive. Cu_2Cl_2 afforded the greatest isolated yield (98%) in preliminary experiments during the dehalogenation of a *p*-iodobenzenesulfonamide with $CuCl_2$ a close second (94%); classical coordinating groups which are also inductively electron-withdrawing such as methoxy and especially carboxymethyl substituted *ortho* to the aryl bromide underwent dehalogenation with enhanced yields of reduced products.

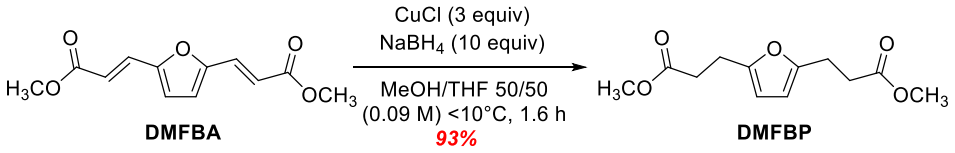
The conjugate reduction strategy employing Cu_2Cl_2 in MeOH and $NaBH_4$ (10 eq.) was shown to be catalytic in terms of Cu_2Cl_2 as they determined the yield of ethyl hydrocinnamate from its ratio to ethyl cinnamate by ^1H NMR spectroscopy; Cu_2Cl_2 loading at 7.5 mol% resulted in 77% yield while Cu_2Cl_2 loading at 75 mol% resulted in quantitative conversion. In their experiments, Cu_2Cl_2 in MeOH with excess $NaBH_4$ was completely unreactive with an internal alicyclic nonconjugated olefin (androst-2-en-17-ol) while $NiCl_2$ quantitatively reduced it; the conjugated olefin *trans*-stilbene was partially reduced (8%) with the Cu_2Cl_2 system whereas $NiCl_2$

again completely reduced the substrate to 1,2-diphenylethane. Selectivity was the most lacking in reduction of the terminal olefin of safrole (Cu_2Cl_2: 83% reduction, $NiCl_2$: quantitative reduction). Chiefly, in an internal competition experiment an α,β-unsaturated ethyl ester which also contained an internal alicyclic olefin only the conjugated ester's olefin was reduced. The authors specified no observations of transesterification, despite employing ethyl esters in MeOH with superstoichiometric borohydride.

Deuterium labeling experiments indicated that the hydrogen added to the β-position originated from borohydride while the hydrogen added to the α-position originated from solvent. Gasometric measurements determined hydrogen gas (2.5–2.6 molar equivalents) was evolved during the vigorous effervescences observed during the addition of $NaBH_4$ to the mixture methanolic Cu_2Cl_2. These measurements implicated the catalytic formation of a transient species susceptible to immediate decomposition to borane—*which reacts with MeOH to evolve dihydrogen (H_2) gas*. Satoh, Nanba, and Suzuki (1971) had previously investigated the conjugate reduction of methyl cinnamate in MeOH with $NaBH_4$ modified by addition of: hydrated nickel (II), cobalt (II), and copper (II) chloride salts.[253] In their study, the potential for catalytic transition metal halide salts was established and nickel was the most active catalyst capable of reducing the internal olefin of a fatty ester (methyl oleate).

In a control experiment, Narisada *et al.*[251] added ethyl cinnamate 10 min following the completion of borohydride addition (all under H_2 atmosphere); there was no ethyl hydrocinnamate formed and thusly the reduction by some form of catalytic hydrogenation was excluded from relevancy. This was an important point, since attempts to prepare dimethyl 2,5-furanbis(acrylate) (DMFBA) by catalytic hydrogenation were extremely unreliable and often led to saturation of the furan ring; Dominguez *et al.* claimed to have prepared diethyl 2,5-furanbis(propanoate) (80%

yield) in EtOAc under 1 bar H_2 over 5% Pd-C with a reaction time of five min. Likely due to inconsistencies in catalyst activity, those results could not be suitably replicated in our laboratory. A conjugate reduction protocol was adapted and applied with great success to DMFBA which afforded dimethyl 2,5-furanbis(propanoate) (DMFBP) (Scheme 4.16). By this route, in high overall yield, a dicarboxylate containing C2,C5-disubstituted furan-diene was prepared with electronics expected to emulate 2,5-dimethylfuran while maintaining their incipient potential for founding a new class of sustainable bicyclic polyester precursors (Chapter 5).



Scheme 4.16. Preparation of dimethyl 3,3'-(furan-2,5-diyl)dipropionate (DMFBP) from DMFBA

4.4.3. Chapter Conclusions

Furan-dienes have been prepared with varying electronics for study in the Diels-Alder cycloaddition strategy for valorization of cellulosic biomass. Bio-renewable furanic aldehydes afforded furoic acids of practical importance such as 2,5-furandicarboxylic and 5-(hydroxymethyl)-2-furancarboxylic acid by chlorous acid oxidation in aqueous acetone (>80% yield, 10 examples). MnO_2 in benign solvents effectively afforded furanic aldehydes in turn. Facile protocols afforded high-purity and scalable preparation of renewable furanics by chemoselective reactions including reductions and esterification.

Due to their high oxygen content, bio-based platform chemicals attract organic chemists seeking novel and challenging scaffolds. However, full development of their potential remains elusive in many cases due to the lack of feasible laboratory scale production methods. Inarguably, catalytic chemistry is going to be the future of industrial scale production of any single desirable

intermediate. In the meantime, there exists a need for reliable methods including the chemoselective oxidation of renewable furanics.

The halogenated solvents typically employed in heterogeneous MnO_2 oxidations of activated primary alcohols such as allylic, benzylic, furylic was effectively replaced by both EtOAc and cyclopentyl methyl ether. In a complimentary methodology, use of acetone as a cosolvent in aqueous chlorous acid oxidations facilitated the preparation of furanic acids from furanic aldehydes including those with only sparing aqueous solubility. This set of technologies affords rapid and ready access to a suite of high-purity bio-renewable furanics exploitable for applications in sustainable materials science.

An eclectic set of cellulose-derivable C2,C5-disubstituted furan-dienes has been prepared from HMF. These represent a continuum of electronic substituents as defined by their varying oxidation states. These furan-dienes were synthesized by high yielding and chemoselective techniques. Consideration was made throughout for the principles of green chemistry.

4.5. Experimental

4.5.1. General Procedures

Unless otherwise stated, all commercially procured materials were used as received without further purification. Melting points were determined on a REACH Devices RD-MP digital melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 MHz instrument and processed with Topspin software. Infrared spectra were recorded with a Nicolet™ iS™ 10 Fourier transform infrared spectrometer using a diamond sample plate for attenuated total reflectance and processed using Omnic; the FTIR figures were prepared using Origin Pro. High resolution mass spectra were recorded on a Waters Synapt G2-Si high definition mass spectrometer and were processed using MassLynx. Unless otherwise stated,

all reactions were stirred magnetically by polytetrafluoroethylene coated magnetic spin-bars. All mention of silica gel refers to Sorbtech standard grade silica gel: 230–400 mesh. Biorenewable FDCA and HMF were purchased from AVA Biochem in 80% and 95% respectively.

4.5.1.1. Iodometric Titrations of sodium Chlorite Provided by Catherine Sutton

During the course of this study, the concentration of sodium chlorite ($NaClO_2$) was taken to be 80% (as was indicated on the bottle). Upon completion of the project, iodometric titration determined the active chlorine content to be 78.9 % $NaClO_2$. Since a slight excess of $NaClO_2$ was always utilized, it may seem like an exact titration would be inconsequential. While there were several indications that over oxidation was not an issue in the application of chlorous acid to the systems described, incomplete oxidation would be. As the excess oxidizer was attenuated to reduce waste, in inexact knowledge of active chlorite content could significantly complicate purification of acid derivatives.

A fresh 0.20 $M_{(aq)}$ of $Na_2S_2O_3$ was prepared in a 200 mL volumetric flask with 9.92 g (0.04 mol) $Na_2S_2O_3$. A 50.0 mL burette was primed then charged with 0.20 M $Na_2S_2O_{3\ (aq)}$. A 3 M solution of hydrochloric acid (HCl) was prepared from 2.5 mL conc. HCl by diluting it to a volume of 7.5 mL with DI H_2O. A saturated starch solution, 1 g starch in 20 mL DI H_2O, was also prepared.

Table 4.5. Iodometric titration of $NaClO_2$ trial information

Trial	$NaClO_2$ (g)	KI (g)	$Na_2S_2O_3$ (mL of 0.20 M)
1	0.20	1.50	35.0
2	0.20	1.50	35.1
3	0.20	1.50	34.9

Per trial, a 250 mL beaker was charged with 0.20 g $NaClO_2$, 1.50 g potassium iodide (KI), and 100 mL DI H_2O. The receiving beaker's contents were stirred throughout the titration process and a complete solution rapidly formed upon addition of analyte and reagents. Immediately prior

to the titration, 4.0 mL of 3 M HCl solution was added to the beaker's contents, which resulted in a deep brown solution.

Thiosulfate solution was carefully added by burette which changed the analyte solution to a yellow color, 0.8 mL of the saturated starch solution was added to the beaker. After the yellow color dissipated, a turbid blue appearance manifested through the interaction of the starch with triiodide ions. The titration was complete when the solution was totally colorless.

Iodometric titration of $NaClO_2$ Trial 1:

$$0.0350\ \text{L} \times \frac{0.20\ \text{mol}\ {S_2O_3}^{-2}}{\text{L}} \times \frac{1\ \text{mol}\ I_2}{2\ \text{mol}\ {S_2O_3}^{-2}} \times \frac{1\ \text{mol}\ Cl^-}{2\ \text{mol}\ I_2} \times \frac{1\ \text{mol}\ NaClO_2}{1\ \text{mol}\ Cl^-} \times \frac{90.44\ \text{g}}{1\ \text{mol}\ NaClO_2}$$

$$= \frac{0.158\ \text{g}\ NaOCl_2\ \text{by titration}}{0.200\ \text{g sample}} \times 100 = 79.1\% \tag{4.1}$$

Iodometric titration of $NaClO_2$ Trial 2:

$$0.0351\ \text{L} \times \frac{0.20\ \text{mol}\ {S_2O_3}^{-2}}{\text{L}} \times \frac{1\ \text{mol}\ I_2}{2\ \text{mol}\ {S_2O_3}^{-2}} \times \frac{1\ \text{mol}\ Cl^-}{2\ \text{mol}\ I_2} \times \frac{1\ \text{mol}\ NaClO_2}{1\ \text{mol}\ Cl^-} \times \frac{90.44\ \text{g}}{1\ \text{mol}\ NaClO_2}$$

$$= \frac{0.159\ \text{g}\ NaOCl_2\text{by titration}}{0.201\ \text{g sample}} \times 100 = 79.0\% \tag{4.2}$$

Iodometric titration of $NaClO_2$ Trial 3:

$$0.0349\ \text{L} \times \frac{0.20\ \text{mol}\ {S_2O_3}^{-2}}{\text{L}} \times \frac{1\ \text{mol}\ I_2}{2\ \text{mol}\ {S_2O_3}^{-2}} \times \frac{1\ \text{mol}\ Cl^-}{2\ \text{mol}\ I_2} \times \frac{1\ \text{mol}\ NaClO_2}{1\ \text{mol}\ Cl^-} \times \frac{90.44\ \text{g}}{1\ \text{mol}\ NaClO_2}$$

$$= \frac{0.158\ \text{g}\ NaOCl_2\ \text{by titration}}{0.201\ \text{g sample}} \times 100 = 78.7\% \tag{4.3}$$

4.5.1.2. Determination of Metrics

Following the generalized equations presented by Roschangar *et al.*:[226]

Simple *E* Factor (s*E*F):

$$s\mathit{E}\text{F} = \frac{\sum \text{Raw Materials}_{(\text{mass})} + \sum \text{Reagents}_{(\text{mass})} - \text{Product}_{(\text{mass})}}{\text{Product}_{(\text{mass})}} \tag{4.4}$$

Complete *E* Factor (c*E*F):

$$cEF = \frac{\sum \text{Raw Materials}_{(\text{mass})} + \sum \text{Reagents}_{(\text{mass})} \sum \text{Solvents}_{(\text{mass})} + \sum H_2O_{(\text{mass})} - \text{Product}_{(\text{mass})}}{\text{Product}_{(\text{mass})}} \quad (4.5)$$

Determination of simple *E* Factor (s*E*F):

$$sEF = \frac{\sum HMF_{(g)}, H_3NO_3S_{(g)}, NaClO_{2(g)} - HMFA_{(g)}}{HMFA_{(g)}} \quad (4.6)$$

Determination of complete *E* Factor (c*E*F):

$$cEF = \frac{\sum HMF_{(g)}, H_3NO_3S_{(g)}, NaClO_{2(g)}, \text{Solvents}_{(g)}, H_2O_{(g)}, NaCl_g, \text{Asc. Acid} - HMFA_{(g)}}{HMFA_{(g)}} \quad (4.7)$$

4.5.1.3. Metric Determinations from Literature

Comparison between methodologies across diverse literature reports is inherently difficult and prone to bias from multiple sides. To place the work presented herein, attempts have been made to collect a series of relevant examples either of HMFA or of related chlorous acid oxidations.

4.5.1.4. Reichstein's Preparation of HMFA

An early preparation of HMFA was reported by Reichstein (1926).[61] That method employed vacuum distilled HMF(17.5 g) as substrate, and freshly prepared silver oxide in aqueous solution to afford HMFA (16.5 g, 84% yield). From that report, enough detail could be gleaned from the experimental section to calculate a simple *E* Factor (s*E*F):

Determination of simple *E* Factor (s*E*F):

$$sEF = \frac{\sum \text{Raw Materials}_{(\text{mass})} + \sum \text{Reagents}_{(\text{mass})} - \text{Product}_{(\text{mass})}}{\text{Product}_{(\text{mass})}} \quad (4.8)$$

Determination of simple *E* Factor (s*E*F) from Reichstein's HMFA preparation (1926):

$$sEF = \frac{\sum HMF_{(g)}, NaOH_{(g)}, AgNO_{3(g)}, HCl_{(g)} - HMFA_{(g)}}{HMFA_{(g)}} \quad (4.9)$$

$$s\mathit{E}\mathrm{F} = \frac{\sum 17.5_{(g)}, 19.67_{(g)}, 60_{(g)}, 5.1_{(g)} - 16.5_{(g)}}{16.5_{(g)}} = 5.2 \tag{4.10}$$

4.5.1.5. Lindgren and Nilsson's Chlorous Acid Oxidations

Lindgren and Nilsson (1973) reported pioneering work in the field of practical chlorous acid oxidations and also in the realm of bioderivable-substrate-oxidations.[216] Enough detail was presented in their experimental section to make reasonable determinations of s*E*F: 1.7 and estimation of complete *E* Factor (c*E*F): 156 for the preparation of vanillic acid (13.9 g, 84% yield):

Determination of simple *E* Factor (s*E*F) from Lindgren and Nilsson's preparation of vanillic acid (1973):

$$s\mathit{E}\mathrm{F} = \frac{\sum \mathrm{vanillin}_{(g)}, \mathrm{H_3NO_3S}_{(g)}, \mathrm{NaClO_2}_{(g)} - \mathrm{vanillic\ acid}_{(g)}}{\mathrm{vanillic\ acid}_{(g)}} \tag{4.11}$$

$$s\mathit{E}\mathrm{F} = \frac{\sum 15_{(g)}, 13_{(g)}, 9.3_{(g)} - 13.9_{(g)}}{13.9_{(g)}} = 1.7 \tag{4.12}$$

Determination of complete *E* Factor (c*E*F) from Lindgren and Nilsson's preparation of vanillic acid (1973):

$$c\mathit{E}\mathrm{F} = \frac{\sum \mathrm{vanillin}_{(g)}, \mathrm{H_3NO_3S}_{(g)}, \mathrm{NaClO_2}_{(g)}, \mathrm{H_2O}_{(g)} - \mathrm{vanillic\ acid}_{(g)}}{\mathrm{vanillic\ acid}_{(g)}} \tag{4.13}$$

$$c\mathit{E}\mathrm{F} = \frac{\sum 15_{(g)}, 13_{(g)}, 9.3_{(g)}, 2144_{(g)} - 13.9_{(g)}}{13.9_{(g)}} = 156 \tag{4.14}$$

In a related reaction, Lindgren and Nilsson reported the preparation of *o*-vanillic acid (1.3 g, 80% yield) from *o*-vanillin (1.52 g); s*E*F: 2.1 and c*E*F: 401.[216] Extraction solvent (diethyl ether) was not specified, so 500 mL assumed for the calculation of c*E*F.

Determination of simple *E* Factor (s*E*F) from Lindgren and Nilsson's preparation of *o*-vanillic acid (1973):

$$s\mathit{E}\mathrm{F} = \frac{\sum o\text{-}\mathrm{vanillin}_{(g)}, \mathrm{H_3NO_3S}_{(g)}, \mathrm{NaClO_2}_{(g)} - o\text{-}\mathrm{vanillic\ acid}_{(g)}}{o\text{-}\mathrm{vanillic\ acid}_{(g)}} \tag{4.15}$$

$$sEF = \frac{\sum 1.52_{(g)}, 1.22_{(g)}, 1.26_{(g)} - 1.3_{(g)}}{1.3_{(g)}} = 2.1 \tag{4.16}$$

Determination of complete *E* Factor (c*E*F):

$$cEF = \frac{\sum o\text{-vanillin}_{(g)}, H_3NO_3S_{(g)}, NaClO_{2(g)}, H_2O_{(g)}, Et_2O_{(g)} - o\text{-vanillic acid}_{(g)}}{o\text{-vanillic acid}_{(g)}} \tag{4.17}$$

$$cEF = \frac{\sum 1.52_{(g)}, 1.22_{(g)}, 1.26_{(g)}, 518_{(g)}, 357_{(g)} - 1.3_{(g)}}{1.3_{(g)}} = 401 \tag{4.18}$$

4.5.1.6. Moore and Partain's Application of Chlorous Acid Oxidation

Moore and Partain (1985) extended the sulfamic acid mediated reaction between hydrolytically unstable bioderivable furanic aldehydes such as 5-(acetoxymethyl)furfural (AMF) to afford acids such as 5-(acetoxymethyl)furan-2-carboxylic acid (AMFA) selectively with no ring opening of the furan system observed.[223] Their utilization of continuous liquid-liquid extraction significantly reduced the associated c*E*F: 60 for this process while their improved isolated yield (99%) in combination with equivalent stoichiometry led to a superior s*E*F: 0.9. The same procedure afforded only a 55% yield of furan-2-carboxylic acid from furfural. Since the amount of diethyl ether used in their continuous liquid-liquid extraction was not specified, the same 500 mL of extraction solvent was assumed as for Lindgren and Nilsson's preparation of *o*-vanillic acid which seemed reasonable given the greater solubility of AMFA *versus o*-vanillic acid.

Determination of simple *E* Factor (s*E*F) from Moore and Partain (1985):

$$sEF = \frac{\sum \text{AMF}_{(g)}, H_3NO_3S_{(g)}, NaClO_{2(g)} - \text{AMFCA}_{(g)}}{\text{AMFCA}_{(g)}} \tag{4.19}$$

$$sEF = \frac{\sum 16.8_{(g)}, 9.7_{(g)}, 9.1_{(g)} - 18.3_{(g)}}{18.3_{(g)}} = 0.9 \tag{4.20}$$

Determination of complete *E* Factor (c*E*F) from Moore and Partain (1985):

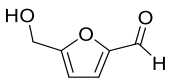
$$cEF = \frac{\sum \text{AMF}_{(g)}, H_3NO_3S_{(g)}, NaClO_{2(g)}, H_2O_{(g)}, Et_2O_{(g)} - \text{AMFCA}_{(g)}}{\text{AMFCA}_{(g)}} \tag{4.21}$$

$$cEF = \frac{\sum 16.8_{(g)}, 9.7_{(g)}, 9.1_{(g)}, 723_{(g)}, 357_{(g)} - 18.3_{(g)}}{18.3_{(g)}} = 60 \quad (4.22)$$

4.5.2. HMF and Derivatives

This section describes the purification of commercially available HMF and its conversion into AMF, BHMF, and BAMF.

4.5.2.1. Purification of HMF



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.20 (d, *J*=3.5 Hz, 1H), 6.49 (d, *J*=3.44 Hz, 1H), 4.68 (s, 1H), 3.37 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 161.0, 152.3, 110.1, 57.5; FTIR (ATR, diamond, neat): cm^{-1} 3329, 3267, 3107, 2936, 2847, 1661, 1650, 1522, 1440, 1376, 1348, 1275, 1245, 1197, 1021, 985, 963, 941, 825, 777, 722, 649, 618.

Spectral details of HMF were reported by Musau and Munavu (1987).[77] Commercially available, HMF was purchased in 95% purity from AVA Biochem, dissolved in diethyl ether (10 mL Et_2O/1 g HMF), dried (Na_2SO_4) and decolorized (Norit A) overnight. The ethereal solution was isolated by suction filtration through a pad of diatomaceous earth, concentrated and allowed to crystallize in the freezer. Upon crystallization, the residual HMF was vacuum dried to remove remaining ether. HMF purified in this manner was stable in the freezer for weeks and was a pale yellow crystalline solid, melting point range: 34–36 °C.[75, 95]

4.5.2.2. Flash Colum Chromatographic Purification of HMF

HMF (1.365 g), was purified by flash column chromatography using Hex modified with EtOAc as mobile phase and amorphous silica gel as stationary phase (Fig. 4.2). The first eluate peak (fractions 1–4) contained a similar but subtly different spectrum to that of furfuryl alcohol as illustrated in Fig 4.3, (30.5 mg of light crystalline solid, or 2.2 % of the input mass). The second eluate peak (fractions 5–15) was taken to be HMF and was concentrated to afford a ghostly yellow oil which was vacuum dried by H_2O aspirator and which crystallized upon storage in the fridge

overnight under argon. The crystalline solid was freed from the internal walls of the flask by shaking and vacuum drying was continued; mass observed was 1.28 g which corresponds to 94% of the input mass which closely matched the commercial supplier's assay. The material was stored on the bench under an argon balloon and slowly decomposed over a month to afford yellow crystalline solid contaminated with red oil.

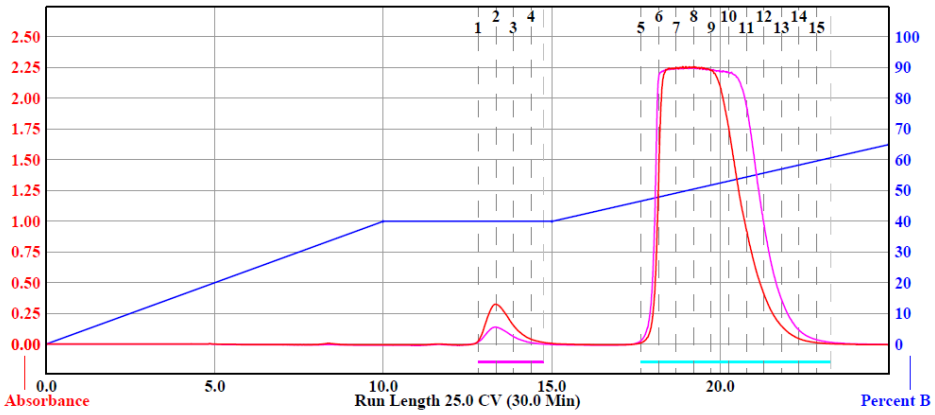


Fig. 4.2. Flash column chromatogram from purification of commercially available HMF

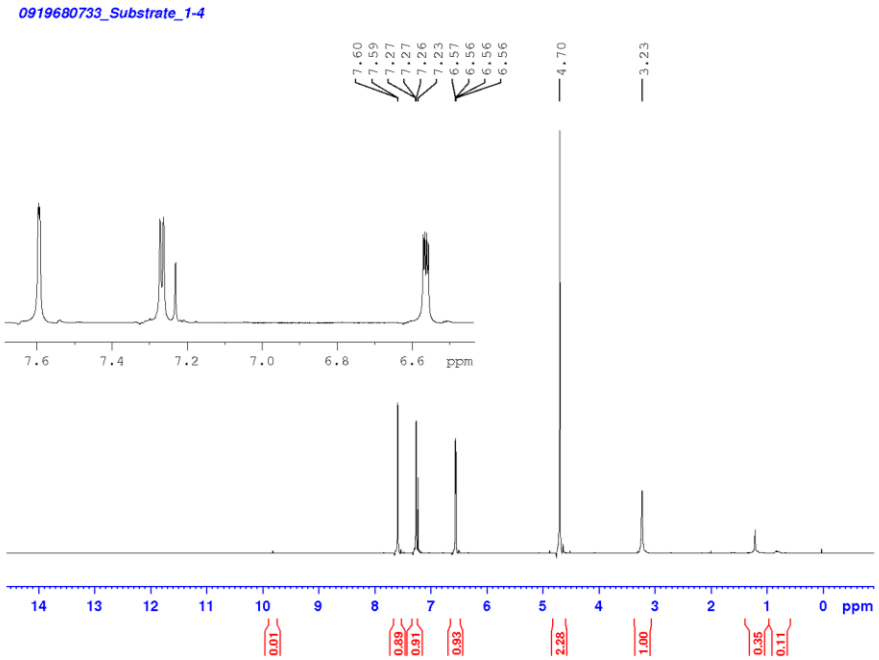


Fig. 4.3. ^{1}H NMR spectrum of minor eluate from flash column chromatographic purification of commercially available HMF

4.5.2.3. Purification of HMF

HMF (57.14 g, AVA Biochem 95% grade) was added to a 1.0 L Erlenmeyer flask and stirred up in 500 mL of diethyl ether. The solution which formed left behind some orange goo, and some fluffy yellow solid. The mixture was diluted to 600 mL with chloroform; The fluffy solid dissolved and 5.5 g of anhydrous sodium sulfate was stirred into the solution where it amalgamated with the orange goo. The mixture was stirred for several min then another 5.5 g of anhydrous sodium sulfate was added. The mixture was a yellow solution with orange residue. The mixture was charged with 5 g of Norit RO pellets (decolorizing carbon) and the flask was covered with aluminum foil, then stirred vigorously for approximately 48 h.

The solution was isolated by suction filtration through a bed of Celite. The ethereal solution was much lighter in color, and the orange goo stuck to the carbon and the sodium sulfate. The ether was removed by rotary evaporation under vacuum. The light yellow oil was further concentrated by direct H_2O aspiration. The residue was stored in the freezer at -12 °C overnight. Some small crystal growths were observed. The mixture was further concentrated by direct aspiration on ice to persuade the substance to crystalize. When no more solvent could be removed, the mixture was again stored in the freezer overnight. The mixture had formed a great mass of crystalline solid. The solid mass was chopped, and vacuum dried further, it became a much harder solid as if the ether had been plasticizing the mixture. The total mass of recovered HMF was circa 41 g (72% recovery). The HMF looked almost white.

4.5.2.4. Purification of HMF

A 2.0 L Erlenmeyer flask was charged with HMF (95% from AVA Biochem, 102.34 g, if pure then 0.811 mole), anhydrous sodium sulfate (Na_2SO_4, 22.27 g), and diethyl ether (800 mL). The mixture was stirred until a yellow solution formed above dark red-brown residue which

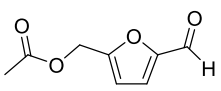
agglomerated with the solid sodium sulfate. Norit A decolorizing carbon (1.36 g) was added to the mixture which was stirred overnight.

A pad of silica gel (4 cm) and Celite (1 cm) was prepared in a 150 mL fritted Büchner funnel and topped with a 5 cm piece of qualitative filter paper. The ethereal solution of HMF was separated by suction filtration through that pad. The silica gel was stained orange at the top following the filtration, while the Celite held no color. The filter pad was rinsed with 200 mL ether three times, the filtrate was light yellow.

The mixture was concentrated by rotary evaporation, stored in the freezer overnight wherein egg yolk yellow crystalline solid appeared. The mass of recovered solid was 95.71 g HMF (94% recovery). The solid was dissolved in circa 100 mL HPLC grade acetone (80.20 g) and stored under inert atmosphere. The total mass of solution was 175.91 g.

To determine the effective concentration of the HMF in acetone solution, 10 mL was taken up in a disposable polypropylene syringe, dispensed into a 250 mL round bottom flask (9.851 g), concentrated by rotary evaporation to constant mass of viscous yellow oil (5.60 g or 56.9 wt% or 0.56 g HMF/mL solution). Using that calibration factor with the total mass of the HMF in acetone solution, the total HMF recovered was determined to be 100.09 g or 98% recovery. The difference in determination from the bulk crystalline HMF (94%) versus the calibrated solution concentrate (98%) serves as an indication of HMF's propensity to trap solvent. *The HMF was stable when stored away from light and oxygen at room temperature with no observable change for months.*

4.5.2.5. Preparation of AMF



^{1}H (DMSO-d_6 400 MHz): δ 9.59 (s, 1H), 7.51 (d, J=3.6 Hz, 1H), 6.80 (d, J=3.6 Hz, 1H), 5.14 (s, 2H), 2.07 (s, 3H); ^{13}C (DMSO-d_6 100 MHz): δ 178.5, 169.8, 155.4, 152.4, 123.7, 112.9, 57.5, 20.4; FTIR (ATR, Diamond, Neat): cm^{-1} 3127, 2847, 1729, 1666,

1526, 1445, 1402, 1364, 1273, 1237, 1195, 1049, 1022, 988, 957, 940, 924, 825, 775, 723, 609, 513, 460.

To a 500 mL Erlenmeyer flask was added HMF (37.1 g, 0.294 mol 1 eq.), 95% AVA Biochem), and the solid was stirred as acetic anhydride (55 mL, 0.588 mol, 2 eq.) was slowly poured into the flask. An orange solution slowly began to form as the mixture stirred. The mixture was submerged into a room temperature H_2O bath (23 °C) and pyridine (10 mL, 0.124 mol 2.4 eq.) was added slowly from a graduated cylinder. The mixture rapidly transitioned to a red-orange solution. The mixture was stirred overnight in that bath after being covered with a small watch glass.

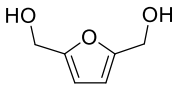
The mixture was poured over ice (550 mL). The mixture was mashed up and stirred with a thick glass rod. The vigorous mixing gave a red oil which became a light tan colloid, and finally once more than half of the ice had melted, gave a graham colored crystalline solid. The mixture was stirred periodically until the ice had thawed and warmed to room temperature.

The solid was isolated by suction filtration through qualitative paper, and the residue was rinsed heavily with H_2O until the filtrate volume was slightly above 900 mL. The filter cake was pressed dry, dried on the filter with suction, then chopped and spread on paper to air-dry. The powder had become quite friable. The powder was transferred to a jar and its mass was 31.09 g (62% of the theoretical).

4.5.2.6. Reduction of HMF

This section describes the preparation of 2,5-bis(hydroxymethyl)furan (BHMF) by sodium borohydride reduction of HMF in EtOH. It also describes the preparation of 2,5-bis(acetoxymethyl)furan (BAMF) and 2,5-bis(benzoyloxymethyl)furan (BBMF) either directly from HMF or from BHMF.

4.5.2.7. 2,5-Bis(hydroxymethyl)furan



^{1}H NMR (400 MHz, DMSO-d_6) δ 6.23 (s, 1H), 4.58 (s, 2H), 2.17 (br s,1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.2, 108.7, 57.6; FTIR (ATR, diamond, neat): cm^{-1} 3313, 3232, 2943, 1561, 1453, 1429, 1398, 1359, 1243, 1198, 1182, 1005, 9999, 968, 921, 810, 756, 726, 657.

The preparation and spectral details of BHMF were reported by Timko and Cram (1974).[71] Following modifications to the procedure of Cottier, Descotes, and Soro (2003),[73] to a 250 mL Erlenmeyer flask was added HMF (from AVA Biochem, 95%, 100 mmol, 13.27 g, 1 eq.), absolute EtOH (100 mL) and the mixture was stirred into solution. The amber solution was chilled on an ice bath and sodium borohydride (1.13 g, 30 mmol, 30 mol%) was carefully added to the open flask in a well-ventilated fume hood as it was stirred. The reaction mixture was stirred on ice for 1 h then allowed to warm to room temperature; stirring continued for 12 h.

The reaction was quenched by the addition of silica gel (50 g), and the EtOH was removed by rotary evaporation under reduced pressure to adsorb the residue onto the silica gel. The solid slurry was packed into a 65 g sample cartridge and the product was washed free of the silica gel by elution with DCM/MeOH (gradient 0 to 5% MeOH) with observation at 225 nm for detection of the 2,5-dialkylsubstituted furan ring. Only a single large peak was observed on the chromatograph; the fractions corresponding with that peak were combined and concentrated by rotary evaporation under reduced pressure to afford a colorless viscous oil. Crystallization was induced by the addition of diethyl ether (5 mL) with hand swirling. The slurry of white crystalline solid was freed of ether and other residual solvent by vacuum drying. The mass of the white crystalline solid was 13.14 g, 99%, melting point range was 77–78 °C.[75]

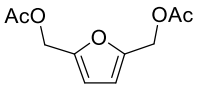
4.5.2.8. 2,5-Bis(hydroxymethyl)furan

A 500 mL single neck round bottom flask was charged with purified HMF in a minimal amount of THF solution (0.33 g/mL, 12.54 g, 100 mmol, 1 eq.), Abs. EtOH (100 mL) and a complete solution formed. The light-yellow solution was stirred while submerged in an ice bath. The mixture gave light colored precipitate and the mixture's headspace was flushed with argon from a balloon. Sodium borohydride (1.514 g, 40 mmol, 0.4 eq.) was added carefully as a granular solid and the argon balloon was quickly replaced. The reaction mixture became bright yellow and rapidly became less turbid while solid sodium borohydride was observed stirring around the flask.

The mixture was stirred overnight as the ice bath melted (~13 h) and the mixture had become a ghostly-yellow solution. In a well-ventilated fume hood, the reaction mixture was quenched by the addition of silica gel; the combination of reaction solution and silica gel led to out gassing with a noticeable exotherm (the outer walls of the flask jumped from 19 to 27 °C). The mixture was chilled and swirled in an ice bath until the reaction subsided. The mixture was concentrated by rotary evaporation under reduced pressure to afford a free-flowing slurry.

A 120 g polypropylene reusable flash column was half-charged with silica gel above which was added the slurry of BHMF to set up a large solid phase extraction. Through the column was eluted DCM and MeOH with observation at 225 nm (furan ring). Aside from an almost negligible bump early in the chromatogram while also excluding the dragged out tailing fractions, the fractions containing product (2–30) were combined, concentrated by rotary evaporation and some diethyl ether was added to trigger crystallization which occurred upon removal of the ether by H_2O aspirator. The solid was chopped and spread on paper to dry, mass was 12.06 g or 96%.

4.5.2.9. 2,5-Bis(acetoxymethyl)furan



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.99 (s, 2H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 150.3, 111.7, 58.2, 21.0; FTIR (ATR, diamond, neat) cm^{-1} 3114, 2991, 1732, 1570, 1437, 1378, 1355, 1236, 1020, 966, 959, 913, 818, 601.

The reduction of HMF and the subsequent masking of hydroxyl functionalities with acetate esters could be telescoped without completely isolating the diol. This combined process eliminated the need for flash column chromatographic purification which utilized MeOH and DCM as the mobile phase and thereby significantly contributed to the sustainability of this reaction. A 250 mL beaker was charged with HMF(12.3 g, 95%, 93 mmol, 1.0 eq.), and absolute EtOH (50 mL). The mixture was stirred in thermal equilibrium with a H_2O bath (23 °C) until it formed a turbid solution. Sodium borohydride (1.1 g, 30 mmol, 0.3 eq.) was added bit by bit as a granular solid. The mixture immediately became a dark orange solution, which began to effervesce, and was stirred in the H_2O bath overnight open to the air during which it had air concentrated. The residue was diluted with 95% EtOH (75 mL). The new mixture was stirred with a glass rod. The mixture was neutralized with 2 M HCl (aq) added by Pasteur pipette with frequent pH checks (universal indicator paper). The mixture formed a clear yellow solution and some colorless viscous oil separated out.

The mixture was stirred until it had formed nearly a complete solution which was light orange in color. The mixture was diluted with concentrated ammonium hydroxide (universal indicator paper was turned blue). The color of the solution became dark orange upon basification. The dark orange solution was stirred and white solid precipitated. The solution was decanted into a 500 mL round bottom flask. The mixture was concentrated by rotary evaporation under reduced pressure resulting in viscous orange oil. It was chilled on an ice bath, diluted with 25 mL of EtOAc and two phases formed. The lower phase was dark orange. Acetic anhydride (50 mL, 539 mmol,

5.7 eq.) was stirred in while the mixture was on ice. Pyridine (6.5 mL, 81 mmol, 0.9 eq.) was added and the mixture became one solution. The mixture was stirred at room temperature for six h, poured onto 1.0 L of ice with hand stirring. The mixture began to precipitate as the ice melted.

The mixture was suction filtered and rinsed heavily with H_2O. The filter cake was a cream colored crystalline solid which was pressed dry. The filter cake was chopped and spread on paper to air dry. The crystalline solid was identified as 2,5-bis(acetoxymethyl)furan (16.0 g, 75.3 mmol, 81% isolated yield, melting point range: 65.9–66.9 °C, recrystallized from IPA 67.2–68.4 °C) and was used without further purification. The material was characterized by ^{1}H and ^{13}C NMR as well as FTIR.[74]

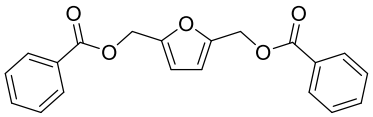
4.5.2.10. 2,5-Bis(acetoxymethyl)furan

Alternatively, BAMF could be prepared in very high yield (97%) from BHMF. A 100 mL single neck round bottom flask was charged with pure BHMF (white crystalline solid, 1.65 g, 13 mmol, 1.0 eq.), and EtOAc as reaction solvent (15–20 mL, ~1 M). The mixture was stirred at room temperature, but white solid residue was observed. Acetic anhydride (2.7 mL, 2.2 eq.) was added by syringe and the mixture remained cloudy. An acyl transfer catalyst, DMAP (26 mg, 1.7 mol%), was added as a white crystalline solid; the turbidity of the solution cleared up almost immediately so that only the largest chunks of white solid residue could be observed. The reaction was exothermic. The reaction was stirred resting on a cork ring above a stir-plate and formed a complete solution in circa 10 min. The reaction mixture was stirred at ambient temperature for 33 h and an aliquot was taken, concentrated, and analyzed by ^{1}H NMR. The aliquot was quite pure 2,5-bis(acetoxymethyl)furan with trace amounts of the acyl transfer catalyst.

The reaction mixture was concentrated to afford a light yellow oil which crystallized upon vacuum drying with a H_2O aspirator. The solid residue was scraped from the walls of the flask,

diluted with H_2O ice (charged to about half fill the flask) and the new mixture was stirred as the ice thawed. The resulting slurry of white crystalline solid in H_2O was isolated by suction filtration as the last bits of ice melted. The residue was rinsed with ice cold H_2O. The filter cake was pressed and sucked dry, then was chopped and spread on paper to air dry. The constant mass of white crystalline solid was 2.67 g, 98% isolated yield.

4.5.2.11. 2,5-Bis(benzoyloxymethyl)furan



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J_1=7.2 Hz, J_2=1.2, 2H), 7.54 (td, J_1=6.0 Hz, J_2=1.2 Hz, 2H),7.38 (td, J_1=6.0 Hz, J_2=1.2 Hz, 1H), 6.47 (s, 1H), 5.30 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 150.5, 133.3, 130.1, 130.0, 128.6, 112.0, 58.8; FTIR (ATR, diamond, neat) cm^{-1} 3124, 3105, 3067, 2968, 1710, 1600, 1582, 1451, 1435, 1368, 1314, 1250, 1204, 1175, 1158, 1094, 1068, 1023, 1005, 970, 935, 919, 823, 743, 760, 703, 687, 618, 501.

To a 250 mL round bottom flask which contained BHMF (2.55 g, 20 mmol, 1.0 eq.) was added chloroform (50 mL) and pyridine (3.3 mL). The mixture was stirred up and it formed a light yellow solution with some white solid residue. A solution of 25 mL of chloroform and benzoyl chloride (5.1 mL, 44 mmol, 2.2 eq.) was prepared and added dropwise *via* Pasteur pipette to the stirring diol mixture. The first few drops were not noticeably exothermic, so most of the benzoyl chloride mixture was poured into the diol solution. The total addition of the acid chloride to the diol/pyridine solution was exothermic, and as it progressed, some smoke appeared above the reaction mixture: presumably pyridinium hydrochloride. Upon unification of the substrate and reagent solutions, the reaction mixture had formed a complete solution. The walls of the flask were rinsed down with the reaction mixture and it was stirred at room temperature as it cooled. Thin layer chromatography (TLC) indicated that there were at least four components comprising the

reaction mixture. The mixture was heated to reflux under a Dimroth condenser overnight (oil bath temperature was set to 80 °C).

The mixture was diluted with ethyl alcohol to quench any residual acylating species. The mixture of compounds likely included ethyl benzoate (based upon the smell of the highly motile spot from TLC analysis). The mixture was concentrated by rotary evaporation under reduced pressure, adsorbed onto silica gel, and purified by flash column chromatography (EtOAc: Hex). From the fractions collected, one set was matched to the desired product 2,5-bis(benzyloxymethyl)furan by TLC. The product fractions were combined and concentrated by rotary evaporation *in vacuo* to afford a yellow-cream colored solid which was flushed with nitrogen overnight. A quick check indicated that the product had not dried to a constant mass. The residue was chopped and spread on paper to air-dry. The yellow crystalline solid weighed 3.68 g (54%) and was pure according to ^{1}H NMR.

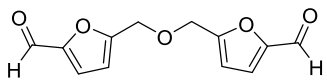
4.5.2.12. Preparation of 2,5-Bis(benzoyloxymethyl)furan

To a 50 mL single neck round bottom flask was added benzoic acid (1.22 g, 10 mmol, 2 eq.), BHMF (0.640 g, 5 mmol, 1.0 eq.), and 26 mL of DCM. Acyl transfer catalyst, DMAP (0.130 g, 1 mmol, 20 mol%) was added and it dissolved. The reaction slurry was chilled on an ice bath for several min before DCC (2.2 g, 10.5 mmol, 2 eq.) was added bit by bit to the reaction mixture and it dissolved on contact with the DCM. The reaction mixture was allowed to warm to room temperature upon completion of the addition. The mixture was stirred vigorously overnight.

Thin layer chromatographic (TLC) analysis indicated that the reaction was not completed so a small shot of additional DCC (0.22 g 1.05 mmol, 20 mol%) was added and the mixture was stirred overnight again. The thick white slurry was suction filtered and purified by flash column chromatography to afford 1.36 g of 2,5-bis(benzoyloxymethyl)furan or 81% isolated yield.

4.5.3. Furanic Dialdehydes

4.5.3.1. 5,5'-[Oxybis(methylene)]bis[2-furancarboxaldehyde]



^{1}H ($CDCl_3$ MHz): δ 9.58 (s, 1H), 7.17 (d, *J*=3.6 Hz, 1H), 6.52 (d, *J*=3.6 Hz, 1H), 4.59 (s, 2H); ^{13}C ($CDCl_3$ 100 MHz): δ 177.9, 157.4, 153.0, 122.1, 112.0, 64.8; FTIR (ATR, diamond, neat): cm^{-1} 3162, 3111, 2931, 2849, 1666, 1522, 1446, 1404, 1358, 1274, 1196, 1034, 984, 948, 885, 829, 773, 733.

Was prepared as described in Vijjamarri *et al.*,[75] in 48% of the theoretical yield; melting point range was 118–121 °C. The mass of the recovered starting material was 5.01 g which made the yield based upon recovered starting material in this reaction: 57 %.

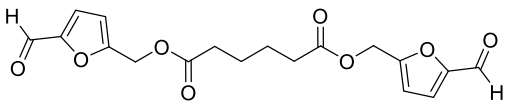
4.5.3.2. 5,5'-[Oxybis(methylene)]di(2-furaldehyde)

A 1 L single neck round bottom flask was charged with HMF (purified, 22.18 g, 176 mmol, 1.0 eq.), and chloroform (400 mL, 0.44 M). The faintly yellow solution was stirred as Amberlyst 15 (dry granules, 4.1 g, ~19 mmol, ~11 mol%) was added. The reaction flask was attached to a moisture trap (for solvents with specific gravity greater than one), then sealed with a reflux condenser and an argon balloon. The mixture was continuously distilled at ambient pressure for 2.5 h. The dark reaction mixture was separated by suction filtration through qualitative filter paper. The residue was rinsed heavily with EtOAc. The residue was black granules, the filtrate was black solution.

The filtrate was concentrated by rotary evaporation under reduced pressure to afford a tan solid residue. The residue was adsorbed onto silica gel and purified by flash chromatography (EtOAc and Hex). The major eluate fractions were combined, concentrated, and digested in IPA (55 °C) for 24 h. Upon cooling, orange powdery solid was isolated by suction filtration. The residue was rinsed with IPA, pressed, dried on the filter, chopped and spread on paper to

completely dry. Mass of the orange powder was 9.997 g, 42.7 mmol, 49% yield and the material was characterized as pure 5,5'-(oxybis(methylene))bis(furan-2-carbaldehyde) (OBMF) by FTIR, ^{1}H and ^{13}C NMR.

4.5.3.3. Bis((5-formylfuran-2-yl)methyl) adipate



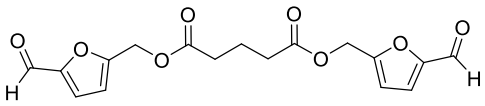
^{1}H ($CDCl_3$ 400 MHz): δ 9.59 (s, 1H), 7.17 (d, *J*=3.6 Hz, 1H), 6.55 (d, *J*=3.6 Hz, 1H), 5.09 (s, 2H), 2.40–2.30 (m, 2H), 1.70–1.50 (m, 2 H); ^{13}C ($CDCl_3$ 101 MHz): δ 178.0, 172.7, 155.6, 153.0, 121.9, 112.7, 57.9, 33.6, 24.3; ^{1}H (DMSO-d_6 400 MHz): δ 9.59 (s, 1H), 7.51 (d, *J*=3.6 Hz, 1H), 6.79 (d, *J*=3.6 Hz, 1H), 5.15 (s, 2H), 2.45–2.30 (m, 2H), 1.64–1.47 (m, 2 H); ^{13}C (DMSO-d_6 101 MHz): δ 178.4, 172.2, 155.5, 152.4, 123.7, 112.8, 57.4, 32.7, 23.6; FTIR (ATR, Diamond, Neat): cm^{-1} 3130, 2952, 2839, 1722, 1669, 1532, 1463, 1400, 1352, 1351, 1252, 1194, 1154, 1028, 981, 942, 931, 794, 731.

Following the procedure of Zuffanti (1948),[80] with Mason Tacke's technical assistance, a 100 mL conical flask was charged with adipic acid (7.406 g, 50.7 mmol, 0.5 eq.), then thionyl chloride (29.5 mL, 404 mmol, 3.6 eq.) was added with stirring. The flask was fitted such that a stream of dry nitrogen could pass through the system and out into a gas trap charged with saturated sodium bicarbonate solution chilled in an ice bath. The flask was lowered into a preheated oil bath (65–75 °C over an h). The thionyl chloride-adipic acid mixture formed a complete solution within 90 min. The reflux was continued for a total of 4 h. A distillation trap was fitted into the system and 14.05 g out of 18.1 g (theoretical excess of thionyl chloride) was collected which was suitable for reuse in subsequent reactions. Toluene (55 mL) was added to the reaction mixture and distilled under normal pressure to relieve the mixture of any residual thionyl chloride. The residue following distillation was a dark amber oil which dissolved in diethyl ether.

A solution of HMF (15.0 g, 95%, 110 mmol, 1.0 eq.) and diethyl ether (300 mL, 0.28 M) was prepared in a 1 L single neck round bottom flask which was chilled in an ice bath. The acyl transfer catalyst, DMAP (0.631 g 5 mmol, 4.6 mol%), was added as a colorless solid and the transparent solution turned cloudy. Triethylamine (14 mL, 0.100 mol, 0.9 eq.) was added as a colorless liquid. The freshly prepared adipoyl chloride was diluted with ether (~60 mL) and added to the reaction dropwise *via* Pasture pipette over an h. The reaction was left to stir at room temperature for 20 min, and then refluxed for several h. The mixture had formed a tan powdery slurry.

H_2O ice (~300 mL) was added and the mixture was concentrated by rotary evaporation under reduce pressure to afford an aqueous slurry which was separated by suction filtration. The filter cake was pressed, chopped and spread on paper to air-dry to constant mass: 32.0 g, 78% isolated yield. Melting point of the material was 96.8 °C and could be column purified with only slight improvement in the color and melting point range was 98.4–101.4 °C. Also, 1.012 g of Crop 1 afforded 0.972 g of isolated product following flash column chromatographic purification which equated to 96% by weight pure bis((5-formylfuran-2-yl)methyl) adipate.

4.5.3.4. Bis((5-formylfuran-2-yl)methyl) glutarate



^{1}H ($CDCl_3$ 400 MHz): δ 9.61 (s, 1H), 7.18 (d, *J*=3.6 Hz, 1H), 6.56 (d, *J*=3.6 Hz, 1H), 5.10 (s, 2H), 2.41 (t, 2H, *J*=7.3 Hz), 1.95 (p, 1H, *J*=7.3 Hz); ^{13}C ($CDCl_3$ 100 MHz): δ 178.0, 172.3, 155.5, 153.1, 121.9, 112.8, 58.0, 33.0, 20.0; ^{1}H (DMSO-d_6 400 MHz): δ 9.59 (s, 1H), 7.51 (d, *J*=3.5 Hz, 1H), 6.79 (d, *J*=3.5 Hz, 1H), 5.16 (s, 2H), 2.42 (t, *J*=7.5 Hz, 2H), 1.79 (p, *J*=7.5 Hz, 1H); ^{13}C (DMSO-d_6 100 MHz): δ 178.4, 171.9, 155.4, 152.4, 123.7, 112.8, 57.5, 32.1, 19.7; FTIR (ATR, Diamond, Neat):

cm^{-1} 3126, 2953, 2839, 1734, 1672, 1588, 1523, 1439, 1403, 1348, 1314, 1274, 1192, 1142, 1060, 1021, 983, 946, 810, 755.

A 250 mL single neck round bottom flask was charged with HMF (purified, 5.60 g, 44 mmol, 1.0 eq.), acetone (HPLC grade, 93 mL) and the mixture was stirred as a complete solution formed. Triethylamine (99%, 6.2 mL, 44 mmol, 1.0 eq.) was filtered through basic alumina into a graduated cylinder. The addition of colorless amine to the very faintly-yellow HMF/acetone solution caused the solution to yellow slightly.

Acyl transfer catalyst, DMAP (0.145 g, 1 mmol, 3 mol%) was added as a granular solid which rapidly dissolved in the stirring reaction mixture. Glutaryl dichloride (97%, 2.8 mL, 22 mmol, 0.5 eq., amber liquid) was drawn into a 3 mL disposable polypropylene syringe and injected below the vigorously stirring reaction solution within one min.

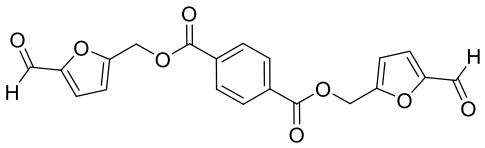
The combination was quite exothermic (outer walls of the flask rose to 40 °C). The last 25% or so of diacid chloride had to be added dropwise into the stirring mixture as it became thick with precipitate. A reflux condenser was installed, and the headspace was flushed with argon. The mixture was allowed to stir as the latent heat of the reaction dissipated: 2 h. The mixture was composed of orange solution and creamy white precipitate.

The mixture was separated by gravity filtration through a plug of cotton. The residue was rinsed with EtOAc. The filtrate was concentrated by rotary evaporation under reduced pressure. The residue from concentration was light tan solid with obvious crystallites forming on the upper walls of the flask. H_2O ice (~60 mL) was added to the tan solid to dissolve ionic impurities and residual aldehyde substrate while crashing out the desired dialdehyde product. The mixture was shaken with the ice, scraped, crushed, and agitated under the surface of H_2O as the ice thawed. The aqueous slurry was chilled in an ice chest. The tan solid was isolated by suction filtration through

qualitative filter paper in a 5 cm Büchner funnel. The filtrate was bright yellow. The residue was rinsed with ice-cold H_2O.

The volume of filtrate after rinsing was ~100 mL. The filter-cake was pressed, dried on the filter, chopped, and spread on paper to further air-dry (2 days). The filtrate was cloudy after those two days. The mass of cream-colored solid was 6.532 g, 19 mmol, 85% of the theoretical maximum. Melting point analysis was performed by Rachel Day, 92.7–94.5 and 92.5–94.8 °C. The solid was determined to be bis((5-formylfuran-2-yl)methyl) glutarate with high purity by ^{1}H and ^{13}C NMR in two solvents $CDCl_3$ and DMSO-d_6 as well as FTIR.

4.5.3.5. Bis((5-formylfuran-2-yl)methyl) terephthalate



^{1}H ($CDCl_3$ 400 MHz): δ 9.63 (s, 1H), 8.09 (s, 2H), 7.21 (d, *J*=3.5 Hz, 1H), 6.67 (d, *J*=3.5 Hz, 1H,), 5.37 (s, 2H); ^{13}C ($CDCl_3$ 101 MHz): δ 178.0, 165.2, 155.1, 153.2, 133.7, 130.1, 121.9, 113.3, 58.8; ^{1}H (DMSO-d_6 400 MHz): δ 9.61 (s, 1H), 8.10 (s, 2H), 7.55 (d, *J*=3.6 Hz, 1H), 6.92 (d, *J*=3.5 Hz, 1H), 5.47 (s, 2H); ^{13}C (DMSO-d_6 101 MHz): δ 178.5, 164.4, 154.9, 152.6, 133.1, 129.8, 123.7, 113.4, 58.7; FTIR (ATR, Diamond, Neat): cm^{-1} 3119, 3094, 3007, 2827, 1717, 1678, 1529, 1458, 1403, 1371, 1265, 1246, 1198, 1117, 1100, 1031, 1009, 978, 940, 825, 774, 727, 708, 507; FTIR (ATR, Diamond, thin film from $CDCl_3$ solution): cm^{-1} 3124, 2836, 1719, 1673, 1588, 1524, 1439, 1408, 1371, 1249, 1194, 1097, 1018, 978, 944, 875, 812, 768, 727.

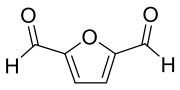
A 300 mL single neck round bottom flask was charged with HMF (5.55 g, 44 mmol, 1.0 eq.) The flask was charged with HPLC grade acetone (75 mL) and a solution formed as the mixture was stirred. Triethyl amine was filtered through a plug of basic alumina (6.6 mL) and added to the

reaction solution. Acyl transfer catalyst, DMAP (134 mg, 3 mol%) was added to the stirring solution.

Terephthaloyl dichloride (4.46 g, white solid flakes, 0.5 eq.) was added to the vigorously stirring amber reaction mixture. Within a min, the mixture became hot and thick with precipitated cream colored solid. A reflux condenser was added. Within five min, the mixture had loosened up enough to stir. An addition of HPLC grade acetone was made (88 mL) and the mixture was refluxed for two h, then stirred overnight at room temperature. The amber solution was isolated from cream colored precipitate by gravity filtration with EtOAc rinsing. The filtrate was concentrated by rotary evaporation under reduced pressure to afford cream colored solid caked onto the inner walls of the flask. The mixture was diluted with ice, scraped, chopped, and triturated.

The resulting mixture was separated by suction filtration, with ice cold H_2O rinsing. The volume of the filtrate was circa 200 mL. The off-white filter-cake was pressed, dried on the filter, chopped and spread on paper to further air dry. The mass of powder was 7.93 g or 94% of the theoretical maximum. The product was characterized as bis((5-formylfuran-2-yl)methyl) terephthalate by FTIR, ^{1}H and ^{13}C NMR.

4.5.3.6. DFF



^{1}H (DMSO-d_6 400 MHz): δ 9.81 (s, 1H), 7.67 (s, 1H); ^{13}C (DMSO-d_6 100 MHz): δ 180.7, 153.6, 122.0; ^{1}H ($CDCl_3$ 400 MHz): δ 9.84 (s, 1H), 7.31 (s, 1H); ^{13}C ($CDCl_3$ 100 MHz): δ 179.4, 154.4, 119.4; FTIR (ATR, Diamond, Neat): cm^{-1} 3132, 3102, 1673, 1561, 1512, 1412, 1269, 1239, 1188, 1042, 976, 958, 845, 797, 532.

4.5.3.7. DFF (Table 4.1 Entry 4)

A 100 mL single neck round bottom flask (14/20) was charged with HMF (95%, 1.32g, 10 mmol, 1.0 eq.), bulk EtOAc (40 mL), and the mixture was stirred to form an amber solution (0.25

M). As the solution stirred, MnO_2 (88%, 5.01 g, 51 mmol, 5.1 eq.) was added as a black powder. The headspace of the flask was flushed with argon and the mixture was refluxed beneath a tall West condenser and argon balloon (in an oil bath heated to 85 °C) for 150 min. The entire reaction mixture was transferred to a 100 mL single neck recovery flask (24/40) and adsorbed onto silica gel prior to purification by flash column chromatography.

The very major eluate was contained within the initial fractions which were combined, concentrated and vacuum dried to constant mass to afford ^{1}H NMR pure DFF: 1.00 g, or 82% yield. Additionally, the less motile eluate fractions were combined, concentrated and vacuum dried to constant mass to afford 30 mg of yellow oil which contained >90% HMF by ^{1}H NMR with ~5% OBMF and some traces of DFF. This was calculated to be approximately 2% of the total input mass. Conclusion: These conditions are degrading the HMF in some way related to dehydrative polymerization.

4.5.3.8. DFF (Scaleup from Table 4.1, with Dried Distillate)

A two neck 1 L round bottom flask was charged with HMF (12.6 g, 100 mmol, 1.0 eq.) and dissolved in EtOAc (400 mL, ~0.25 M). A solid addition auger was placed in the side neck while a Soxhlet extractor was placed in the central neck. The extractor contained oven dried 4 Å molecular sieves. The auger was charged with MnO_2 (26 g, 88%, 260 mmol, 2.6 eq.). Nitrogen was flushed through the auger and out a condenser topping the extractor. The reaction solution was pale yellow and was heated to distillation without discoloration. The addition of MnO_2 was carried out bit by bit in six portions at 20 min intervals.

At the 4 h mark, (the final addition had been ~20 min prior) the mixture was analyzed by ^{1}H NMR. A small aliquot of the material was filtered through a monster pipette charged with silica gel and rinsed with EtOAc. The solid residue of MnO_2 was contained on the silica gel plug, and

the bright-yellow eluate solution was collected in a 6-dram vial. EtOAc was removed from the sample by concentration *in vacuo*. The solid residue seemed to be a mixture of DFF and some HMF or oligomers thereof in a ratio of 1:1.2 based on aldehyde integration.

The side-neck of the reaction vessel was sealed with a yellow-capplug, the condenser was sealed with an argon balloon. The mixture was stirred and distilled for another 6 h. Analysis in the fashion described above indicated that the molar ratio based on aldehyde integration was 1:0.6. The extraction thimble containing molecular sieves weighed 79 g (after drying in the fume hood, the thimble/MS lost 8 g and lost another 3 g upon oven drying). The reaction mixture was suction filtered through a pad of amorphous silica gel. The filtrate was golden-yellow, the filter-aid was rinsed copiously with EtOAc (total filtrate volume: 750 mL). The filtrate was concentrated by rotary evaporation under reduced pressure, but the resulting solid was a bit gummy. The mixture was dissolved in acetone to afford an orange solution which was adsorbed onto silica gel.

The mixture was purified by column chromatography. The very major eluate peak's fractions were combined, concentrated to afford white crystalline solid stained faintly yellow which smelled of caramel and weighed 10.0 g, 81 mmol, 81% isolated yield. The tail fractions which were not combined with the major eluate were also combined and concentrated to afford 0.348 g of yellow solid.

4.5.3.9. DFF

As described by Vijjamarri *et al*.,[75] HMF (32.73 g of 95% from AVA Biochem, 247 mmol, 1 eq.), in DCM (300 mL), beneath a heavier than H_2O Dean-Stark trap, was treated with MnO_2 (97 g, 88% active electrolytically precipitated, 0.982 mmol, 4 eq.). The mixture was heated to distillation and the oxidizer was added in portions over the course of 6 h. Each addition of oxidizer was directly followed by the evolution of wet distillate. The unified reaction mixture was distilled

for 12 h, then diluted while still hot with EtOAc (100 mL). Upon isolation, the mass of the solid residue was identified as DFF and was 27.1 g, 89% yield, melting point range: 115–116 °C.

4.5.3.10. DFF

Also as described by Vijjamarri *et al*.,[75] HMF (19.5 g, 155 mmol, 1 eq.), in toluene (500 mL), with MnO_2 (60 g of 88% active, 620 mmol, 4 eq.) added carefully to the stirring mixture under argon beneath a distilling receiver, the black was slowly heated to boiling and distillate was collected within 30 min. The reaction was stirred under distillation for 120 min. Following isolation, solid product was obtained with a mass of 16.28 g, 84%, melting point range: 112–116 °C; recrystallized from IPA, melting point range: 118–120 °C.

4.5.3.11. DFF

As described by Serum *et al.*,[95] HMF (32.43 g, 95% pure, 244 mmol, 1 eq.), in DCM (300 mL), with the aid of a solid addition auger reacted with MnO_2 (66 g, 88% active electrolytically precipitated, 2.73 eq.), in 2.5 h, and the mixture was refluxed overnight under positive nitrogen pressure. Isolation included recrystallization and afforded three crops: crop one: 24.4 g off white crystalline solid (80.5%), melting point range: 114–116 °C; crop two: 0.9 g of off white crystalline solid (3.0 %), melting point range: 115–118 °C; crop three: 2.3 g of off white crystalline solid (7.6%), melting point range: 116–117 °C.

4.5.3.12. DFF (Scaleup Investigating MeOH in the Reaction Workup)

A 1 L single neck round bottom flask was charged with HMF (95%, 39.430 g, 300 mmol, 1 eq.), DCM (600 mL, 0.5 M) and an amber-solution formed. The mixture was stirred and charged with MnO_2 (88%, 108 g, 1,100 mmol, 3.7 eq.). A moisture trap (for solvents with specific gravity greater than one) was inserted in the neck of the reaction flask, topped with a condenser and argon balloon. The mixture was heated to distillation for six h.

While still warm (outer walls of the flask were determined to be ~28 °C), the mixture was diluted with MeOH (100 mL). The mixture was stirred overnight as it cooled to room temperature. The mixture was separated by suction filtration through a pad of Celite 545. The residue was washed with DCM and MeOH. The amber filtrate was concentrated by rotary evaporation under reduced pressure. The residue had a mass of 36 g and appeared as a brown-solid residue which seemed a bit sticky.

That crude yield contained 97% of the isolated mass which was expected. ^{1}H NMR indicated that the material was ~85% pure DFF contaminated mostly with HMF. MeOH addition looks like a favorable work up method but may also have been responsible for the abnormal dark color of the residue. The crude-mixture was suspended in an equivalent amount (~36 mL) of IPA with a bit of acetone. The mixture was triturated and chilled in an ice chest. Brown-crystalline solid was isolated from the amber-liquor by suction filtration with washing by ice-cold IPA. The residue was pressed, chopped, and spread on paper to air dry. The mass of tan-crystalline solid 29 g, or 78% of the theoretical maximum yield and 81% through the digestion/crystallization. The material was characterized as DFF by NMR.

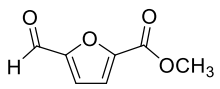
4.5.3.13. DFF (MnO_2 (3.6 eq.) Mixed with Silica Gel)

A two neck 1 L round bottom flask was charged with HMF (13.3 g, 95%, 100 mmol, 1.0 eq.), and EtOAc (600 mL, 0.167 M solution). The solution was amber in color. MnO_2 (36 g, 88%, 360 mmol, 3.6 eq.) was mixed with silica gel (16 g), then added gradually through a jointed powder addition funnel. The black heterogeneous mixture was capped with a yellow cap-plug on its side neck and sealed with a Friederichs condenser on the central neck. The headspace of the flask was flushed with argon.

The mixture was heated to reflux by heating mantle with stirring for 91 min. Saturated aqueous sodium chloride (60 mL) was added through the central neck. The new triphasic mixture was stirred for an h beneath argon. The mixture was separated by suction filtration through a bed of silica gel. The aqueous slurry was so thick that it had to be diluted with saturated sodium chloride. The silica gel held back all the black slurry while allowing a yellow solution to filter through. The filter cake was washed with EtOAc. The filtrate was composed of two yellow solutions which were separated in a 1 L separatory funnel. The EtOAc solution was washed with saturated aqueous sodium chloride twice. The yellow aqueous solution was about 250 mL in volume. The EtOAc solution was approximately 800 mL in volume. The EtOAc solution was dried (anhydrous sodium sulfate).

The yellow organic solution was isolated by gravity filtration through a cotton plug. Concentration by rotary evaporation under reduced pressure afforded a crude yellow-stained crystalline solid. The solid was digested in IPA (65 mL) by sonication in a 50 °C H_2O bath for 90 min. The mixture was made of light crystalline solid and yellow solution. The mixture was chilled in an ice bath, then separated by suction filtration. The filter cake was pressed and rinsed with ice-cold IPA. The filtrate was about 150 mL in volume. The mass of light-tan crystalline solid was 11.3 g or 88% isolated yield in crop one. The aqueous yellow washes from the first filtration were back extracted with EtOAc (300 mL) thrice. The extracts were combined, dried (anhydrous sodium sulfate) and concentrated to afford 410 mg of light crystalline solid or ~3% of the total input mass.

4.5.3.14. Methyl 5-formylfuran-2-carboxylate (Table 4.1 Entry 7)



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77, (s, 1H), 7.23 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.2, 158.6, 154.0, 147.8, 119.1, 118.9, 52.8; FTIR

(ATR, diamond, neat) cm^{-1} 3156, 3138, 1958, 1724, 1679, 1568, 1508, 1436, 1407, 1292, 1253, 1209, 1140, 1019, 933, 964, 923, 832, 800, 763, 606, 517.

A 100 mL single neck round bottom flask was charged with methyl 5-(hydroxymethyl)furan-2-carboxylate (1.572 g, 10.07 mmol, 1.0 eq.) as a light-yellow oil, DCM (40 mL, 0.25 M) and the mixture was stirred into a complete solution. MnO_2 (88% electrolytically active, 4.7 g, 47 mmol, 4.7 eq.) was added to the stirring DCM solution. A moisture trap for solvents with density greater than one was charged with DCM and affixed to the reaction flask. The headspace of the system was flushed with argon and the mixture was heated to distillation (heating mantle).

The mixture was distilled continuously for 10 h, then diluted with acetone while still hot. The DCM/acetone mixture was stirred till it had cooled to room temperature. Thin layer chromatographic analysis was performed on the reaction mixture alongside the substrate. Measured at the center of circular spots on UV-254 silica gel plates (three) and eluted with [Hex(mL), EtOAc(mL)]; [6,0] R_f substrate: 0, product: 0; [5,2] R_f substrate: 0.26, product: 0.50; [3,3] R_f substrate: 0.43, product: 0.64.

The reaction mixture was suction filtered through a pad of Celite 545 and rinsed with acetone (total volume ~200 mL). The filtrate was a brighter-yellow than the initial solution. The solution was concentrated by rotary evaporation under reduced pressure to afford yellow solid with a constant mass of 1.357 g, 8.802 mmol, 87% of the theoretical maximum.

4.5.3.15. Methyl 5-formylfuran-2-carboxylate (MnO_2 (3.3 eq.) Ground with Silica Gel)

The thought was to add silica gel as a dehydrating agent and as a dispersant for the manganese sludge. A 2 L 2 neck round bottom flask was charged with methyl 5-(hydroxymethyl)furan-2-carboxylate (24.563 g, 157 mmol, 1.0 eq.), and EtOAc (1,200 mL, 0.13

M). A pale yellow solution formed upon mixing the substrate and solvent by stirring. A pressure equalizing solid addition auger was fitted to the central neck, while a calibrated moisture trap was fitted to the side neck and topped with a West condenser cooled with flowing tap H_2O. A nitrogen line was attached to the top of the auger and a line to an air free gas bubbler was attached to the top of the West condenser.

MnO_2 (51.105 g of 88% active electrolytically precipitated, 520 mmol, 3.3 eq.) was thoroughly mixed with silica gel (25.6 g) and charged into the solid addition auger. The mixture was heated to distillation, some of the oxidant was added, and a timer was started. The oxidant was added bit by bit over 80 min. Contrary to the typical reactions, no H_2O was observed in the moisture trap, which indicated the effectiveness of silica gel as an internal moisture trap. The mixture was distilled for another 40 min, and still no H_2O was observed in the trap.

The heat was terminated, and circa 125 mL of distilled H_2O was added while the mixture was still warm. The mixture was stirred for 30 min, then separated by suction filtration through a pad of Celite (2 cm) in a 300 mL fritted glass Büchner funnel. The MnO_2 was sludgy but could be poured. The mixture was pressed, rinsed heavily with EtOAc, and the filtrate partitioned into two pale yellow solutions. The filtrate was poured into a 2 L separatory funnel and the mixture was diluted with 100 mL of saturated aqueous sodium chloride solution, shaken and allowed to partition. The EtOAc solution was isolated, dried with anhydrous sodium sulfate, then concentrated by rotary evaporation under reduced pressure to afford 21.868 g of pale yellow solid: crude yield 90%. The residue was analyzed by ^1H NMR. The material seemed to be composed product and either starting material or dehydrative dimer in an integration ratio of 1:0.05.

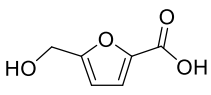
The oxidant containing residue and flask were rinsed into a 600 mL beaker with MeOH, diluted to a total volume of 500 mL with acetone, then stored covered with aluminum foil for

several days. The crude product was recrystallized from isopropyl alcohol: (1) material was dissolved in 125 mL of hot (50 °C) isopropyl alcohol upon sonication, (2) as the solution cooled, crystals rained from the liquor, and (3) the mixture was chilled in an ice bath. Pure white crystalline solid was isolated from yellow isopropyl alcohol liquor by suction filtration. The filter-cake was rinsed with ice cold isopropanol, the flowers were pressed until free of solvent, chopped and spread on paper to air dry. The dry mass of pure methyl 5-formyl-2-furancarboxylate was 18.746 g (77% isolated yield). It was characterized by ^{1}H, ^{13}C NMR and FTIR.

The recrystallization liquor clearly contained some product which began to crystallize during the filtration. TLC analysis indicated at least three components. TLC analysis of the oxidant digestion indicated no motile substances, so it was discarded. The recrystallization filtrate was adsorbed onto silica gel and purified by flash column chromatography. The early fractions began to deposit crystalline precipitate on the inner walls of the flask as they slowly concentrated in the fume hood before final concentration. The second motile eluate peak's fractions were combined, concentrated and characterized as methyl 5-formyl-2-furancarboxylate by ^{1}H NMR. They comprised 1.071 g, 4% of the theoretical maximum yield, bringing the total isolated yield up to 81%. The third motile eluate's fractions were combined and concentrated to afford a light yellow oil which was identified as methyl 5-(hydroxymethyl)-2-furancarboxylate by ^{1}H NMR: 1.346 g, 5% of the initial substrate.

4.5.4. Chlorous Acid Oxidations

4.5.4.1. HMFA



^{1}H NMR (400 MHz, DMSO-d_6) δ 13.0 (br s, 1H), 7.15 (d, J=3.6 Hz, 1H), 6.45 (d, J=3.5 Hz, 1H,), 5.43, (br s, 1H), 4.40 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.7, 159.4, 143.9, 118.6, 109.0, 55.8; FTIR (ATR, diamond, neat): cm^{-1} 3608, 3454, 3132,

3103, 3060, 2934, 2601, 1694, 1634, 1563, 1517, 1488, 1398, 1328, 1285, 1252, 1194, 1154, 1023, 957, 838, 811, 767, 735, 704, 567.

4.5.4.2. HMFA (Table 4.2, Entry 1)

A 1 L single neck round bottom flask was charged with purified HMF (1.79 g, 14.2 mmol, 1.0 eq.). DI H_2O (450 mL) was added to prepare a 0.032 M solution of HMF which was tinted light-yellow. Sulfamic acid (1.83 g, 18.85 mmol, 1.33 eq.) was added as a granular-solid and the yellow color of the solution dissipated. A solution of sodium chlorite (78.9%, 2.20 g, 19.19 mmol, 1.35 eq.) in DI H_2O (20 mL, ~1 M) was prepared and added dropwise by pressure equalizing dropping funnel over 100 min.

The reaction solution had taken on a yellow color and remained a complete solution. The solution was transferred to a 1 L separatory funnel and extracted with 500 mL diethyl ether (Et_2O). The yellow color completely transferred to the organic phase. The aqueous layer was extracted with 250 mL Et_2O, twice. The organic extracts were combined, backwashed with 100 mL saturated sodium chloride solution, dried (anhydrous sodium sulfate) and an aliquot was taken. The aliquot was concentrated by rotary evaporation under reduced pressure, and white crystalline solid was observed forming from the residue. An attempt to dissolve the material in $CDCl_3$ utterly failed. The $CDCl_3$ was removed by rotary evaporation under reduced pressure to afford white crystalline solid. The material appeared to be the desired product, HMFA monohydrate.

The extracts were decanted away from drying agent and concentrated by rotary evaporation under reduced pressure; a yellow color was carried over to the solvent trap during concentration which indicated the presence of the hazardous gaseous side product of hypochlorite's reaction with chlorite: chlorine dioxide. The residue retained in the flask was a yellow viscous oil, which was diluted with toluene and concentrated to afford a white crystalline solid, 0.97 g, 48% of the

theoretical maximum, s*E*F=5.0 and c*E*F=1347. The product was characterized as HMFA by FTIR, ^{1}H, and ^{13}C NMR.

Determination of simple *E* Factor (s*E*F):

$$sEF = \frac{\sum 1.79_{(g)}, 1.83_{(g)}, 2.20_{(g)} - 0.97_{(g)}}{0.97_{(g)}} = 5.0 \quad (4.23)$$

Determination of complete *E* Factor (c*E*F):

$$cEF = \frac{\sum 1.79_{(g)}, 1.83_{(g)}, 2.20_{(g)}, 713_{(g\ Et_2O)}, 552.82_{(g\ H_2O)}, 36_{g\ NaCl}, -0.97_{(g)}}{0.97_{(g)}} = 1347 \quad (4.24)$$

4.5.4.3. HMFA (Table 4.2, Entry 2)

A 2 L beaker was charged with ice-cold HMF as received (95%, 23.08 g, 0.17 mol, 1 eq.), H_2O (800 mL, 0.22 M) and the mixture was stirred but did not form a complete solution. Sulfamic acid (23.33 g, 0.24 mol, 1.4 eq.) was added to the HMF mixture and a solution of sodium chlorite (80%, 21.88 g, 0.19 mol, 1.1 eq.) in H_2O (200 mL, ~2 M) was prepared. The temperature of the reaction mixture was monitored internally with an alcohol thermometer. The chlorite solution was added over 20 min and the temperature of the reaction mixture plateaued at 30 °C. The mixture transitioned to a light-yellow solution during the addition. The reaction was stirred for another 100 min as the temperature returned to 22 °C.

The reaction mixture was transferred to a 2 L separatory funnel and extracted with EtOAc (4 × 375 mL). The aqueous layer was saturated with sodium chloride and extracted EtOAc (2 × 400 mL). The extracts were combined, backwashed with saturated sodium chloride, gravity filtered through cotton, and concentrated by rotary evaporation under reduced pressure. As the mixture concentrated, white solid was observed. However, upon complete concentration, the solid had been stained golden. The solid was scraped and chopped to afford a mass of cream-colored-powdery-residue: 19.16 g, or 0.13 mol or 77% crude yield, s*E*F=2.6, c*E*F=163. The solid smelled faintly of acetic acid, so the residue was digested in IPA.

$$sEF = \frac{\sum 23.08_{(g)}, 23.33_{(g)}, 21.88_{(g)} - 19.16_{(g)}}{19.16_{(g)}} = 2.6 \quad (4.25)$$

$$cEF = \frac{\sum 23.08_{(g)}, 23.33_{(g)}, 21.88_{(g)}, 2075_{(g\,EtOAc)}, 997_{(g\,H_2O)}, -19.16_{(g)}}{19.16_{(g)}} = 163 \quad (4.26)$$

Upon addition of IPA, a liquor formed which was golden yellow. Chilling the mixture in an ice chest led to obvious precipitation of copious white solid. The crystalline solid was isolated by suction filtration, the filter-cake was rinsed copiously with ice-cold IPA (total filtrate volume was ~150 mL) but the residue was still stained a light golden color. The filter-cake was pressed, chopped and spread on paper to air dry. The dry weight of recovered solid was crop 1: 10.40 g, 42% overall yield 54% through the recrystallization. ^{1}H and ^{13}C NMR (DMSO-d_6) indicated a pure product. Thusly, IPA was found to be an unsuitable solvent for purification. The filtrate was concentrated to afford crop 2: 8.35 g, 33% overall yield, 44% of the crude yield which went into the recrystallization so 75% over 2 crops.

4.5.4.4. HMFA (Table 4.2, Entry 3)

The aqueous concentration of HMF and sulfamic acid (dissolved together) was increased to ~1 M and the sodium chlorite was added dropwise. The mixture was exothermic to the point an ice bath was required to control the reaction temperature below 30 ℃.

A 250 mL single neck round bottom flask was charged with purified HMF (14.68 g, 116 mmol, 1.0 eq.) and H_2O (~125 mL, ~0.93 M). The mixture was stirred, the mixture appeared milky and yellow. Sulfamic acid (14.55 g, 150 mmol, 1.29 eq.) was added as granular solid. The mixture formed an amber solution which gradually darkened. Aqueous sodium chlorite (13.61 g, 78.9%, 118 mmol, 1.01 eq., 50 mL H_2O, 2.4 M) was prepared and added dropwise to the deeply amber reaction mixture as it stirred. The temperature was monitored by observing the outer walls of the flask with an infrared thermometer.

The reaction mixture lightened rapidly as the chlorite solution was added dropwise. The temperature of the mixture also rose rapidly. The reaction mixture was submerged in an ice bath and the drip-rate was decreased so that it took ~ 4 h to complete the addition. The color of the reaction mixture transitioned from a burnt-orange to bright yellow during the addition. The ice bath was allowed to thaw following the completion of addition. The mixture had significantly lightened in color by 90 min following completion of the addition. The mixture was stirred overnight (total reaction time ~24 h) and the mixture had almost completely bleached.

The solution was continuously extracted with diethyl ether (500 mL) to afford white crystalline solid. This was presumably the monohydrate. EtOAc was added, and the mixture was concentrated again. H_2O was observed separating from the organic distillate in the rotary evaporator's catch flask. A side effect of adding EtOAc was a staining of the solid with yellow color; presumably the hydrate was more stable than the anhydrous product. The residue was scraped off the walls of the flask and vacuum dried, although the smell of acetic acid never was removed. The mass of isolated powdery solid was 11.10 g or 67% of the theoretical maximum, s*E*F=2.9, and c*E*F=75.

The residue was triturated under a layer of DCM, but it gummed up. A small amount of EtOAc was added by wash bottle and the mixture became free. The solid residue was isolated by suction filtration and rinsed with more DCM/EtOAc. The mass of the filter-cake following chopping and air drying was 7.51 g, or 45% overall yield and 67% yield through the filtration. Melting point ranges: 162–165 °C with decomposition and 161–164 °C.

$$sE\mathrm{F} = \frac{\sum 14.68_{(\mathrm{g})}, 14.55_{(\mathrm{g})}, 13.61_{(\mathrm{g})} - 11.10_{(\mathrm{g})}}{11.10_{(\mathrm{g})}} = 2.9 \tag{4.27}$$

$$cE\mathrm{F} = \frac{\sum 14.68_{(\mathrm{g})}, 14.55_{(\mathrm{g})}, 13.61_{(\mathrm{g})}, 357_{(\mathrm{g\ Et_2O})}, 271_{(\mathrm{g\ EtOAc})}, 176_{(\mathrm{g\ H_2O})}, -11.10_{(\mathrm{g})}}{11.10_{(\mathrm{g})}} = 75 \tag{4.28}$$

4.5.4.5. HMFA (Table 4.2, Entry 4)

In an attempt to create a more general method which would display tolerance for many functional groups especially in furan substrates which do not readily dissolve in H_2O*, EtOH was employed as cosolvent. Following the supposition that the major detractor to the isolated yield of product in these reactions was not a lack of conversion but rather the great degree of* H_2O *solubility of the product, a concentrated reaction mixture should afford facile workup. The additional benefit lies in the ease of separating an organic cosolvent such as EtOH as opposed to* H_2O.

A 2 L beaker was charged with HMF as received (12.82 g, 95%, 97 mmol, 1.0 eq.), H_2O (400 mL, 0.24 M solution) and EtOH (400 mL), and a light-amber solution formed (~0.12 M). Aqueous solutions (~1 M) were prepared of sulfamic acid (11.38 g, 117.2 mmol, 1.2 eq.) and sodium chlorite (80%, 11.87 g, 105 mmol, 1.1 eq.). The reaction beaker was submerged in a cool H_2O bath and the temperature was monitored internally.

Concurrent addition of sulfamic acid solution and sodium chlorite solution was initiated while the reaction mixture was 15 °C; the sulfamic solution's addition was about twice the velocity of the chlorite. The temperature of the reaction was controlled between 15 and 20 °C by the periodic addition of ice directly to the reaction mixture. The addition of the chlorite took ~1 h, and the mixture was stirred for an additional 1 h. The reaction was quenched by the addition of ascorbic acid (~0.15 eq) until the yellow-color of the reaction had completely dissipated.

The mixture was concentrated by rotary evaporation under reduced pressure, then continuously extracted with EtOAc (500 mL) for 2 h. The extract solution was a light-yellow color and was concentrated by rotary evaporation. The cream-colored powdery-solid smelled faintly of acetic acid and weighed 11.05 g. The mixture was triturated with Hex, but the material gummed

up. The slurry was diluted with a bit of EtOAc from a wash bottle, and free powder beneath a colorless solution was obtained. The mixture was separated by suction filtration. The filter cake was rinsed with Hex slightly diluted with EtOAc, pressed, chopped and spread on paper to air dry.

The mass of the fine powder was 10.72 g and was ~88% pure by NMR with the major contaminant determined to be ethyl 5-hydroxymethylfuroate, or 72% in Crop 1; melting point range 159–161 °C with decomposition. The continuous extraction of the aqueous reaction mixture with EtOAc (500 mL) continued for 3 h. The extracts were treated as before. The filter-cake was dried to constant mass (2.378 g, or 16% overall yield) This material was less contaminated with ethyl ester. By calculation, 13.10 g of ~ 88% pure HMFA equates to 11.52 g product, 82% yield, s*E*F: 2.1, c*E*F: 162.

$$\mathrm{s}E\mathrm{F} = \frac{\sum 12.82_{(\mathrm{g})}, 11.38_{(\mathrm{g})}, 11.87_{(\mathrm{g})} - 11.52_{(\mathrm{g})}}{11.52_{(\mathrm{g})}} = 2.1 \tag{4.29}$$

$$\mathrm{c}E\mathrm{F} = \frac{\sum 12.82_{(\mathrm{g})}, 11.38_{(\mathrm{g})}, 11.87_{(\mathrm{g})}, 317_{(\mathrm{g\ EtOH})}, 902_{(\mathrm{g\ EtOAc})}, 618_{(\mathrm{g\ H_2O})}, 2.62_{(\mathrm{g\ asc.acid})} - 11.52_{(\mathrm{g})}}{11.52_{(\mathrm{g})}}$$

$$= 162 \tag{4.30}$$

4.5.4.6. HMFA (Table 4.2, Entry 5)

This reaction was a prelude to the standardized reaction conditions used to explore substrate scope. To avoid esterification of a reactive intermediate by solvolysis, acetone was used rather than EtOH. To explore the chemoselective margin in this reaction, twice the desirable amount of oxidizer and sulfamic acid was utilized during the main reaction. The excess oxidizer was neutralized by excess ascorbic acid solution.

A 250 mL beaker was charged with purified HMF (1.80 g, 14 mmol, 1.0 eq.) and acetone (70 mL). A complete slightly-yellow solution formed, and it was diluted with distilled H_2O (80 mL). Sulfamic acid (3.22 g, 33 mmol, 2.3 eq.) was dispensed onto weigh paper, and sodium

chlorite (78.9%, 3.56 g, 28 mmol, 2.0 eq.) was dissolved in H_2O (30 mL) in a 150 mL separatory funnel.

The reaction beaker was placed in a room temperature H_2O bath and stirred. The sulfamic acid was added as a solid-lump sum, and the sodium chlorite solution was added dropwise over 11 min. During the addition, the reaction solution turned bright yellow. The mixture was sealed with aluminum foil and stirred for 19 min.

The mixture was quenched with solid ascorbic acid (20 mmol), and the bright yellow color completely disappeared. The mixture was concentrated by rotary evaporation under reduced pressure at 29–35 °C. The concentrated clear and colorless solution was extracted with EtOAc (125 mL, three times). The extracts were combined, backwashed with saturated sodium chloride solution (100 mL), isolated and dried overnight (sodium sulfate, Na_2SO_4, not measured so excluded from the determination of metrics). The extract was concentrated by rotary evaporation to afford 1.83 g of off-white crystalline solid which smelled faintly of acetic acid and was a little sticky. The solid was triturated beneath Hex, however the stickiness persisted until a bit of EtOAc was added by wash bottle. The mixture became free crystalline white solid and colorless solution.

The off-white solid was collected by suction filtration and washed copiously with Hex diluted with a bit of EtOAc to free it of the liquor. The filtrate was colloidal, indicating that some product was lost in this step. The filter cake was pressed and dried on the filter, then chopped and charged into a poly-capped scintillation vial. The mass of the solid was 1.70 g, which was vacuum dried overnight to a constant mass of 1.65 g, 12 mmol, 82% of the theoretical maximum, s*E*F=4.2, and c*E*F=384; melting point ranges were: 157–155 °C and 156–159 °C with decomposition.

$$sEF = \frac{\sum 1.80_{(g)}, 3.22_{(g)}, 3.56_{(g)} - 1.65_{(g)}}{1.65_{(g)}} = 4.2 \tag{4.31}$$

$$cEF$$

$$= \frac{\sum 1.80_{(g)}, 3.22_{(g)}, 3.56_{(g)}, 55_{(g\ acetone)}, 338_{(g\ EtOAc)}, 194_{(g\ H_2O)}, 36_{(g\ NaCl)}, 3.44_{(g\ asc.acid)} - 1.65_{(g)}}{1.65_{(g)}}$$

$$= 384 \tag{4.32}$$

4.5.4.7. HMFA (Table 4.2, Entry 6)

A 1.0 L single neck round bottom flask was held in a room temperature H_2O bath, was charged with purified HMF stock solution in acetone (10 mL, 5.58 g, 44 mmol, 1.0 eq.), then diluted with bulk acetone (220 mL) while the solution was stirred. The solution persisted as DI H_2O (220 mL) was added to form a 0.1 M solution of HMF. Solid sulfamic acid (4.72 g, 49 mmol, 1.1 eq.) was added and dissolved completely.

A 1 M solution of sodium chlorite (5.24 g, 78.9%, 46 mmol, 1.03 eq.) in DI H_2O was prepared and charged into a pressure equalizing dropping funnel affixed to the neck of the reaction flask. The chlorite solution was added dropwise over ten min. The reaction was allowed to stir for an additional 20 min; during that time, the reaction solution slowly developed a yellow color. Ascorbic acid (0.68 g, 4 mmol, 9 mol%) was added to the reaction mixture to quench any residual oxidizer; as a result, the yellow color of the reaction solution completely dissipated before all granular solid had dissolved.

The reaction mixture was concentrated by rotary evaporation under reduced pressure to remove the acetone cosolvent. The concentrate was a colorless solution and was partitioned with 300 mL of EtOAc in a 1.0 L separatory funnel. The EtOAc solution was isolated, the aqueous solution was extracted twice more with 300 mL of EtOAc. The organic solutions were combined, backwashed with 100 mL saturated sodium chloride solution, isolated and dried (Na_2SO_4, not measured so excluded from the determination of metrics).

The solution was concentrated by rotary evaporation under reduced pressure to afford white flaky crystalline solid which was vacuum dried to a constant mass of 5.22 g, 37 mmol, 83% of the theoretical yield; s*E*F: 2.0, c*E*F 265. The melting point ranges for this preparation were: 165–168 °C with decomposition and 164–168 °C with decomposition. Within one day of storage on the bench whilst capped, the solid began to discolor, and became tan.

$$sEF = \frac{\sum 5.58_{(g)}, 4.72_{(g)}, 5.24_{(g)} - 5.22_{(g)}}{5.22_{(g)}} = 2.0 \tag{4.33}$$

$$cEF = \frac{\sum 5.58_{(g)}, 4.72_{(g)}, 5.24_{(g)}, 172_{(g\ acetone)}, 812_{(g\ EtOAc)}, 349_{(g\ H_2O)}, 36_{(g\ NaCl)}, 0.68_{(g\ asc.acid)} - 5.22_{(g)}}{5.22_{(g)}}$$

$$= 265 \tag{4.34}$$

4.5.4.8. HMFA (Table 4.2, Entry 7)

This procedure became the standard protocol for oxidations with chlorous acid during the substrate scope screening. A 250 mL single neck round bottom flask was charged with commercially available HMF as received (95%, 1.29 g, 10 mmol, 1.0 eq.), bulk acetone (50 mL), and the mixture was stirred to form a slightly turbid light amber solution. DI H_2O (50 mL) was added and the turbid solution persisted with no change. Sulfamic acid (1.08 g, 11 mmol, 1.1 eq.) was rinsed in with a minimal amount of H_2O. The mixture was stirred while submerged in a H_2O bath at ambient temperature

A solution of sodium chlorite (78.9%, 1.26 g, 11 mmol, 1.1 eq.) in DI H_2O (10 mL) was prepared and added drop-wise to the stirring reaction mixture in under four min. The mixture was stirred for a total of 30 min and quenched by the addition of solid ascorbic acid (0.20 g, 1 mmol, 11 mol%), and the yellow color which had developed in the reaction mixture dissipated as the vitamin C was stirred into solution. The reaction mixture was a clear and colorless solution.

The mixture was concentrated by rotary evaporation under reduced pressure with an ambient temperature H_2O bath to remove acetone. The solution took on a ghostly yellow color during concentration. The reaction mixture was partitioned with EtOAc (100 mL) in a separatory funnel. The H_2O phase was clear, whereas the EtOAc was translucent and appeared to be holding H_2O. A small amount of saturated aqueous sodium chloride was added but did not really change the consistency of the two phases.

The EtOAc was isolated and the aqueous phase was extracted twice more with EtOAc (100 mL each). The EtOAc solutions were combined, capped and stored overnight in a Florence flask. The following day, the solution had clarified by excluding H_2O droplets which clung to the flask. The clear colorless solution was decanted into a dry Florence flask, dried (anhydrous sodium sulfate, not measured so excluded from the determination of metrics), and gravity filtered through cotton and concentrated by rotary evaporation under reduced pressure. The residual solid was scraped off the walls of the flask and vacuum dried to a constant mass of 1.37 g, 99% yield; s*E*F: 1.6; c*E*F: 272.

$$sEF = \frac{\sum 1.29_{(g)}, 1.08_{(g)}, 1.26_{(g)} - 1.37_{(g)}}{1.37_{(g)}} = 1.6 \tag{4.35}$$

$$cEF = \frac{\sum 1.29_{(g)}, 1.08_{(g)}, 1.26_{(g)}, 39_{(g\ acetone)}, 271_{(g\ EtOAc)}, 60_{(g\ H_2O)}, 0.20_{(g\ asc.acid)} - 1.37_{(g)}}{1.37_{(g)}} = 272 \tag{4.36}$$

4.5.4.9. HMFA (Table 4.2, Entry 8)

This experiment was a duplicate of entry 7 and followed the exact same protocol with HMF as received (95%, 1.30 g, 10 mmol, 1.0 eq.) to afford HMFA: 1.35 g or 97% yield.

$$sEF = \frac{\sum 1.30_{(g)}, 1.07_{(g)}, 1.21_{(g)} - 1.35_{(g)}}{1.35_{(g)}} = 1.7 \tag{4.37}$$

$$cEF = \frac{\sum 1.30_{(g)}, 1.07_{(g)}, 1.21_{(g)}, 39_{(g\ acetone)}, 271_{(g\ EtOAc)}, 60_{(g\ H_2O)}, 0.19_{(g\ asc.acid)} - 1.35_{(g)}}{1.35_{(g)}} = 276 \tag{4.38}$$

4.5.4.10. HMFA (Table 4.2, Entry 9)

This procedure followed the standard protocol for oxidations with chlorous acid but did not employ an ascorbic acid quench. HMF, as received, (95%, 1.30 g, 10 mmol, 1.0 eq.) was used. Following addition of aqueous chlorite by the method described in the general protocol, the mixture was stirred for a total of 90 min and was sparged with compressed air in a well ventilated fume hood as the yellow color which had developed in the reaction mixture dissipated (30 min). The reaction mixture was a clear and colorless solution. From this point, the workup was identical to that described for entry 7 (Table 4.2) and afforded HMFA: 1.38 g or 99% yield; s*E*F 1.6, c*E*F: 269. While the sparging method took a bit more time, there is clearly no need to add the chlorine dioxide quenching agent to the reaction flask.

$$sEF = \frac{\sum 1.30_{(g)}, 1.07_{(g)}, 1.26_{(g)} - 1.37_{(g)}}{1.37_{(g)}} = 1.6 \tag{4.39}$$

$$cEF = \frac{\sum 1.30_{(g)}, 1.07_{(g)}, 1.26_{(g)}, 39_{(g\ acetone)}, 271_{(g\ EtOAc)}, 60_{(g\ H_2O)} - 1.35_{(g)}}{1.35_{(g)}} = 269 \tag{4.40}$$

4.5.4.11. HMFA (Table 4.2, Entry 10)

This procedure followed the standard protocol for oxidations with chlorous acid but did not employ an ascorbic acid quench or acetone cosolvent. HMF, as received, (95%, 1.28 g, 10 mmol, 1.0 eq.) was used and the exact procedure described for entry 9 (Table 4.2) was followed without acetone cosolvent to afford HMFA: 1.20 g or 88% yield; s*E*F: 2.0, c*E*F: 319. Clearly, the use of acetone as a cosolvent facilitates the recovery of materials which were completely H_2O soluble.

$$sEF = \frac{\sum 1.28_{(g)}, 1.08_{(g)}, 1.26_{(g)} - 1.23_{(g)}}{1.23_{(g)}} = 2.0 \tag{4.41}$$

$$cEF = \frac{\sum 1.28_{(g)}, 1.08_{(g)}, 1.26_{(g)}, 271_{(g\ EtOAc)}, 110_{(g\ H_2O)} - 1.23_{(g)}}{1.23_{(g)}} = 319 \tag{4.42}$$

4.5.4.12. HMFA (Table 4.2, Entry 11)

Chlorous Acid Oxidation of HMF. Quenched with an Equivalent of Ascorbic Acid and Continuously Extracted. A 1000 mL single neck round bottom flask was charged with HMF (26.50 g, 95% from AVA Biochem, 200 mmol, 1.0 eq.), and 600 mL DI H_2O. The mixture formed a turbid honey colored solution. Sulfamic acid (21.43 g, 99%, 221 mmol, 1.1 eq.) was added as granular solid which readily dissolved in the reaction mixture. The mixture was stirred while submerged in an ice bath. The internal temperature was observed by Traceable digital thermal probe.

A solution of sodium chlorite (78.9%, 24.11 g, 210 mmol, 1.05 eq.) in DI H_2O (200 mL) was prepared. The chlorite solution was added dropwise at such a rate that the temperature of the reaction mixture was controlled between 10 and 19 °C. The addition was completed in 20 min, and the color/consistency of the reaction mixture had significantly changed from turbid amber to bright yellow and faintly translucent.

The mixture chilled to 11 °C within 13 min of stirring following the completion of chlorite addition. The mixture was pulled from the ice bath and stirred for 60 additional min. The mixture was then treated with of ascorbic acid (38.70 g, 220 mmol 1.1 eq.) to quench any active chlorine species.

The yellow color of the reaction mixture largely dissipated. The mixture was gravity filtered as it was poured into a continuous liquid-liquid extractor. The extraction with EtOAc (700 mL) proceeded for 8.75 h under argon, but the aqueous solution continually darkened while the extract became extremely orange then dark amber with black flecks. The mixture was gravity filtered and concentrated by rotary evaporation under reduced pressure. The concentrate afforded light solid stained with dark amber solution.

The residue was dispersed in EtOAc (150 mL), sonicated with heating in a bath for 90 min, and allowed to cool. Light colored solid separated from dark amber solution. The mixture was chilled in an ice bath and isolated by suction filtration over a ceramic Büchner funnel and qualitative filter paper. The filter cake was pressed and rinsed with ice cold EtOAc. The residue was light powder solid while the filtrate was very dark acetic smelling solution. The solid was dried on the filter, chopped, and spread on paper to dry to constant mass of 19.73 g or 70% of the theoretical maximum; s*E*F: 2.7 and c*E*F: 84.

The continuous extraction of the original reaction mixture was continued for another 3 h, but when that material was concentrated only black garbage was isolated. When the filtrate was concentrated, only dark crud was isolated. The powdery crop one was characterized by ^{1}H NMR.

$$s\mathit{E}\mathrm{F} = \frac{\sum 26.50_{(g)}, 21.43_{(g)}, 24.11_{(g)} - 19.73_{(g)}}{19.73_{(g)}} = 2.7 \tag{4.43}$$

$$c\mathit{E}\mathrm{F} = \frac{\sum 26.50_{(g)}, 21.43_{(g)}, 24.11_{(g)}, 767_{(g\ EtOAc)}, 798_{(g\ H_2O)}, 38.70_{(g\ asc.acid)} - 19.73_{(g)}}{19.73_{(g)}} = 84 \tag{4.44}$$

4.5.4.13. HMFA (Table 4.2, Entry 12)

Following the inspiration of Imaizumi et al.,[233] and paralleling the thoughts of Dalcanale et al.,[232] but with favorable reaction stoichiometries, a Lindgren[216] oxidation was performed in the presence of one molar equivalent of sulfamic acid, 1 molar equivalent of dimethyl sulfoxide, and one molar equivalent of sodium chlorite in the aqueous solution.

A 1 L single neck round bottom flask was charged with commercially procured HMF (AVA Biochem 95%, 13.29 g, 100 mmol, 1.0 eq.) and the mixture was diluted with DI H_2O (300 mL) with stirring to afford an amber solution with some turbidity. Dimethyl sulfoxide (Alfa Aesar, 99.9%, 7.1 mL, 100 mmol, 1.0 eq.) was added as a clear and colorless liquid without altering the appearance of the reaction mixture. Sulfamic acid (10.71 g, 110 mmol, 1.1 equivalents) was added

as a granular white-crystalline solid to the stirring reaction mixture. The addition of sulfamic acid altered the appearance of the reaction by making it less turbid and brighter yellow.

A clear and colorless solution was prepared from sodium chlorite (white flakes, 80% but titrated to be 78.9 wt%, 12.05 g, 105 mmol, 1.05 eq.) in DI H_2O (100 mL) was prepared in a dropping funnel. The dropping funnel was mounted above the reaction flask and the temperature of the reaction was monitored internally by a stainless steel digital thermal probe. The reaction mixture was thermally equilibrated with a room temperature H_2O bath at 19 °C. Chlorite solution was added dropwise to the yellow reaction mixture and a significant exotherm was noted even compared with the typical procedure. This was attributed to the secondary reactions between DMSO and hypochlorous acid.

The internal temperature of the reaction mixture was maintained between 16 and 21 °C by modulating the dropwise addition of chlorite solution and by mixing ice with the H_2O bath. The addition of chlorite was completed in 20 min. The yellow color of the reaction mixture dissipated significantly from the initial amber color but was much more yellow than in reactions where the secondary oxyhalide species were allowed to develop in significant concentration.

The reaction mixture was removed from the H_2O bath, and allowed to rise in temperature to 21 °C, then submerged in the chilly H_2O until its temperature reached 16 °C. The reaction cooled constantly when exposed to the chilly bath and warmed slowly to ambient temperature when removed from the bath with stirring for an h. This was taken as an indication of a complete reaction.

The yellow, slightly turbid reaction mixture was gravity filtered through glass wool as it was charged into a continuous liquid-liquid extractor prefilled with EtOAc (600 mL). An aliquot was taken from the extract return during near the end of reaction mixture charging (mass of aliquot: 15.06 g). That aliquot was concentrated by rotary evaporation under reduced pressure, vacuum

dried to constant mass (0.12 g, or 1.6% solids) and analyzed by ^{1}H NMR (DMSO-d_6). The solid residue of the zero aliquot comprised primarily anhydrous HMFA with dimethyl sulfone (1: 2 molar ratio) with traces of EtOAc, HMF, and trace amounts of at least three other impurities containing furanic doublets, oxymethylene, as well as a symmetrically 2,5-disubstituted furan such as FDCA, and a monosubstituted furan such as furoic acid.

Extraction aliquots were taken periodically over six h and worked up as described above then analyzed by ^{1}H NMR. By the 60-min mark, the concentrated aliquots began to smell of acetic acid which could also be discerned in the ^{1}H NMR spectrum resolved from EtOAc. Possibly, an alternative solvent with greater thermal and hydrolytic stability in the presence of aqueous acid should be considered. The relative concentration of dimethyl sulfone and acetic acid in the extract increased during the extraction compared with HMFA, while the total %solids decreased. The extraction of HMFA practically complete in six h. The extraction was run for 9.5 h, then the extract solution was allowed to cool. The aqueous solution never turned black like it does when neutralized with ascorbic acid, but the EtOAc solution was orange by the end of nine and a half h distillation/extraction.

The extract solution afforded some wet looking cream colored solid upon cooling. It was concentrated by rotary evaporation under reduced pressure to afford light colored solid with dark impurities. The material was digested in Hex:EtOAc (~75:25 volumetric ratio, ~150 mL), heated to 50 °C in a sonicating H_2O bath for 90 min. The resulting mixture was off-white solid and orange solution. The mixture was chilled in an ice bath, separated by suction filtration and the filter cake was washed with ice cold Hex. The residue was pressed free of solvent over suction, then chopped and spread on a paper plate to air-dry overnight.

The resulting off-white powdery solid had a mass of 16.73 g but also contained dimethyl sulfone according to ^{1}H NMR analysis of crop one in a molar ratio of 100 parts HMFA: to 95 parts dimethyl sulfone. That works out to 142 g HMFA:89 g sulfone or solid mixture of 61% HMFA, or a 72% yield of HMFA (10.21 g, s*E*F: 2.7 and c*E*F: 109) and a 69% yield of dimethyl sulfone (6.52 g) in the mixture. There was obvious solid product crystallizing from the cold orange filtrate, however when it was concentrated by rotary evaporation, the mixture afforded a black oily residue.

$$sEF = \frac{\sum 13.29_{(g)}, 10.71_{(g)}, 12.05_{(g)} - 10.21_{(g)}}{10.21_{(g)}} = 2.7 \quad (4.45)$$

$$cEF = \frac{\sum 13.29_{(g)}, 10.71_{(g)}, 12.05_{(g)}, 677_{(g\ EtOAc)}, 399_{(g\ H_2O)}, 7.8_{\ (g\ DMSO)} - 10.21_{\ (g)}}{10.21_{(g)}} = 109 \quad (4.46)$$

4.5.4.14. HMFA(Table 4.2, Entry 13)

Chlorous Acid Oxidation with Hypochlorous Acid Scavenged by Dilute Hydrogen Peroxide and Sulfamic Acid. A 1 L single neck round bottom flask was charged with HMF (95%, 13.37 g, 101 mmol, 1.0 eq.), and a small amount of H_2O was used to assist with the transfer (~10 mL). The mixture began to form a dark amber solution above lighter solid and was quite endothermic. The outer wall of the bottom of the flask was determined to be 9 °C (room temperature was 21 °C)

The mixture was diluted with DI H_2O (140 mL), and it formed a cloudy lightly tan colloidal mixture. Sulfamic acid (10.71 g, 110 mmol, 1.1 eq.) was added as a granular solid. The mixture was stirred to form an amber colloidal mixture. The temperature of the mixture was monitored internally by glass thermometer (18 °C). Hydrogen peroxide (3%, McKesson, 150 mL, 170 g, 150 mmol, 1.4 eq.) was added with no change in the mixture's temperature. The solution appeared more complete and took on an orange hue. The mixture was submerged in an ice bath and cooled to 10 °C. As it stirred and cooled, the color of the mixture began to lighten.

A solution of sodium chlorite (78.9%, 12.60 g, 110 mmol, 1.1 eq.) and DI H_2O (100 mL) was prepared in a dropping funnel. The chlorite solution was added dropwise to the reaction

mixture over 15 min with the internal temperature of the reaction mixture maintained between 10 and 15 °C. By the completion of the addition, the reaction mixture was translucent and light yellow.

The ice bath was replaced by an ambient temperature H_2O bath and the mixture was stirred until the reaction time was 95 min after the first addition of chlorite. The temperature of the mixture was 19 °C, and its appearance was nearly colorless. The reaction mixture was sparged with air into a sodium sulfite solution to remove any volatile chlorine oxides for 60 min. There was no apparent change in the reaction mixture's appearance.

Knowing of a catalytic reaction which employs MnO_2 and leads to the dismutation of hydrogen peroxide into H_2O and oxygen gas, some MnO_2 (20 mg) was added to the stirring reaction mixture. The mixture evolved gas as the MnO_2 was stirred in, however, the MnO_2 dissolved in the acidic reaction mixture! The addition of more MnO_2 led to the same phenomenon. Since there was potentially 50 mmol of hydrogen peroxide to destroy, this seemed like a losing strategy.

The mixture was determined to be pH ~2 by universal indicator strip. The mixture was gravity filtered into a 2 L separatory funnel, extracted with 600 mL of diethyl ether, then four times with 400 mL of EtOAc. All the extracts were cloudy, so some anhydrous sodium sulfate was added (not measured so not included in the determination of metrics), and the mixtures were allowed to rest for two days. During that time, the extracts became clear and colorless solutions above granular sodium sulfate, while the aqueous solution had air concentrated from ~500 mL to ~ 300 mL. Potassium iodide-starch test paper was used to detect the possible presence of peroxides in the solutions. All the extracts failed to indicate oxidizers, while the aqueous solution readily reacted with the test strip.

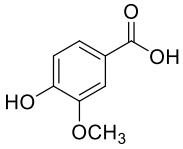
The extracts were concentrated individually to determine the extent of extraction with increasing extraction cycles. A total of 13.70 g of crude white crystalline solid was isolated which if pure HMFA would be 96% isolated yield. The residues were stored under a layer of EtOAc and capped for storage over several days. The fractions of white solid which had been stored under a layer of EtOAc had ***NOT*** discolored. The fractions were combined and concentrated, vacuum dried to constant mass by H_2O aspirator, chopped/scraped off the walls and stored under argon. The mass of recovered white solid was 13.35 g or 94% isolated yield; s*E*F: 1.7 and c*E*F: 142. While the HMFA prepared thusly was strikingly white it actually did not look any more pure than typical by ^{1}H NMR.

$$sEF = \frac{\sum 13.37_{(g)}, 10.71_{(g)}, 12.60_{(g)} - 13.35_{(g)}}{13.35_{(g)}} = 1.7 \quad (4.47)$$

$$cEF = \frac{\sum 13.37_{(g)}, 10.71_{(g)}, 12.60_{(g)}, 428_{(g\ Et_2O)}, 1443_{(g\ EtOAc)}, 419_{(g\ H_2O)}, 5.1_{\ (g\ DMSO)} - 13.35_{\ (g)}}{13.35_{(g)}}$$

$$= 142 \quad (4.48)$$

4.5.4.15. Standard Protocol: Vanillic Acid



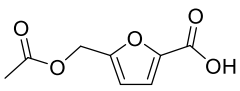
^{1}H (DMSO-d_6 400 MHz): δ 12.47 (br s, 1H), 9.82 (s, 1H), 7.51–7.36 (m, 2H), 6.84 (d, *J*=8.5 Hz, 1H), 3.80 (s, 3H); ^{13}C (DMSO-d_6 100 MHz): δ 167.2, 151.1, 147.2, 123.5, 121.6, 115.0, 112.7, 55.5; FTIR (ATR, Diamond, Neat): cm^{-1} 3482, 3099, 2953, 2849, 2697, 1670, 1595, 1521, 1472, 1454, 1433, 1375, 1276, 1236, 1200, 1109, 1026, 915, 880, 819, 756, 722, 636, 587, 499.

Vanillin (99%, 1.520 g, 10.0 mmol, 1.0 eq.) was charged into a 300 mL single neck round bottom flask and dissolved in bulk acetone (50 mL). The clear and colorless solution was diluted with H_2O (50 mL) and a complete solution persisted. Sulfamic Acid (99%, 1.062, 10.9 mmol, 1.1 eq.) was measured onto weigh paper and a solution of sodium chlorite (78.9% 1.176 g, 10.4 mmol, 1.0 eq.) in H_2O (16 mL, 0.65 M) was prepared in a 150 mL separatory funnel.

The reaction flask was placed in a room temperature H_2O bath and the sulfamic acid was added to the stirring vanillin solution. The sodium chlorite solution was added dropwise over 12 min. The reaction flask was sealed with a yellow cap-plug and the solution was stirred for 35 min during which time the solution took on a slightly yellow-tint. The reaction was quenched by addition of solid ascorbic acid (a few pinches) and unlike the furan-substrates, the yellow color did not really change.

The reaction solution was slowly concentrated by rotary evaporation under reduced pressure (H_2O bath at around 30 °C). As the acetone was preferentially removed, the mixture became gravid with white crystalline precipitate. The mixture was chilled in an ice chest for at least 30 min along with a wash bottle of distilled H_2O, then the white solid precipitate was isolated by suction filtration through a 5 cm porcelain Büchner funnel. The filtrate carried the yellow-tint, and the filter cake was pressed, rinsed with H_2O till the total volume of the filtrate was ~100 mL and dried on the filter overnight. The filter-cake was chopped, spread on paper to air dry and the constant mass of the solid was 1.478 g, 88% isolated yield. FTIR, ^{1}H, and ^{13}C NMR were employed to characterize the solid as pure vanillic acid.

4.5.4.16. AMFA



^{1}H (DMSO-d_6 400 MHz): δ 13.17 (br s, 1H), 7.18 (d, J=3.4 Hz, 1H), 6.67 (d, J=3.4 Hz, 1H), 5.08 (s, 2H), 2.06 (s, 3H); ^{13}C (DMSO-d_6 101 MHz): δ 169.9, 159.1, 153.2, 145.1, 118.4, 112.5, 57.4, 20.5; FTIR (ATR, Diamond, Neat): cm^{-1} 3127, 2997, 2870, 2671, 2579, 2506, 1735, 1685, 1597, 1528, 1426, 1376, 1360, 1307, 1250, 1209, 1163, 1021, 984, 959, 945, 919, 893, 820, 763, 740, 660, 612, 553, 463.

4.5.4.17. AMFA with EtOH

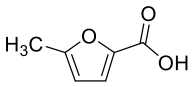
To a 500 mL single neck round bottom flask was added AMF (1.680 g, 10.0 mmol, 1.0 eq.). To the flask was added EtOH (95%, 50 mL) the mixture was stirred until a solution formed which was very slightly turbid. The solution was diluted with H_2O (50 mL) and a complete solution formed which was lightly yellow in color. Sodium chlorite (78.9%, 1.187 g 10.5 mmol, 1.05 eq.) was dissolved in H_2O (10 mL), then diluted to circa 20 mL with H_2O. To the stirring reaction solution was added sulfamic acid (1.068 g, 11.0 mmol, 1.1 eq.) as a granular solid which mostly dissolved. The sulfamic acid was rinsed down with a squirt of H_2O from a wash bottle. A pressure equalizing calibrated dropping funnel was affixed to the top of the reaction flask, then charged with the sodium chlorite solution with a bit of H_2O used to assist complete transfer.

The temperature of the outer wall of the flask was observed to be 21 °C with an infrared thermometer. The addition of chlorite solution to the AMF solution was initiated before all the sulfamic acid had been added. The chlorite solution was added dropwise over ~20 min. When half the solution remained, the outer wall of the flask was observed to be 25 °C. The reaction flask was submerged in a sizable H_2O bath at 19 °C and the reaction proceeded. The dropping funnel was rinsed into the reaction solution with some H_2O and the mixture was stirred in the H_2O bath for 25 min by which time it was a light green color with a bit of turbidity. The stir bar was pulled, and the mixture was concentrated by rotary evaporation under reduced pressure.

Some brown residue was observed to precipitate on the inner walls of the flask. The residual material following removal of EtOH was transferred to a separatory funnel with EtOAc (~75 mL) and shaken with saturated ascorbic acid. The EtOAc solution was isolated, and the aqueous layer was extracted twice more with 75 mL EtOAc. The organic extracts were combined, backwashed with saturated sodium chloride, isolated, dried (Na_2SO_4) and concentrated by rotary

evaporation under reduced pressure. The residue crystallized to afford an off-white solid which smelled of acetic acid. The material was scraped and vacuum dried to constant mass, then chopped and spread on paper. The final mass of crystalline solid was 1.795 g or 97% of the theoretical maximum; melting point ranges: 125.5–125.6 °C, 124.6–126.0 °C, and 125.8–128.0 °C which compared favorably with the literature: 117.5–119 °C.[223]

4.5.4.18. 5-Methylfuran-2-carboxylic Acid



^{1}H (DMSO-d_6 400 MHz): δ 12.80 (br s, 1H), 7.10 (d, J=3.4 Hz, 1H), 6.27 (d, J=3.4 Hz, 1H), 2.33 (s, 3H); ^{13}C (DMSO-d_6 100 MHz): δ 159.2, 156.5, 143.3, 119.1, 108.6, 13.5; FTIR (ATR, Diamond, Neat): cm^{-1} 3132, 2993, 2872, 2696, 2570, 1667, 1597, 1518, 1422, 1365, 1305, 1209, 1162, 1025, 963, 946, 909, 808, 766, 554.

4.5.4.19. 5-Methylfuran-2-carboxylic Acid with MeOH

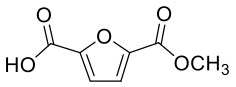
A 600 mL beaker was charged with 5-methylfurfural (column purified, light yellow oil, 4.068 g, 36.9 mmol, 1.0 eq.), and DI H_2O (190 mL, 0.19 M). The mixture was stirred, however the substrate remained in a separate phase from the bulk of the H_2O. MeOH (19 mL) was added and a light-yellow solution formed. The beaker was submerged in a room temperature H_2O bath. Two solutions were prepared in 125 mL separatory funnels: (1) sulfamic acid (3.95 g, 40.6 mmol, 1.1 eq.) was dissolved in H_2O (50 mL, 0.8 M), (2) sodium chlorite (78.9%, 4.385 g, 38.8 mmol, 1.05 eq.) was dissolved in H_2O (50 mL). The funnels were suspended above the stirring reaction mixture by iron ring-stand. The sulfamic acid was started dripping first, closely followed by the sodium chlorite solution at approximately 2 to 1 drops. The sulfamic acid had been completely added in ~10 min, while the chlorite was completed at ~25 min. The reaction had initially lightened during the additions but took on a yellow color as they completed. The mixture was stirred open

to the air for 30 min after the completion of the addition during which time, the color lightened considerably.

A pinch of ascorbic acid was added to dispel any residual oxyhalides, and the mixture was partitioned with 200 mL of EtOAc in a 1 L separatory funnel. The organic solution was isolated, the aqueous was extracted with EtOAc (2 × 200 mL). The organic solutions were combined, backwashed with saturated sodium chloride (100 mL), isolated, and dried (Na_2SO_4). The dried solution was concentrated by rotary evaporation under reduced pressure to afford an off-white crystalline solid which seemed to be stained yellow.

The material smelled a bit of acetic acid, and also like oil of winter green (methyl benzoate), the crude yield of concentrate was ~3.9 g. The material was washed with Hex, however it appeared to clump up. A bit of EtOAc was squirted into the mixture and cream-colored crystalline solid separated. The solid was isolated by suction filtration through a 1 cm Hirsch funnel and was rinsed with a mixture of dilute EtOAc in Hex. The crystalline solid residue was chopped and spread on paper to air dry. Crop one weighed 2.38 g or 51% of the theoretical maximum; melting point ranges of: 111.2–112.7 °C, and 112.6–114 °C.

4.5.4.20. Monomethyl 2,5-furandicarboxylate



^{1}H (DMSO-d_6 400 MHz): δ 13.70 (br s, 1H), 7.39 (d, *J*=3.7 Hz, 1H), 7.32 (d, *J*=3.7 Hz, 1H), 3.85 (s, 3H); ^{13}C (DMSO-d_6 100 MHz): δ 158.8, 157.9, 147.4, 145.7, 119.0, 118.4, 52.3; FTIR (ATR, Diamond, Neat): cm^{-1} 3133, 2971, 2791, 2697, 2531, 1719, 1680, 1579, 1523, 1435, 1418, 1287, 1230, 1198, 1180, 1133, 1031, 980, 954, 919, 855, 835, 806, 758, 612, 577, 500.

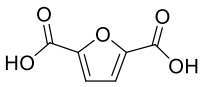
A 100 mL single neck round bottom flask was charged with methyl 5-formylfuran-2-carboxylate (0.593 g, 3.85 mmol, 1.0 eq.), acetone (19 mL), a spin bar, then DI H_2O (19 mL) to

form an approximately 0.1 M solution. Sulfamic acid (0.424 g, 4.37 mmol, 1.1 eq.) was added as a granular solid. Sodium chlorite (0.469 g, 78.9%, 4.2 mmol, 1.1 eq.) was dissolved in circa 5 mL DI H_2O, then added to the stirring reaction mixture dropwise in under five min. The reaction was stirred for 30 min, then quenched with ascorbic acid (90 mg) to afford a slightly turbid colorless solution.

The mixture was concentrated by rotary evaporation under reduced pressure to remove acetone (~11 mL) and white crystalline solid precipitated. The mixture was chilled in an ice bath, then isolated by suction filtration with ice cold H_2O rinsing. The filter cake was white solid, was pressed dry on the filter, then chopped and spread on paper to air dry. The mass of solid was 0.480 g, or 73% isolated yield of monomethyl 2,5-furandicarboxylate as identified by ^{1}H ^{13}C NMR and FTIR.

Following the precipitation method, the yields were fairly inconsistent with the average of three runs coming out to 77%. When the experiments were repeated but the reaction mixture extracted as HMFA was following the standardized protocol, the isolated yield was 97%.

4.5.4.21. Commercially Available FDCA



^{1}H NMR (400 MHz, DMSO-d_6) δ 13.59 (br s,1H), 7.28 (s,1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.0, 147.1, 118.4; FTIR (ATR, neat) cm^{-1} 3150, 2994, 2640, 2560, 1690, 1571, 1521, 1417, 1264, 1222, 1186, 1161, 1039, 960, 847, 761, 583, 524, 486.

4.5.4.22. FDCA from Chlorous Acid Oxidation

^{1}H (DMSO-d_6 400 MHz): δ 13.60 (br s, 1H), 7.29 (s, 1H); ^{13}C (DMSO-d_6 100 MHz): δ 158.9, 147.0,118.4; FTIR (ATR, Diamond, Neat): cm^{-1} 3151, 2872, 2638, 2559, 2518, 1668, 1571, 1523, 1417, 1269, 1226, 1186, 1163, 1040, 961, 844, 762, 604, 583, 526, 486.

4.5.4.23. FDCA from Potassium Permanganate Oxidation

Following a deviation in the main method for FDCA preparation published in patent literature[254] for the express purpose of preparing FDCA in high purity with an improved E Factor. A 500 mL beaker was charged with purified HMF (12.6 g, 100 mmol, 1 eq.) and diluted to a total volume of 400 mL with DI H_2O (0.25 molar solution). The pale-yellow solution was stirred and submerged in an ice bath. The temperature of the solution was monitored internally by glass/alcohol thermometer.

When the mixture had chilled to 10 °C, sodium hydroxide (NaOH) (14.16 g, commonly assumed to be ~85% pure, so 12 g really, 300 mmol, 3 eq.) was combined with ~20 mL H_2O in an 80 mL beaker and stirred into solution. Ice was added to cool and dilute the alkaline solution to ~60 mL. The caustic solution was added to a 125 mL separatory funnel. The alkaline mixture was slowly dripped into the stirring HMF solution which had chilled to 4 °C. The addition of base to the HMF solution led to an increase in the turbidity of the mixture.

Solid $KMnO_4$ (47.29 g, 300 mmol, 1 eq.), was added bit by bit to the chilled and stirring reaction mixture (~17 g in the first 30 min). The addition of oxidizer was accompanied with an observable exotherm, and the temperature of the reaction mixture was kept below 10 °C by controlling the rate of $KMnO_4$ addition. The addition was completed within an h, and the mixture was allowed to stir overnight as the ice bath thawed.

Dark brown residue was observed to settle from a light-yellow solution (~400 mL), which was separated by suction filtration through a pad of Celite 545 packed into a 350 mL glass-course-fritted Büchner funnel (the bed was ~3 cm). The filter pad was rinsed copiously with H_2O (total volume of the filtrate was 1000 mL of orange solution).

The mixture was concentrated by rotary evaporation under reduced pressure to afford a light orange solid. That solid was dispersed and transferred to a 300 mL beaker to afford a brown solution with light colored solid residue (~150 mL). A 500 mL beaker was charged with 50 mL of concentrated HCl and stirred up with ice (~375 mL). Apparently, some of the solid residue was carbonate salts, because when the reconstituted filtrate was poured rapidly into the vigorously stirred acidic acid, the mixture not only gave cream colored precipitate but also foamed. Luckily, the combination had been carried out over a fresh polypropylene plate. The icy cream-colored slurry was transferred to a 1 L beaker which contained even more ice, and the spilled mixture from the overflow was also rinsed in with H_2O.

The mixture was observed to be weakly acidic by universal indicator paper, chilled by submersion in an ice bath, and stirred vigorously while more concentrated HCl was added to completely acidify the mixture. Light colored solid was observed to precipitate from a bright yellow solution. When nearly all the ice had melted, the mixture was separated by suction filtration through a finely fritted glass Büchner funnel to afford a tan solid residue.

Once the mixture had been rinsed copiously with H_2O (total filtrate volume was 1400 mL), the residue was transferred by rinsing with H_2O to a ceramic Büchner funnel with qualitative filter paper. The filter cake was pressed dry, and the total volume of the filtrate was ~1600 mL of yellow solution. Notably, some turbidity developed during the second rinsing which accompanied the transfer to ceramic Büchner funnel. The residue was pressed dry on the filter, chopped and spread on paper overnight to air-dry. The filtrate was saved for observation and had discolored overnight. The mass of tan solid was 10.991 g or 70.4 mmol or 70% isolated yield.

Determination of simple *E* Factor (s*E*F):

$$s\mathit{E}\mathrm{F} = \frac{\sum \mathrm{HMF_{(g)}}, \mathrm{NaOH_{(g)}}, \mathrm{KMNO_{4(g)}} - \mathrm{FDCA_{(g)}}}{\mathrm{FDCA_{(g)}}} \tag{4.49}$$

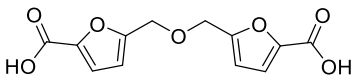
$$sEF = \frac{\sum 12.6_{(g)}, 14.6_{(g)}, 47.29_{(g)} - 10.99}{10.99_{(g)}} = 5.8 \quad (4.50)$$

Determination of complete *E* Factor (c*E*F):

$$cEF = \frac{\sum \mathrm{HMF}_{(g)}, \mathrm{NaOH}_{(g)}, \mathrm{KMNO_4}_{(g)}, \mathrm{Celite}_{(g)}, \mathrm{H_2O}_{(g)}, \mathrm{conc.\ HCl}_{(g)} - \mathrm{FDCA}_{(g)}}{\mathrm{FDCA}_{(g)}} \quad (4.51)$$

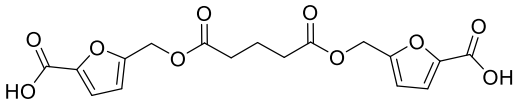
$$cEF = \frac{\sum 12.6_{(g)}, 14.6_{(g)}, 47.29_{(g)}, \sim 150_{(g\ celite)}, \sim 2500_{(g\ H_2O)}, 60_{(g\ conc.HCl)} - 10.99_{(g)}}{10.99_{(g)}} = 252 \quad (4.52)$$

4.5.4.24. 5,5'-[Oxybis(methylene)]bis[2-furancarboxylic Acid]



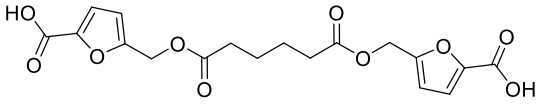
^{1}H (DMSO-d_6 400 MHz): δ 13.09 (br s, 1H), 7.17 (d, *J*=3.4 Hz, 1H), 6.63 (d, *J*=3.4 Hz, 1H), 4.53 (s, 2H); ^{13}C (DMSO-d_6 100 MHz): δ 159.2, 155.0, 144.9, 118.3, 111.7, 63.39; FTIR (ATR, Diamond, Neat): cm^{-1} 3126, 2913, 2856, 2647, 2561, 1671, 1590, 1524, 1424, 1368, 1343, 1287, 1209, 1159, 1058, 1019, 949, 891, 820, 762, 635, 546.

4.5.4.25. 5,5'-((Glutaroylbis(oxy))bis(methylene))bis(furan-2-carboxylic Acid)



^{1}H (DMSO-d_6 400 MHz): δ 13.11 (br s, 1H), 7.17 (d, *J*=3.4 Hz, 1H), 6.66 (d, *J*=3.4 Hz, 1H), 5.10 (s, 2H), 2.40 (t, *J*=7.5 Hz, 2H,), 1.78 (p, *J*=7.5 Hz, 1H); ^{13}C (DMSO-d_6 100 MHz): δ 172.0, 159.1, 153.2, 145.1, 118.4, 112.4, 57.5, 32.2, 19.7; FTIR (ATR, Diamond, Neat): cm^{-1} 3127, 2928, 2571, 1736, 1671, 1597, 1532, 1430, 1415, 1386, 1340, 1292, 1209, 1149, 1097, 1028, 973, 940, 896, 812, 756, 552.

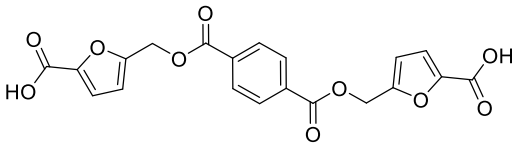
4.5.4.26. 5,5'-((Adipoylbis(oxy))bis(methylene))bis(furan-2-carboxylic Acid)



^{1}H (DMSO-d_6 400 MHz): δ 13.16 (br s, 1H), 7.17 (d, *J*=3.4 Hz, 1H), 6.66 (d, *J*=3.6 Hz, 1H), 5.09 (s, 2H), 2.42–2.29 (m, 2H), 1.60–1.46 (m, 2H); ^{13}C (DMSO-d_6 101 MHz): δ 172.2, 159.1, 153.2, 145.0, 118.4, 112.4, 57.4, 32.8, 23.7; FTIR (ATR, Diamond, Neat): cm^{-1} 3128, 2948, 2571, 1733, 1671,

1598, 1532, 1471, 1430, 1389, 1358,1293, 1250, 1213, 1149, 1136, 1045, 1028, 977, 937, 869, 813, 766, 728, 552.

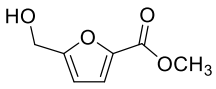
4.5.4.27. 5,5'-((Terephthaloylbis(oxy))bis(methylene))bis(furan-2-carboxylic Acid)



^{1}H (DMSO-d_6 400 MHz): δ 13.21 (br s, 1H), 8.09 (s, 2H), 7.21 (d, *J*=3.3 Hz, 1H), 6.79 (d, *J*=3.3 Hz, 1H), 5.41 (s, 2H); ^{13}C (DMSO-d_6 101 MHz): δ 164.5, 159.2, 152.8, 145.4, 133.3, 129.8, 118.4, 113.0, 58.7; FTIR (ATR, Diamond, Neat): cm^{-1} 3137, 2803, 2671, 2575, 1730, 1682, 1597, 1531, 1430, 1407, 1357, 1310, 1245, 1213, 1167, 1119, 1092, 1017, 969, 927, 830, 762, 720, 553, 502.

4.5.5. Furan-Dienes

4.5.5.1. Methyl 5-(hydroxymethyl)furan-2-carboxylate (Table 4.4, entry 1)



HRMS $[C_7H_8O_4Na]^+$ Calcd.: 179.0320, found: 179.0323; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J*=3.4 Hz, 1H), 6.38 (d, *J*=3.4 Hz, 1H), 4.64 (s, 2H), 3.85 (s, 3H), 2.60 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 158.6, 144.2, 119.1, 109.6, 57.7, 52.2; FTIR (ATR, diamond, thin film from $CDCl_3$ solution) cm^{-1} 3402, 2952, 1712, 1595, 1523, 1437, 1304, 1208, 1137, 1017, 811, 761.

The AB type parent compound, HMFA, is commercially available and its preparation has been described above and has been reported in the literature.[255, 256] AB type hydroxyester, methyl 5-(hydroxymethyl)furan-2-carboxylate, has been reported by Schmuck and Machon (2006)[257] as well as by Serum *et al.* (2019).[74] Following the report of Moore and Kelly (1984),[129] a 300 mL single neck round bottom flask was charged with HMFA (7.524 g, 53.0 mmol 1.0 eq.), MeOH (bulk, 100 mL) and the mixture was stirred until a complete light amber solution formed. To the solution was added concentrated hydrochloric acid (4.2 mL, 1.0 eq., forming a 2 wt% solution)

dropwise. The flask was lowered into a warming oil bath (25–88 °C), affixed to a condenser, and the headspace of the flask was flushed with argon. The reaction was stirred vigorously at reflux for six h.

The reaction mixture was allowed to cool to room temperature, treated with anhydrous sodium sulfate (~10 g) and concentrated by rotary evaporation under reduced pressure. The concentrated amber paste was diluted with diethyl ether (~100 mL) and analyzed by thin layer chromatography (TLC); A series of three TLC plates (dyed with UV-254) were spotted with the ethereal solution and developed in chambers containing mixtures [Hex (mL), EtOAc (mL)]: [6, 0], [5, 2], and [5, 5]. Corresponding retention factor (R_f) values measured at the center of the major motile fraction follow: 0.0, 0.24, 0.48.

TLC indicated one major fraction consistent with the described material. The ether slurry was separated by gravity filtration, however some orange oil separated from the ethereal solution (which remained cloudy). The filtrate was neutralized with sodium carbonate, adsorbed onto amorphous silica gel, and purified by column chromatography. The very major eluate's fractions were combined, concentrated to an orange oil and characterized by ^{1}H, ^{13}C NMR and FTIR, and HRMS as methyl 5-(hydroxymethyl)furan-2-carboxylate. The mass of orange oil was 7.216 g or 87% isolated yield. Moore and Kelly (1984) isolated 85% yield on twice this scale by vacuum distillation.

4.5.5.2. Methyl 5-(hydroxymethyl)furan-2-carboxylate (Representative Example: Table 4.4)

Investigations of HMFA Esterification: Replicating Literature Downscaled

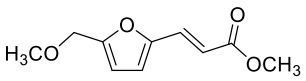
A 50 mL single neck round bottom flask was charged with HMFA (1.410 g, 10.0 mmol, 1.0 eq.), and HPLC grade MeOH (20 mL). The mixture was stirred to form a very faintly amber tinted solution and concentrated hydrochloric acid was added as a couple of drops (0.83 mL, 0.990

g, 1.0 eq.). To the flask was affixed a tall West condenser plumbed with cool flowing H_2O. The headspace of the flask was flushed with argon and the mixture was refluxed by heating within an oil bath for six h.

The mixture was quenched by addition of saturated aqueous sodium bicarbonate (1 mL). The light amber reaction solution was concentrated by rotary evaporation under reduced pressure, partitioned between saturated aqueous sodium chloride solution (~10 mL) and EtOAc (~40 mL) in a 60 mL separatory funnel. The organic extract was isolated, dried (anhydrous sodium sulfate), and adsorbed onto silica gel prior to final purification by flash column chromatography.

The fractions containing the major eluate peak were combined, then concentrated by rotary evaporation under reduced pressure to afford a colorless oil. The mass of concentrate was 1.363 g, or 87% isolated yield which closely matched the larger scale preparation for the Pure and Applied chemistry manuscript in 2019.[74] The material was characterized as methyl 5-(hydroxymethyl)-2-furancarboxylate by ^{1}H NMR. The hydroxyl proton was coupled the furylic methylene in this spectrum.

4.5.5.3. Methyl (E)-3-(5-(Methoxymethyl)furan-2-yl)acrylate

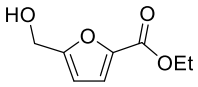


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J*=15.7 Hz, 1H), 6.53 (d, *J*=3.4 Hz, 1H), 6.37 (d, *J*=3.4 Hz, 1H), 6.30 (d, *J*=15.7 Hz, 1H), 4.39 (s, 2H), 3.75 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 154.5, 151.2, 131.2, 115.8, 115.7, 111.8, 66.7, 58.4, 51.9; FTIR (ATR, neat) cm^{-1} 3122, 2997, 2936, 2895, 2860, 2840, 2819, 1698, 1638, 1583, 1530, 1436, 1404, 1348, 1308, 1258, 1193, 1170, 1117, 1022, 989, 947, 881, 861, 811, 777, 734, 685, 643, 523; FTIR (ATR, thin film from $CDCl_3$) cm^{-1} 3122, 2991, 2950, 2822, 1710, 1637, 1581, 1524, 1435, 1374, 1307, 1258, 1193, 1160, 1088, 1019, 970, 942, 856, 799, 732, 680, 517.

Dyuti Dawn had prepared (2*E*)-3-(5-(hydroxymethyl)furan-2-yl)acrylic acid following the procedure reported by Serum *et al.* for the preparation of (2*E*,2'*E*)-3,3'-(Furan-2,5-diyl)diacrylic acid.[95] A 500 mL single neck round bottom flask was charged with (2*E*)-3-(5-(hydroxymethyl)furan-2-yl)acrylic acid (6.000 g, 35.68 mmol, 1.0 eq.), bulk MeOH (100 mL to prepare a 0.3 M solution), and an amber solution formed upon stirring. Concentrated hydrochloric acid (2.9 mL, 1.0 eq.) was added dropwise to the stirring solution. The headspace of the flask was flushed with argon, and the system was sealed beneath a tall Findenser beneath an argon balloon. The mixture was heated to reflux for 6 h within an oil bath. The appearance of the reaction mixture had darkened significantly during the reaction.

The mixture was neutralized by addition of solid sodium carbonate (1.912 g, 0.5 eq.), TLC analysis indicated only one motile spot with significantly decreased retention compared to HMFA. The mixture was concentrated, adsorbed onto silica gel and purified by flash column chromatography. The very major eluate's fractions (5–16) were combined, concentrated to afford a light yellow oil which crystallized upon scratching to afford a white crystalline solid characterized as methyl (*E*)-3-(5-(hydroxymethyl)furan-2-yl)acrylate (5.346 g, 76% isolated yield) by ^{1}H and ^{13}C NMR as well as FTIR.

4.5.5.4. Ethyl 5-(Hydroxymethyl)furan-2-carboxylate



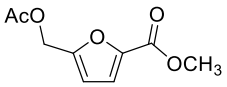
HRMS $[C_8H_{10}O_4Na]^+$ Calcd.: 193.0477, found: 193.0476; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J*=3.4 Hz, 1H), 6.38 (d, *J*=3.4 Hz, 1H), 4.64 (d, *J*=6.3 Hz, 2H), 4.32 (q, *J*=7.1 Hz, 2H), 2.42 (t, *J*=6.4 Hz, 1H), 1.34 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 158.5, 144.5, 118.9, 109.6, 61.2, 57.7, 14.5; FTIR (ATR, diamond, thin film from $CDCl_3$ solution) cm^{-1} 3412, 2984, 1705, 1596, 1523, 1396, 1296, 1206, 1135, 1012, 811, 761.

AB type hydroxyester, ethyl 5-(hydroxymethyl)furan-2-carboxylate, has been reported by Tsuboi, Mimura, Ono, Watanabe and Takeda (1987)[258] as well as by Serum *et al.* (2019).[74] Following modification of Moore and Kelly's protocol,[129] a 300 mL single neck round bottom flask was charged with HMFA (9.973 g, 70.2 mmol, 1.0 eq.). Absolute EtOH (138 mL, 0.51 M) was added as the reaction solvent. Concentrated hydrochloric acid (5.3 mL, 0.92 eq.), was carefully added in dropwise fashion as the orange suspension of hydroxyacid in EtOH was stirred. The headspace of the flask was flushed with argon, sealed beneath a condenser and argon balloon, then heated to reflux for six h.

Upon cooling to ambient temperature, the mixture was neutralized by addition and stirring with anhydrous sodium carbonate (7.108 g, 67.1 mmol, 0.95 eq.) overnight. The dark-amber mixture was concentrated by rotary evaporation under reduced pressure. The black syrup was taken up in diethyl ether and separated by suction filtration through a fritted Büchner funnel. The mixture was analyzed by thin layer chromatography (TLC); A series of four TLC plates (dyed with UV-254) were spotted with the ethereal solution and developed in chambers containing solvent mixtures; [Hex (mL), EtOAc (mL)]: [6, 0], [9, 1], [5, 1] and [5, 2]. Corresponding retention factor (R_f) values measured at the center of the major motile fraction follow: 0.03, 0.05, 0.10, 0.25.

The ethereal solution was concentrated and adsorbed onto silica gel, then purified by flash column chromatography.[69] The fractions comprising the major eluate were combined concentrated by rotary evaporation under reduced pressure to a afford an orange oil of constant mass: 7.216 g, 42.4 mmol, 60% isolated yield. The light-orange oil was confirmed as ethyl 5-(hydroxymethyl)-2-furoate by FTIR, HRMS, ^{1}H and ^{13}C NMR.

4.5.5.5. Methyl 5-(Acetoxymethyl)furan-2-carboxylate



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J*=3.5 Hz, 1H), 6.47 (d, *J*=3.4 Hz, 1H), 5.06 (s, 2H), 3.87 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 159.1, 153.7, 144.9, 118.9, 112.4, 58.0, 52.2, 20.9; FTIR (ATR, diamond, thin film from $CDCl_3$ solution) cm^{-1} 2952, 1724, 1599, 1524, 1437, 1375, 1302, 1208, 1134, 1021, 762.

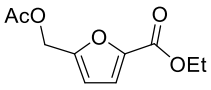
Reported by Schmuck and Machon (2006)[257] as well as by Serum *et al.* (2019).[74] A 25 mL single neck round bottom flask was charged with methyl 5-(hydroxymethyl)furan-2-carboxylate (1.575 g, 10 mmol, 1.0 eq.) and a solution was prepared by addition of HPLC grade acetone (10 mL, 0.9 M solution formed). The mixture was stirred as acetic anhydride (1.0 mL, 11 mmol, 1.1 eq.) was added dropwise. Acyl transfer catalyst, DMAP (0.041 g, 0.3 mmol, 3 mol%) was added to catalyze acyl transfer; an exotherm was noted upon combination of DMAP. The mixture was stirred for 12 h at ambient temperature.

The reaction solution was analyzed by thin layer chromatography (TLC); A series of three TLC plates (dyed with UV-254) were spotted with the acetone solution and developed in chambers containing solvent mixtures; [Hex (mL), EtOAc (mL)]: [6, 0], [5, 2], and [5, 5]. Corresponding retention factor (R_f) values measured at the center of the major motile fraction follow: 0.06, 0.55, 0.69.

The reaction mixture was transferred to a larger flask with acetone, diluted with ice and concentrated by rotary evaporation under reduced pressure. Upon concentration, a yellow oil separated from the aqueous concentrate. The residual mixture was partitioned between EtOAc and H_2O. The aqueous solution was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, backwashed with saturated sodium bicarbonate solution, isolated, and dried (anhydrous sodium sulfate). The solution was isolated from drying agent by gravity filtration through a plug

of cotton, concentrated to afford an orange oil and characterized as the desired product, methyl 5-(acetoxymethyl)furan-2-carboxylate: constant mass was 1.912 g, 9.7 mmol, 97% of the theoretical maximum.

4.5.5.6. Ethyl 5-(Acetoxymethyl)furan-2-carboxylate



HRMS $[C_{10}H_{12}O_5Na]^+$ Calcd.: 235.0582, found: 235.0583; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J*=3.4 Hz, 1H), 6.47 (d, *J*=3.5 Hz, 1H), 5.06 (s, 2H), 4.34 (q, *J*=7.1 Hz, 2H), 2.06 (s, 3H), 1.35 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 158.8, 153.5, 145.3, 118.6, 112.4, 61.3, 58.1, 20.9, 14.5; FTIR (ATR, diamond, thin film from $CDCl_3$ solution) cm^{-1} 2984, 1744, 1716, 1599, 1524, 1446, 1373, 1296, 1207, 1136, 1020, 762.

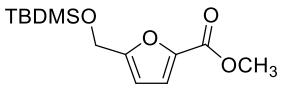
Reported by Zhang, Schen, Chen, and Yin (2017),[83] as well as by Serum *et al.* (2019).[74] A 250 mL single neck round bottom flask was charged with ethyl 5-(hydroxymethyl)furan-2-carboxylate (7.505 g, 44.1 mmol, 1.0 eq.) and a solution was prepared by addition of HPLC grade acetone (50 mL, 0.9 M solution formed). DMAP (0.044 g, 0.4 mmol, 0.8 mol%) was added to catalyze acyl transfer. The mixture was stirred as acetic anhydride (5.0 mL, 0.0529 mol, 1.2 eq.) was added dropwise. The mixture was stirred for 12 h (ambient temperature).

The reaction solution was analyzed by thin layer chromatography (TLC); A series of four TLC plates (dyed with UV-254) were spotted with the acetone solution and developed in chambers containing solvent mixtures; [Hex (mL), EtOAc (mL)]: [6, 0], [9, 1], [5, 1], and [5, 2]. Corresponding retention factor (R_f) values measured at the center of the major motile fraction follow: 0.08, 0.25, 0.32, 0.69.

The reaction mixture was concentrated by rotary evaporation under reduced pressure to afford a golden oil. The oil was transferred to an ice-charged beaker (600 mL). The resulting mixture was extracted with EtOAc and H_2O in a 500 mL separatory funnel. The aqueous solution

was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, backwashed with saturated sodium bicarbonate solution, isolated, and dried (anhydrous sodium sulfate). The solution was isolated from drying agent by gravity filtration through a plug of cotton, concentrated to afford a yellow-oil which was characterized as the desired product, ethyl 5-(acetoxymethyl)furan-2-carboxylate: constant mass was 9.148 g, 43.1 mmol, 98% of the theoretical maximum.

4.5.5.7. Methyl 5-(((tert-Butyldimethylsilyl)oxy)methyl)furan-2-carboxylate



HRMS $[C_{13}H_{22}O_4SiNa]^+$ Calcd.: 293.1185, found: 293.1210; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J*=3.4 Hz, 1H), 6.34 (d, *J*=3.4 Hz, 1H), 4.69 (s, 2H), 3.86 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.41, 159.35, 143.7, 119.1, 108.9, 58.7, 52.0, 26.0, 18.5, -5.2; FTIR (ATR, diamond, thin film from $CDCl_3$ solution) cm^{-1} 2952, 2929, 2857, 1725, 1596, 1534, 1463, 1436, 1342, 1301, 1254, 1208, 1132, 1079, 1019, 925, 833, 776, 759, 719, 663.

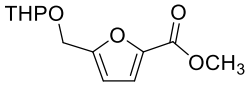
Anna Renner prepared[74] this derivative of methyl 5-(hydroxymethyl)furan-2-carboxylate by following the procedures of: (1) Pezzetta, Veiros, Oble, and Poli (2017),[259] (2) Subbia, Simeonov, Esperança, Rebelo, and Afonso (2013)[85] (3) Coelho, Trindade, André, Teresa, Veiros, and Afonso (2014).[260]

A dry 50 mL flask was charged with methyl 5-(hydroxymethyl)furan-2-carboxylate, 0.995 g, 6.4 mmol, 1.0 eq.) and was flushed with argon. The 50 mL flask was charged with anhydrous DCM (13.0 mL, 0.49 M), imidazole (0.488 g, 7.2 mmol, 1.1 eq.) through the flask's sidearm under positive argon pressure. The resulting mixture was stirred to dissolve the imidazole. To the stirring solution was added *tert*-butyldimethylsilyl chloride (TBDMSCl, 1.060 g, 7.0 mmol, 1.1 eq.). The reaction mixture was left stirring at room temperature overnight.

The reaction solution was analyzed by thin layer chromatography (TLC); A series of three TLC plates (dyed with UV-254) were spotted with the DCM solution and developed in chambers containing solvent mixtures; [Hex (mL), EtOAc (mL)]: [6, 0], [9, 1], and [5, 1]. Corresponding retention factor (R_f) values measured at the center of the major motile fraction follow: 0.08, 0.37, 0.76.

The reaction mixture was transferred with H_2O (30 mL) to a 125 mL separatory funnel; a small amount of DCM was used to rinse the flask. The mixture was extracted with DCM (3 × 30 mL), and the combined organic layers were backwashed with brine (30 mL), dried (anhydrous sodium sulfate), gravity-filtered through a cotton-plug, concentrated *in vacuo*, and adsorbed onto silica gel. The product was isolated by flash column chromatography (Hex/EtOAc gradient as eluent) affording a colorless oil upon combination and concentration of the major fractions. The oil was characterized by ^{1}H and ^{13}C NMR as well as FTIR and HRMS. Mass of oil was 1.509 g, 5.6 mmol, 88% of the theoretical maximum.

4.5.5.8. Methyl 5-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)furan-2-carboxylate



HRMS $[C_{12}H_{16}O_5Na]^+$ Calcd.: 263.0895, found 263.0907; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J*=3.4 Hz, 1H), 6.42 (d, *J*=3.4 Hz, 1H), 4.75–4.64 (m, 2H), 4.69 (d, *J*=13.3 Hz, 1H), 4.51 (d, *J*=13.3 Hz, 1H), 3.87 (s, 3H), 3.9–3.8 (m, 1 H) 3.58–3.47 (m, 1H), 1.9– 1.7 (m, 1H), 1.8–1.6 (m, 1H), 1.7–1.50 (m, 2H), 1.6–1.4 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.6, 144.5, 119.0, 111.0, 98.1, 62.2, 61.1, 52.1, 30.5, 25.5, 19.3; FTIR (ATR, diamond, thin film from $CDCl_3$ solution) cm^{-1} 2943, 2871, 1720, 1597, 1522, 1436, 1341, 1299, 1206, 1117, 1077, 1016, 961, 902, 870, 812, 759.

The ethyl analog was reported by Tsuboi, Mimura, Ono, Watanabe, and Takeda.[258] Procedural references: (1) Grieco, Yoshikoshi, and Miyashita,[261] (2) Okada, Sakaguchi, Shinada,

and Ohfune,[262] (3) Pezzetta, Veiros, Oble, and Poli.[259] Anna Renner prepared this furan-diene.[74]

A dry 50 mL flask was charged with methyl 5-(hydroxymethyl)furan-2-carboxylate,1.017 g, 0.0065 mol, 1 eq.) under positive argon-pressure. Anhydrous DCM (13.0 mL, 0.50 M) was added, and the mixture was stirred. The flask containing substrate was charged with 3,4-dihydro-2*H*-pyran (DHP, 0.70 mL, 0.0077 mol, 1.2 eq.) *via* syringe.

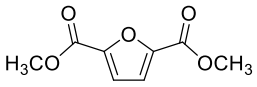
Pyridinium *p*-toluenesulfonate (PPTS) was freshly prepared; *p*-toluenesulfonic acid monohydrate (0.366 g, 0.0019 mol) and pyridine (0.80 mL, 0.0099 mol) were stirred in a 6-dram vial for 25 min. The resulting homogeneous, colorless solution was concentrated *in vacuo* (25–70 °C), affording a moist-looking colorless solid at the bottom of the vial. The residue was azeotropically dried and liberated of pyridine by toluene (1 mL) dissolution and repeated concentration *in vacuo* (65–70 °C). This process afforded white solids on the sides of the vial: 0.5038 g of PPTS.

Freshly prepared PPTS, (0.1604 g, 0.0006 mol, 10 mol%) was added to the stirring reaction mixture on ice. The reaction mixture was stirred at room temperature for 24 h. The reaction solution was analyzed by thin layer chromatography (TLC); A series of three TLC plates (dyed with UV-254) were spotted with the DCM solution and developed in chambers containing mixtures [Hex (mL), EtOAc (mL)]: [6, 0], [9, 1], and [5, 1]. Corresponding retention factors (R_f) values measured at the center of the major motile fraction follow: 0.00, 0.24, 0.61.

The reaction mixture was transferred with DCM (90 mL) to a 250 mL separatory funnel and washed with saturated aqueous sodium bicarbonate (2 × 30 mL) and then brine (30 mL). The organic phase was dried over sodium sulfate and subsequently gravity-filtered through cotton-plug, adsorbed onto silica gel, and purified by flash chromatography. The major eluate peak's

fractions were combined, concentrated *in vacuo* to a constant mass of 1.388 g, 0.0058 mol, 89% of the theoretical maximum.

4.5.5.9. Methyl 2,5-Furandicarboxylate[95]



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 146.8, 118.6, 52.5; FTIR (ATR, neat) cm^{-1} 3117, 3018, 2965, 1718, 1582, 1514, 1464, 1433, 1378, 1309, 1271, 1235, 1190, 1160, 1131, 1029, 985, 921, 835, 797, 764, 613, 480, 426.

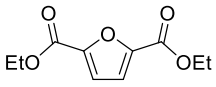
A 2 L single neck round bottom flask was charged with FDCA (55.88 g of 80% purity from AVA Biochem, 286 mmol, 1 eq.). The black-flecked tan solid was suspended in MeOH (1.34 L, HPLC grade). The brown methanolic suspension was stirred vigorously as concentrated sulfuric acid (30 mL of 18 M, 563 mmol, 2 eq.) was slowly added through a funnel; the color of the methanolic solution became black by the completion of the addition. The mixture was stirred beneath a Friedrichs condenser and the headspace was flushed with argon. The reaction was heated to a gentle reflux using a heating mantle/variac beneath an argon balloon; all the observable solid dissolved upon heating and the reflux continued for 16 h.

Upon cooling, the dark solution was concentrated to approximately one half its volume by rotary evaporation under vacuum. The acidic solution was diluted to a volume of nearly 2 L by charging the flask with crushed ice concurrently with vigorous shaking; a powdery-tan precipitate was observed. Once the ice thawed, the mixture was separated by suction filtration using a 2 L filter flask and a 9 cm ceramic Büchner funnel. The first filtrate (1900 mL) was orange in color and was discarded. The filter-cake was rinsed with DI H_2O (600 mL which was amber in color), pressed dry, chopped and spread on paper to air-dry.

The brown solid (53.63 g) gave a pure NMR spectrum, however the sample was an incomplete solution in $CDCl_3$. Fine brown particulate was observed to separate from a light-yellow solution upon standing. The crude product was dissolved in 250 mL of DCM and gravity filtered through a column of silica gel with 500 mL of DCM. The silica gel retained all the black color, and most of the orange; the eluted solution was faintly amber in color.

The DCM solution was concentrated by rotary evaporation under vacuum, and the yellow solid residue was recrystallized from IPA and separated by suction filtration to afford flaky white dimethyl-2,5-furandicarboxylate (46.3 g, 252 mmol, 88% yield) as crop one (melting point range: 110–113 °C). The 350 mL of 2-propanolic liquor was concentrated to afford a second crop (2.26 g, 12.3 mmol, 5% yield, melting point range: 109–113 °C) of faintly yellow flaky solid.

4.5.5.10. Ethyl 2,5-Furandicarboxylate



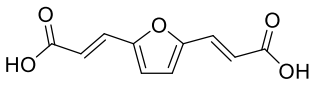
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 4.37 (q, *J*=7.1 Hz, 2H) 1.36 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 149.1, 118.4, 61.8, 14.4; FTIR (ATR, neat) cm^{-1} 3148, 3113, 2990, 2969, 2911, 1733, 1720, 1572, 1509, 1479, 1383, 1368, 1271, 1228, 1182, 1154, 1112, 1041, 1018, 964, 862, 819, 768, 615.

A 3 L single necked round bottom flask was charged with FDCA (57.8 g of 80% purity from AVA Biochem, 296 mmol, 1 eq.). The black-flecked tan solid was suspended in EtOH (1.5 L, absolute). The brown ethanolic suspension was stirred vigorously as concentrated sulfuric acid (30 mL of 18 M, 563 mmol, 2 eq.) was slowly added through a funnel; the color of the ethanolic suspension darkened gradually by the completion of the exothermic addition. The mixture was stirred and heated to reflux with a heating mantle/variac under argon and a Friedrichs condenser. The mixture formed a black solution by the time it had reached reflux.

The reflux was continued for 20 h, allowed to cool to 40 °C and concentrated to half of its volume by rotary evaporation under vacuum. The concentrated solution was poured onto 1.8 L of crushed ice in a 2 L beaker with hand stirring. Brown solid precipitate was observed initially, however by the completion of the addition the ice had melted and the mixture was predominantly a dark solution. Ice was added to bring the total reaction volume to 2 L and brown precipitate began to develop. A second 2 L beaker was charged with 1400 mL of crushed ice and 1 L of the dark ethanolic slurry was poured into it with hand stirring; the initial mixture was then brought back to 2 L by the addition of crushed ice with hand stirring. The brown solid was isolated from the light orange aqueous solution by suction filtration through a finely fritted glass Büchner funnel and rinsed with 600 mL of distilled H_2O.

The brown solid was pressed free of filtrate, dried on the filter, chopped and spread on paper to air dry overnight. The crude product appeared pure by NMR analysis. The brown residue was dissolved in DCM (125 mL) to form a black solution; the dissolution was endothermic. The crude mixture was gravity filtered through a pad of silica gel in a 150 mL fritted glass Büchner funnel. The filter cake was rinsed with 25 mL DCM but remained stained black; the filtrate was still black. The mixture was diluted with circa 25 mL of Hex and gravity filtered through a fresh pad of silica gel which was rinsed with 50 mL of 50% vol/vol Hex/DCM to afford circa 200 mL of clear and light yellow solution. The filtrate was concentrated by rotary evaporation under reduced pressure to afford a viscous amber oil which crystallized upon vacuum drying with chilling on an ice bath. The bright yellow crystalline solid was chopped and spread on paper to air dry overnight and was used directly in the benzyne-Diels-Alder trials. The mass of the yellow crystalline solid was 60.0 g (89%). The material could be recrystallized from IPA.

4.5.5.11. (2E,2'E)-3,3'-(Furan-2,5-diyl)diacrylic Acid[95]



^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (br s, 1H), 7.38 (d, J=15.8 Hz, 1H), 7.03 (s, 1H), 6.38 (d, J=15.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.6, 152.5, 130.4, 118.9, 118.0; FTIR (ATR, neat) cm^{-1} 2979, 2840, 2661, 2530, 1656, 1625, 1549, 1425, 1275, 1232, 1199, 1162, 1017, 965, 892, 798, 740, 661, 570, 539.

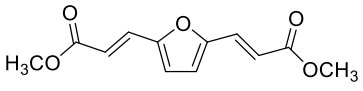
A 500 mL single necked round bottomed flask was charged with DFF (52.5 g, 423 mmol, 1 eq.), malonic acid (106.1 g, 1,019 mmol, 2.4 eq.), piperidine (8.2 mL, 83 mmol, 0.2 eq.), pyridine (150 mL, 1,862 mmol, 4.4 eq.), and the mixture became a viscous syrup with yellow solid residue; the combination of materials was slightly exothermic (the temperature of the outer flask walls rose from 20 to 33 °C). The mixture was lowered into a preheated (50 °C) oil bath. A dark solution formed and bubbled vigorously (bubbles were orange). The viscosity of the mixture was too great to allow bubbles formed from carbon dioxide evolution to burst. In order to avoid effervescence, the mixture was raised from the oil bath and diluted with dry DMF (108 mL, 1,395 mmol, 3.3 eq.). The diluted mixture was lowered into the warm bath again, whereupon bubbles formed and cleanly burst as the reaction mixture was stirred.

The flask and bath were wrapped in aluminum foil and stirred at 50 °C for 8 h beneath a tall West condenser plumbed with running cool H_2O and positive pressure (nitrogen). The mixture was a dark solution without apparent gas evolution. The bath temperature was increased to 100 °C and stirring continued for 5 h. The reaction mixture was allowed to cool, the stir bar was pulled, and the mixture was concentrated by rotary evaporation to a golden solid which coated the inner walls of the flask. The mixture was diluted with DI H_2O then acidified by the careful addition of concentrated sulfuric acid (50 mL, 944 mmol, 2.2 eq.); the mixture lost much of its golden color. The light-yellow solution and tan residue were transferred to a 2 L beaker and diluted to a total

volume of 1 L. The mixture was stirred and heated to 60 °C. The mixture was allowed to concentrate and slowly warm for 11.5 h open in a well-ventilated fume hood to facilitate the hydrolysis of any residual DMF and the neutralization of all nitrogenous bases. The temperature of the mixture was 83 °C and the volume was 600 mL. The mixture was stirred as it was allowed to cool to room temperature then chilled on an ice bath.

The tan residue was isolated by suction filtration through a finely fritted glass Büchner funnel above a 2 L filter flask. The filtrate was a clear amber solution. The residue was powdery tan solid which was washed heavily with ice cold DI H_2O. As the filtrate was diluted, it became turbid. The first 2 L of filtrate were discarded (turbid orange solution) and another 1 L of cold H_2O was used to rinse the residue (that filtrate was very lightly yellow). The residue was rinsed with EtOAc (250 mL) and the resulting filtrate was dark brown. The residue was pressed dry on the filter, chopped and spread on paper then onto aluminum foil to airdry overnight. The light tan powdery residue was identified as (2*E*,2'*E*)-3,3'-(furan-2,5-diyl)diacrylic acid: 77.94 g, 88% yield.

4.5.5.12. Dimethyl 3,3'-(Furan-2,5-diyl)(2E,2'E)-diacrylate[95]



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=15.7 Hz, 1H), 6.63 (s, 1H), 6.40 (d, *J*=15.7 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 152.5, 130.4, 117.7, 116.9, 51.9; FTIR (ATR, neat) cm^{-1} 2966, 1719, 1633, 1553, 1505, 1434, 1386, 1302, 1238, 1163, 958, 858, 791, 659.

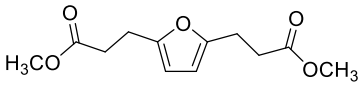
A 500 mL two-necked flask was charged with (2*E*,2'*E*)-3,3'-(furan-2,5-diyl)diacrylic acid (31.82 g, 153 mmol, 1 eq.) and MeOH (300 mL, HPLC grade), and the mixture formed a chalky yellow suspension. The flask was fitted beneath a Graham condenser sealed with a drying tube charged with indicated Drierite. The flask was lowered into a room temperature oil bath and stirred with vigor. Sodium chloride (3 g, 51 mmol, 0.34 eq.) was added as a granular crystalline solid

through the side neck—*for the purpose of decreasing the solubility of the diester product in the methanolic reaction mixture.* A polypropylene syringe was used to add concentrated sulfuric acid (2 mL, 37 mmol, 0.24 eq.) also through the side neck which was then sealed with a yellow cap-plug.

The reaction mixture was refluxed beneath the drying tube for a total of 19 h. Within 30 min of refluxing, the slurry had lost much of its yellow color and appeared chalky. The nature of the solid residue was also observed to change to a slurry of crystalline solid. When the reaction mixture was lifted from the oil bath and allowed to cool without stirring, crystalline solid was observed to precipitate from the yellow liquor. That crystalline solid trapped much of the color from the liquor and appeared darkly amber. The mixture was reheated to reflux, the solid dispersed and the color dissolved. The mixture was allowed to slowly cool with vigorous stirring to retard the agglomeration of particles in the precipitate which might have otherwise captured the colored impurities. Off-white settled from a yellow liquor upon cessation of stirring.

The reaction mixture was stored in the freezer overnight along with a 500 mL wash bottle of isopropyl alcohol. Some colorless crystalline solid was observed to have grown into the liquor which then appeared orange in color. The off-white solid was isolated by suction filtration through a Büchner funnel (ceramic, 9 cm, qualitative filter paper), pressed free of orange liquor then rinsed free of color with cold isopropyl alcohol. The filter-cake was sucked free of washing solvent, chopped, and spread on paper to air dry overnight. The powdery solid was identified as dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate (35.22 g, 153 mmol, 98% isolated yield, melting point was observed at 169 °C) and was used without further purification.

4.5.5.13. Dimethyl 3,3'-(Furan-2,5-diyl)dipropionate[95]



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 3.65 (s, 3H), 2.87 (t, *J*=7.6 Hz, 2H), 2.59 (t, *J*=7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 152.9, 105.9, 51.8, 32.7, 23.6; FTIR (ATR, neat) cm^{-1} 2956, 2915, 1729, 1601, 1516, 1439, 1354, 1292, 1197, 1148, 1040, 980, 826, 748, 583.

Following a modification of Narisada *et al.*,[251] to a 500 mL Erlenmeyer flask was added dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate (4.21 g, 17.8 mmol, 1 eq.) and THF (100 mL of HPLC grade); the mixture was stirred to afford a turbid faintly amber solution which was diluted with MeOH (100 mL, HPLC grade from Fisher Scientific). Copper(I) chloride (5.39 g of 97% extra pure, 52.8 mmol, 2.96 eq.) was stirred into the reaction mixture (gray slurry) which was submerged in an ice bath and its temperature was monitored by internal digital thermometer. Sodium borohydride (6.93 g, 183 mmol, 10.3 eq.) was measured into a polystyrene weigh boat and added bit by bit to the reaction mixture at such a rate that the temperature never rose above 10 °C. Upon the first addition of sodium borohydride to the cuprous reaction slurry, the color shifted from greenish gray to light brown.

Approximately half the borohydride was added within the first h of the reaction and the mixture became opaque and black with no observable particulate. The addition of the second half of the borohydride took place in similar portions as the first, but with more latent time between each addition so that its completion took 104 min. The mixture was stirred as the ice bath thawed and warmed to room temperature (11 h). The mixture was quenched with silica gel and allowed to settle open to the air. The solution above the dark solid which settled to the bottom of the flask was light blue in color. The light blue solution was isolated by suction filtration through a 3 cm pad of silica gel packed into a 9 cm ceramic Büchner funnel above a 1 L filter flask, the residue

was black. The filter cake was rinsed heavily with DCM; the filtrate was slightly turbid and pale blue. The filtrate was transferred to a 1.0 L recovery flask and concentrated by rotary evaporation to afford wet looking pale blue solid. The residue was partitioned between concentrated ammonium chloride (200 mL) and DCM (200 mL); the aqueous phase was deeply blue. The DCM phase appeared colorless, was isolated, and the blue aqueous phase was extracted two more times with 100 mL of DCM. The DCM extracts were combined, backwashed three times with 150 mL of distilled H_2O and once with 150 mL of saturated sodium chloride.

The DCM solution was isolated, dried (Na_2SO_4), and concentrated to a faintly yellow oil by rotary evaporation under vacuum. That residual oil was passed through a microcolumn (monster pipette packed with silica gel) and rinsed with circa 5 mL of DCM into a tared 20 dram sample vial. The silica gel plug held the faint yellow color and the nearly colorless eluate was concentrated by nitrogen stream then vacuum drying to constant mass to afford dimethyl 3,3'-(furanyl-2,5-dipropionate) as a very faintly yellow oil (3.97 g, 17.8 mmol, 93% yield). The light oil was clearly contaminated with a small amount of over-reduced side products; however, these did not interfere with the isolation of clean products in the later reaction sequence.

4.6. References

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5. BIOBASED FURAN-DIENE VALORIZATION WITH BENZYNE

In this chapter aromatic upgrading of renewable furanics has been made the focus. Many diversified cellulose-derived furans have been employed as substrates in cycloaddition strategies. Biomass-derived FDCA (renewable AA type monomer) was valorized by conversion to 1,4-naphthalenedicarboxylic acid (1,4-NDCA) via benzyne-cycloaddition and reductive aromatization in 66% overall yield (four steps). Additionally, renewable novel bicyclic AB type polyester precursors have been prepared in good overall yield from lignocellulosic biomass by application of the direct-access benzyne DAR strategy. The novel bicyclic intermediates take full advantage of the differing oxidation states offered by functional groups in HMF by chemoselective preparation of furanic hydroxy esters—*chapter 4 of this dissertation*—and application of an aromatic upgrade strategy. These advances further develop the diversity and potential end uses of renewable-furanics available from cellulose biorefinery.

As alluded to in chapter 4 of this dissertation, one of the primary interests in the development of sustainable benzyne Diels-Alder reactions with electron-deficient biorenewable furan-dienes was for the preparation of terephthalic acid analogs. The subject matter of this chapter includes preparation of such analogs, during which evidence has been presented for novel reactivity discovered in the family of C1,C4-(electron-deficient)-disubstituted 7-oxabenzonorbornadienes.

5.1. Introduction to Benzyne Diels-Alder Cycloaddition

A series furan-dienes was procured (the subject of Chapter 4 of this document) containing a range of electronics from poor to rich. The thermolysis of benzendizaonium-2-carboxylate by several protocols was investigated as a source of benzyne with a relatively benign precursor which required no particularly hazardous reagents and produced no toxic byproducts in the generation of

benzyne. The protection of certain functional groups was determined to be a requisite for smooth reaction to avoid expected side reactions with either benzyne (carboxylic acid and aldehyde moieties) or with benzenediazonium-2-carboxylate (primary hydroxyl functionalities). The normality of electron-demand pertaining to benzyne Diels-Alder reactions were investigated and found to be moderately dependent on the substitution upon furan-dienes but certainly followed the expected trend. Yields for furan-dienes containing oxyalkyl substitutions at the C2 and C5 positions always afforded higher yields of adducts than for example furan-dienes which contained two carboxylate moieties.

The great reactivity of benzyne as an electrophile and dienophile has been attributed to the disproportionate strain-induced perturbation of the frontier molecular orbitals. The strain is imparted by distortion of the normally linear alkyne system's nonconjugated π-bond by the conjoined aromatic ring. Correspondingly, the lowest unoccupied molecular orbital (LUMO) is lowered by the imposed strain without greatly altering the relative energy of the highest occupied molecular orbital (HOMO). Combined these phenomena have allowed benzyne to participate in even formally forbidden thermal [2+2] cycloadditions with electron rich alkenes albeit by asynchronous mechanism.[1, 2] Additionally, benzyne possesses sufficient reactivity to overcome the thermal barrier to Diels-Alder Reaction with electron deficient furan-dienes while following the trend of normal electron demand.[3, 4]

A brief overview of benzyne chemistry follows to provide a contextual lens for viewing the relatively benign methodologies described herein. For deeper insight, the author implores the reader to examine the saga of benzyne or 1,2-dehydrobenzene compiled by many reviews on the subject.[5-18] This discussion will be devoted to describing the structural elucidation and applications of strained reactive intermediates collectively known as arynes.

Even the name aryne has been subject to debate; for example, the 'yne' suffix disturbed both Wittitg and Hoffmann since there is no true triple bond such as is found in an alkyne; the bond order is actually two and a half as opposed to three given the presence of the intact aromatic system as evinced by spectroscopic observations. Hoffmann, Imamura, and Hehre (1968) applied several molecular orbital methods to deduce "significant and specific interactions among radical lobes in the same molecules separated by a number of intervening σ-bonds".[19] While translating their results into the parlance of valence-bond theory, they concluded that both Kekulé canonical structures make a sizeable contribution which makes Robinson annular structures most apt for arynes (Fig 5.1).

In the spirit of semantic correctness, the term 1,2-dehydrobenzene must be acknowledged while its use has waned. The current vernacular describes such intermediates as *o*-benzynes and even more commonly as benzynes while terminology such as arynes has become general. To further explore the case for a 1,2-dehydrobenzene derived nomenclature, see *Dehydrobenzene and Cycloalkynes* by Hoffmann.[8]

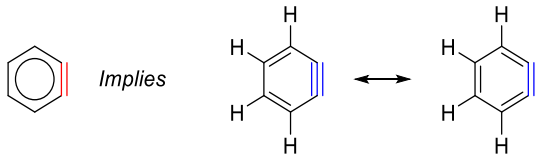


Fig. 5.1. Robinson structure and two prominent canonical (mesomeric) structures of benzyne (1,2-dehydrobenzene)

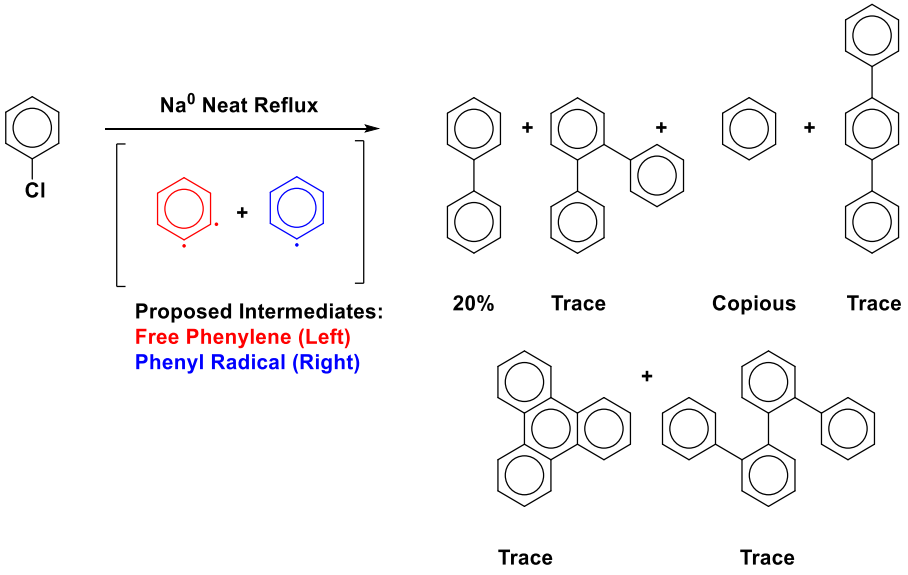
5.1.1. From Free Phenylene to the Benzyne Mechanism

During the first half of the 20th century, chemical scientists made enormous progress to construct modern concepts of organic chemistry. These technical leaps made possible the achievement of laudable goals such as: (1) rationalizing the nature of chemical bonds, (2) describing reaction mechanisms, and (3) the synthetic preparation of molecules integral to

medicinal or material sciences. The role of benzene within the work herein detailed will benefit from a brief historical perspective tracing the conceptual advancements required to arrive at *the benzyne mechanism* in context with the development of modern synthetic organic thinking.

5.1.1.1. Strained Bicycles Relevant to Developing the Aryne Concept

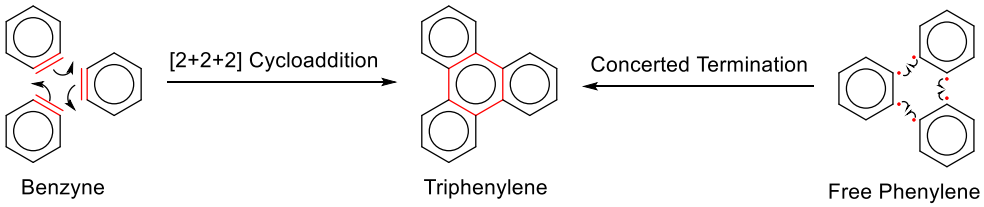
Bachmann and Clarke (1927) reported an array of interesting side products isolated from their attempts to synthesize large quantities of biphenyl *via* the Wurtz-Fittig coupling (Scheme 5.1).[20] Explanation of the Wurtz-Fittig reaction in this context can be identified as an early case wherein the as then undeveloped theory of aryne intermediacy is readily employed in a modern context. Indeed, deprotonation of a halogenated benzene in strongly basic media would later be expanded into the progenitor reaction of aryne chemistry.



Scheme 5.1. Synthesis of biphenyl by Wurtz-Fittig coupling and side products which implicated an intermediate with biradical structure: free phenylene

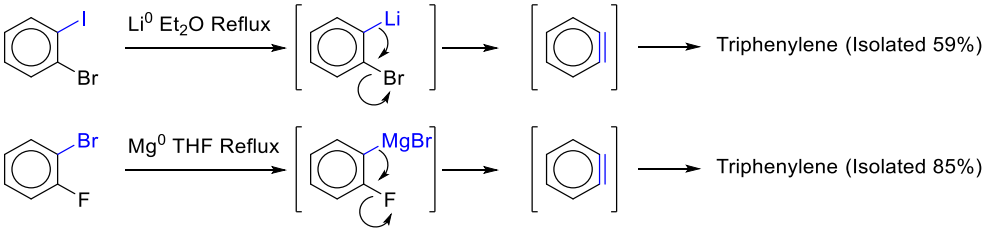
From the laborious workup and isolation of the reaction between sodium and chlorobenzene, Bachmann and Clarke (1927) procured a family of compounds identified speculated to have arisen from reaction between phenyl radicals and a 1,2-phenylene diradical which was termed free phenylene. The characterization was completed by independent synthesis

and melting point analysis of the family of oligocyclic products. The greatest evidence for a diradical intermediate *versus* a phenyl radical chain process was considered to be the detected presence of triphenylene. The envisaged reaction proceeded from reaction between two free phenyl radicals to afford free phenylene diradical and benzene. In general, the study of all reaction products was presented as strong evidence for the intermediacy of the then fresh concept of free radical intermediacy as opposed to accepted arylsodium intermediates in the Wurtz-Fittig reaction.



Scheme 5.2. Triphenylene by [2+2+2] cycloaddition compared with concerted termination of free phenylene

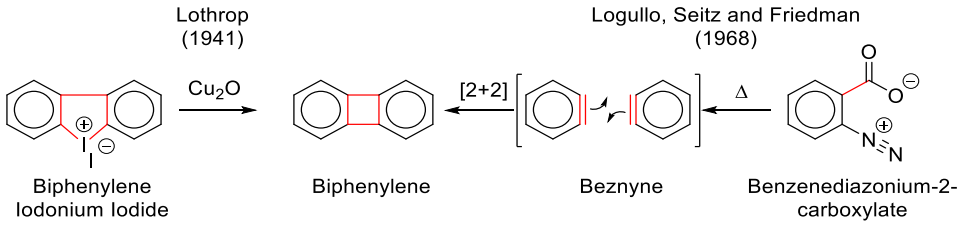
Two extremes of the triphenylene formation mechanism in the Wurtz-Fittig coupling have been illustrated in Scheme 5.2. One may consider a [2+2+2] cycloaddition including three molecules of 1,2-dehydrobenzene while on the other hand one may consider concerted termination of three molecules of free phenylene. Truly, the actual mechanism is likely to entail reaction of two benzyne molecules initially followed by homolytic bond scission to afford biphenylene diradical which could trap a third benzyne. That stepwise mechanism including interplay and interception of benzyne with phenyl radicals describes routes which afford the suite of products observed.



Scheme 5.3. Optimized syntheses of triphenylene employ conditions which favor formation 1,2-dehydrobenzene

Later synthetic protocols for triphenylene reported by Heaney and Millar (1960) achieved greater selectivity for the fee phenylene type intermediate and correspondingly higher yields of triphenylene. Their achievement was secured by employment of mixed halogenated *ortho*-disubstituted arenes (Scheme 5.3) which would have driven down the concentration of radical species present in solution.[21] Optimized syntheses of triphenylene favor conditions which favor formation of a carbanion adjacent to a positively polarized sp^2 hybridized carbon substituted with a leaving group which make the inferior leaving group, fluoride, led to greatest selectivity.

Contributing to the concealment of arynes, Wurtz-Fittig coupling consistently failed to afford isolates of biphenylene. Lothrop (1941) described the lurid tale of biphenylene as well as the first general method for its synthesis (Scheme 5.4).[22] The dearth of strained dibenzofused cyclobutadiene reports to that date capture the air of mystery surrounding strained intermediates which has been a continual driver in developing the sophistication of chemical theory. As benzyne technology matured, the synthesis of biphenylene was significantly simplified by Logullo, Seitz and Friedman (1968).[23] The optimized synthesis of biphenylene relies on an aprotic benzyne precursor: benzenediazonidum-2-carboxylate (Scheme 5.4). Biphenylene was determined to be approximately half as aromatic as benzene by Mitchell and Iyer (1996) and so is a reactive intermediate in its own right.[24]



Scheme 5.4. Syntheses of biphenylene with and without benzyne intermediacy

Another strange bicyclic intermediate—*which would play an key role during investigations into strained bicyclic bridgehead*[25] *and aryne*[26] *reactivity*—was reported by Bartlett, Ryan and

Cohen (1942); it was dubbed: triptycene (Fig. 5.2).[27] The ability of a triaryl methine to stabilize radical, carbanion, or carbocation intermediates is dependent upon coplanarity and delocalization of the charge or radical throughout an extended π-system in valance bond terminology or to maximize overlap of atomic orbitals for the construction of molecular orbitals. As such, *ortho*-substitutions were expected to interfere with such stabilization. Triptycene was envisioned as an extreme test of this phenomenon since it would contain two identically substituted triaryl methines as antipodal bridgeheads which would be pinned by ring-strain out of coplanarity with any of the aromatic π-systems such that only the inductive effect of the phenyl rings would provide stabilization of reactive intermediates. The six-step synthesis of triptycene from anthracene and *para*-quinone would become constricted to elegance by development of benzyne technologies in the following decades.[28-31]

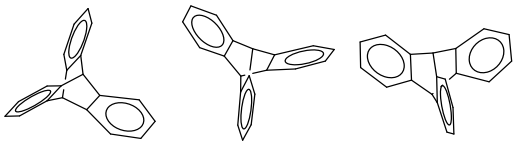


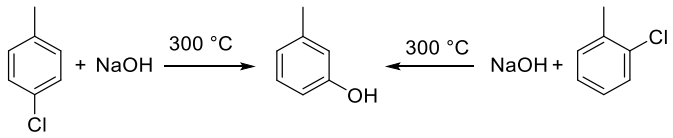
Fig. 5.2. A strained bicycle: triptycene

Lindow and Friedman (1967) considered the possibility of accessing benzyne by pyrolyzing biphenylene in the presence of anthracene by a consecutive cycloreversion to benzyne followed by trapping of the strained dienophile.[32] The expected product, triptycene, was not observed. Instead very high yields of tetraphenylene were reported. They proposed a reversible formation of biphenyl-2,2'-diradical under the higher temperatures of pyrolysis investigated. The diradical intermediate could undergo dimerization to afford tetraphenylene, as well as polymerization reactions. That diradical could decompose into two molecules of benzyne and then afford triphenylene by trimerization or by interception by biphenyl-2,2'-diradical. Friedman and

Lindow (1968) elaborated on the preparation of benzyne from biphenylene *via* electron impact and by pyrolysis.[33] In the liquid phase pyrolysis experiments (~400 °C), nearly quantitative yields of tetraphenylene were observed, and the process was catalyzed by stainless steel. When the pyrolysis was conducted in the vapor phase (735 °C in a nitrogen stream), the yield of tetraphenylene was significantly reduced and some triphenylene was detected.

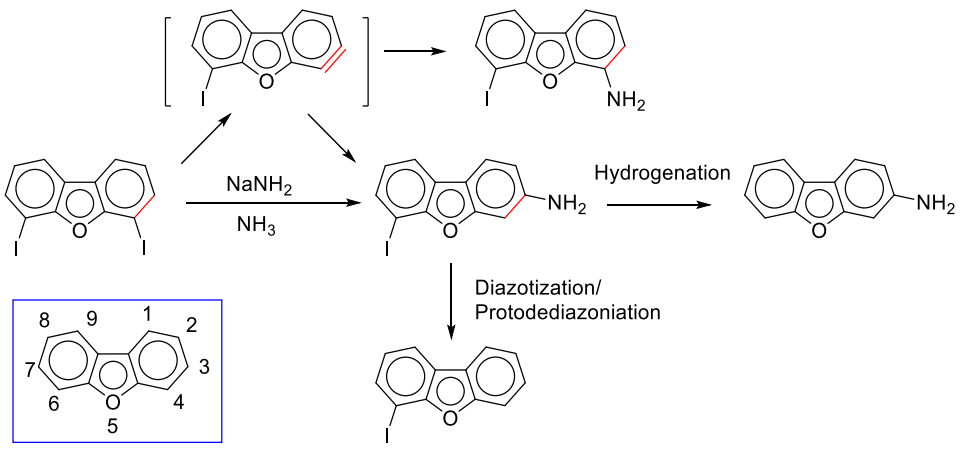
5.1.1.2. Cine Substitution and the Eventuality of a Benzyne Mechanism

Meharg and Allen (1932) reported a molecular rearrangement in the high temperature hydrolysis of chlorotoluenes with alkali (Scheme 5.5) which was expected to proceed by nucleophilic aromatic substitution mechanism and which proceeds with *ipso* substitution *via* intermediacy of a Meisenheimer complex.[34] The yield of *meta*-cresol was 25% from *ortho*-chlorotoluene and 38% from *meta*-chlorotoluene. The investigation was extended to 1-chloro-2-ethylbenzene and indicated that the reaction was general for chloroalkylarenes. Consideration of an elimination-addition mechanism with aryne intermediacy was not evident.



Scheme 5.5. High temperature hydrolysis of chlorotoluenes

As early as 1942, the concept of a *dehydrobenzene* intermediate—*possibly a zwitterionic analog to free phenylene or a neutral but strained benzo-fused alkyne*—had been proposed by Wittig (originally in German).[35] However the contents of that work were not related in an English language review article until 1962.[36] The consequences of Wittig's discovery of *ortho*-metalation and the incipient concept of an addition-elimination mechanism would eventually become recognized, but it would take many years in the United States for that idea to quicken.



Scheme 5.6. Cine-substitution observed in reaction of sodamide and 4,6-diiododibenzofuran

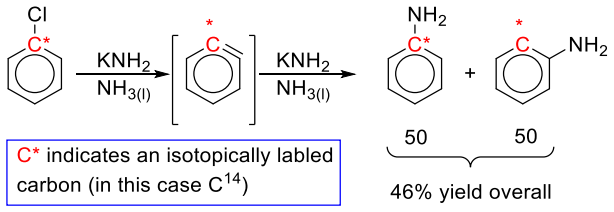
Gilman and Avakain (1945) further explored the so called "*rearrangement chemistry*" by studying the action of sodamide upon 4,6-diiododibenzofuran (Scheme 5.6).[37] They noted amination of C3 and verified their observation by derivatization and comparison chemistry. This was noteworthy since it could not have arisen from the same mechanism typically invoked while explaining nucleophilic aromatic substitution reactions and because hydrolysis of 4,6-diiododibenzofuran afforded the expected 4,6-dihydroxydibenzofuran.

The work of Gilman *et al.* was extended to 4-iododibenzothiophene (1945),[38] α-halogen substituted naphthalenes with lithium diethylamide (1945),[39] *ortho*-bromodimethyl aniline with lithium diethylamide (1946),[40] *para*-bromoanisole and lithium diethylamide (1948),[41] and to triphenyl-(*para*-bromophenyl)silane with lithium diethylamide (1950).[42] Similarly, Bergstrom *et al.* reported substitution at the *ortho* position during reaction of potassium amide with naphthyl halides (1945),[43] as well as the like with halogenated anisoles' reactions with alkali amides (1946).[44]

Benkeser and Severson (1949) related the reaction of sodium amide with *ortho*- and *meta*-chlorotrifluoromethylbenzene wherein the product from each substrate was pure *meta*-trifluoromethylaniline with no *ortho*-substituted aniline recovered.[45] This type of substitution

adjacent to the leaving group is now known as cine-substitution from the Greek work *cine*, to move, and was coined by Bunnet (1951) in a review of nucleophilic aromatic substitution reactions.[46] Cine-substitution would later become considered a hallmark of aryne chemistry.

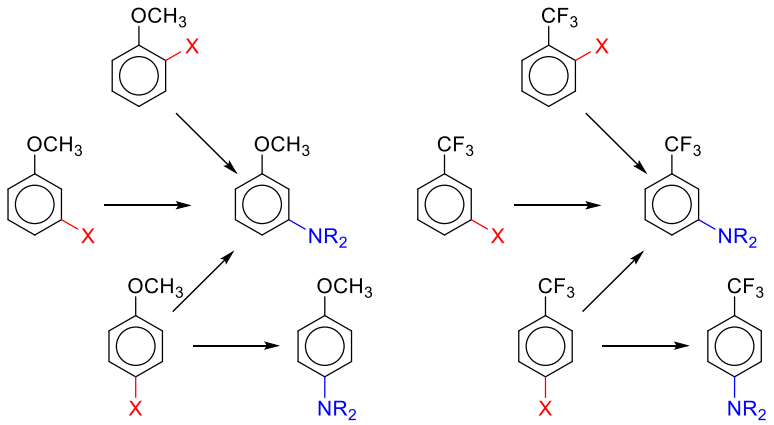
While reflecting in a Journal of Organic Chemistry perspective (2009), the intrepid investigator responsible for breaking the benzyne mechanism wide open wrote:[47] "*It has always been amazing to me that the correct mechanisms for the rearrangements occurring in aminations of aromatic halides were not suggested much earlier. The pattern of rearrangements is at first glance so bizarre that one would expect someone to note right away that the rearranged products are never more than one carbon away from the halogen being displaced, and that, by itself, should trigger expectation of an elimination−addition mechanism. These reactions were called "cine substitutions" by Joseph Bunnett,[46] a plausible mechanism evolved that did not lead to benzyne formation. In hindsight, my stumbling onto the benzyne mechanism, to take a parallel to Newton, was like having a very over-ripe apple fall on my head*". The seminal work relayed by Roberts, Simons, Carlsmith, and Vaughan (1953) illuminated various aspects of cine-substitution.[48] Their proposed mechanism included operation of an elimination-addition step which invoked the transitory existence of an electrically neutral intermediate. That reactive intermediate was termed *benzyne*.



Scheme 5.7. Cine-substitution of isotopically labeled chlorobenzene with the first proposal of benzyne intermediacy

Alkali metal mediated aminations were envisioned as occurring *via* an intermediate wherein the halogenated position and that adjacent to it were—*or could become*—equivalent. The

best structure proposed contained an intact benzene ring with an augmented and weak π-bond normal to the aromatic system as opposed to 1,2-diaminobenzene, or chlorine- and nitrogen-bridged intermediates. Isotopically labeled experiments (illustrated in Scheme 5.7) were consistent with a symmetrical intermediate as the total recovered mass of ^{14}C labeled aniline was made up of circa 50:50 1-^{14}C aniline and 2-^{14}C aniline.



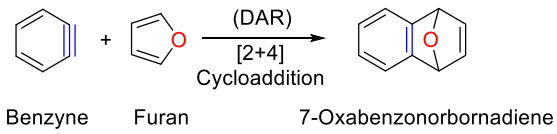
Scheme 5.8. Anomalous reactivity pattern of methoxy and trifluoromethyl substituted halogenated benzenes

Further development of *the benzyne mechanism* was reported by Roberts *et al.* (1956) in back to back publications[49, 50] and expanded on the work of Wittig *et al*. Particularly, the prompt for their investigation was anomalous selectivity for *meta*-substituted products from both *ortho*- and *meta*-halogenated anisole whereas formation of both *meta*- and *para*- substitution patterns from *para*-halogenated anisole was observed. Remarkably, the exact same regioselective process was replicated using halogenated (trifluoromethyl)benzene and has been illustrated in Scheme 5.8.

So, it was known to the Roberts team that despite disparate directing activity in electrophilic aromatic substitution reactions, halo-anisoles and halo-α,α,α,-trifluotoluenes behaved the same in alkali metal mediated amination reactions. It was specifically noted that: (1) the reactions were fast (they proceeded in respectable fashion at -33 °C in liquid ammonia), (2) the nucleophile was never observed farther than one carbon away from where the halide had started,

(3) the products (when isolated) could not be isomerized by repeated exposure to the reaction conditions, (4) arenes lacking a halogen with a proton in the ortho position were unreactive.[49, 50] In line with these results, a test of degeneracy between the leaving group and *ortho*-positions has become a telling diagnostic for identifying the intermediacy of benzyne.

5.1.1.3. First Benzyne Diels-Alder Reaction



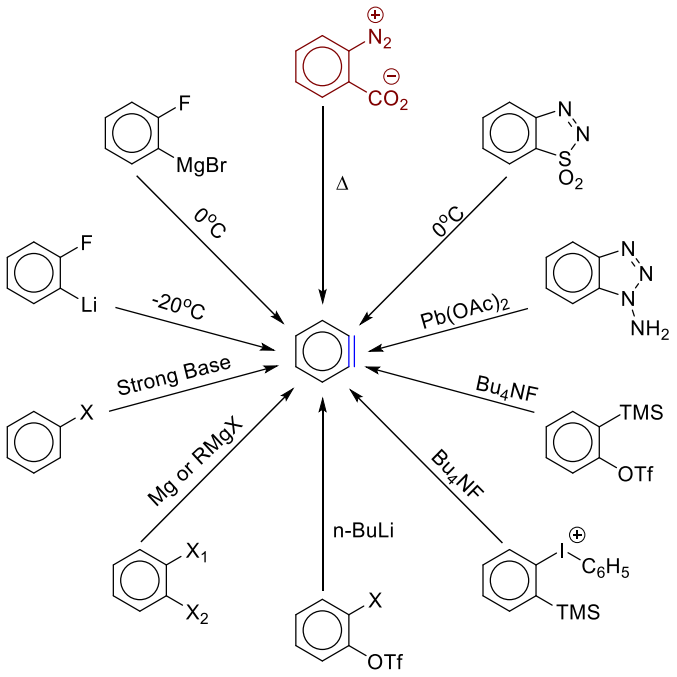
Scheme 5.9. Furan-trapping of benzyne

Wittig and Pohmer (1956) reported on the intermediacy of *dehydrobenzol* (1,2-dehydrobenzene or benzyne) and its dienophilicity.[51] Furan's ability to trap the arynic intermediate in the form of 1,4-dihydronaphthalene-1,4-endoxide (7-oxabenzonorbornadiene) (Scheme 5.9) would later become powerful tool for synthesis and clearly indicated the presence of a neutral intermediate consistent with but independent to the isotopic labeling experiments of Roberts *et al*. The trapping of such strained intermediates by cycloaddition would also become integral to the study of the strain-driven Diels-Alder reaction.[7]

5.1.1.4. General Benzyne Generation

A most useful review of benzyne preparation was published by Kitamura (2010).[12] Upon recognition of benzyne intermediacy as a viable explanation for the many cases of cine-substitution, focus upon its generation and further study of its reactivity dominated the latter 1950's and 1960's. Adapted from the 2012 benzyne review prepared by Tadross and Stoltz,[13] Scheme 5.10 illustrates many strategic variants employed in the generation of 1,2-dehydrobenzene. The general strategy is to prepare a structure wherein the parent aromatic ring contains a negative dipole adjacent to a positive dipole which ripens the system for aryne formation *via* elimination

mechanism. For example, upon generation of an anion by deprotonation adjacent to the positive dipole, the system will spontaneously eliminate a leaving group to afford 1,2-dehydrobenzne when possible.



Scheme 5.10. Various methods for preparing benzyne
Adapted with permission from Tadross, P. M.; Stoltz, B. M., A Comprehensive History of Arynes in Natural Product Total Synthesis. Chem. Rev. 2012, 112 (6), 3550–3577. Copyright 2012 American Chemical Society.

This was the method which first illuminated transient existence of dehydrobenzenes. When sodium was able to exchange with one of the aryl halides under study and the aryl-sodium went on to deprotonate another aryl halide affording what was then termed free phenylene. The modern version of this reaction utilizes ortho lithiation of triflate substituted arenes to spontaneously generate arynes. This method is clearly limited due to the harshness of the requisite conditions and the occurrence of non-exclusive cine-substitution when the aryne is intercepted by the base-*cum*-nucleophile.

Wittig (1965) related one of the first controlled methods for generating 1,2-dehydrobenzene.[36] Starting from 1-halo-2-fluoro arenes—*Wittig found bromo-fluoro systems afforded 1,2-dehydrobezene with greatest utility*—metal halogen exchange leads to the perfect storm of aryne formation: a carbanion adjacent to a leaving group. The leaving group must be fluorine in this case as other halogens will undergo metal halogen exchange and afford a dianion. Clearly this method is limited by the extremely basic media of the reaction. Wittig and Hoffmann (1962) demonstrated the reversibility of 1,2-dehydrobenzene formation in organometallic reaction media.[52]

Himeshima, Sonoda, and Kobayashi (1983) prepared benzyne from *o*-(trimethyl)silylphenyl triflate (also known as (trimethylsilyl)phenyl trifluoromethanesulfonate).[53] The fluoride induced desilylation with consequent expulsion of fluoride to afford benzyne follows the generalized strategy while surmounting the barrier imposed by strongly basic media. In this technology, the fluoride anion attacks the silicon (driven by the enthalpy of formation for the silico-fluoro bond), forming an anion which leads to essentially simultaneous elimination of the triflate faster than the arene-anion can be protonated. Widespread use of desilylation technology is owed to its mild conditions (neutral pH and low temperatures) which provide extreme control over the rate of aryne formation (dependent upon fluoride concentration).

For example, this precursor has lent itself to applications in the synthesis of triazoles from azides by click chemistry as described by Shi, Waldo, Chen, and Larock (2008).[54] The paradigm was extended to the synthesis of indolyne by Bronner, Bahnck, and Garg (2009).[55] The traditional procedure has been modified and optimized to afford this "coveted benzyne precursor" in less than four h of reaction time by Atkinson, Sperry, and Brimble (2009).[56] The routine synthesis of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate was significantly improved by Bronner and Garg

(2009) when they incorporated a directed *ortho*-metalation strategy into its synthesis.[57] Crossley, Kirkham, and Browne (2010) described the development of 2-(trimethylsilyl)iodobenzene as a benzyne precursor.[58] Suh and Chenoweth (2016) studied the side reactions between 2-(trimethylsilyl)phenyl trifluoromethanesulfonate and the solvents commonly employed in its reactions: THF and acetonitrile.[59]

5.1.2. Renewable Benzyne by Thermolysis (Mild Pyrolysis)

Pyrolysis (>400 °C) of phthalic anhydride was studied by Fields and Meyerson (1965).[60] The technique was developed into a novel route for the synthesis of biphenyls by Brown, Gardner, McOmie, and Solly (1966).[61] Meyerson and Fields (1966) developed a method for benzyne generation from pyrolysis (690 °C) of *o*-sulphobenzoic anhydride.[62] Friedman and Lindow (1968) further investigated the reaction of benzyne with benzene at elevated temperatures by the pyrolysis of phthalic anhydride (690 °C).[63] The major product of that reaction was naphthalene.

5.1.2.1. Benzyne from Diazotized Anthranilic Acid

The diazotization of the anthranilic acid by the action of organic nitrites leads to the formation of benzenediazonium-2-carboxylate which exists primarily in zwitterionic form also referred to as an inner salt.[64] Upon heating above 40 °C the inner salt spontaneously underwent decarboxylation with simultaneous dediazoniation to afford benzyne in solution as reported by Stiles and Miller (1960).[65] Compared to all earlier methods which had been based upon organometallic methods, this route toward aryne intermediates employs acidic and even neutral conditions. This development was instrumental in expanding the scope of aryne chemistry. They reported characterization of the isolated inner salt by FTIR, arylation of benzoic acids, and trapping with furan.

The danger of explosion when handling dried benzenediazonium-2-carboxylate was noted by the Stiles and Miller (1960),[65] highlighted by Bunnet (1961)[5] and elaborated upon by Mich, Nienhouse, Farino, and Tufariello (1968).[66] Sullivan (1971) described an incident wherein benzenediazonium-2-carboxylate hydrochloride—*which was purported to be a safe alternative to the inner salt*—was detonated following storage in a refrigerator for five days.[67] It seems likely that some crystalline forms are more shock-sensitive than others, and that the material may eliminate stabilizing hydrogen chloride to form the inner salt even at low temperature.

Friedman and Logullo (1963) circumnavigated this hazard by the *in situ* preparation of benzenediazonium-2-carboxylate—*and thereby benzyne*—from slow addition of solubilized anthranilic acid to a refluxing solution of benzyne acceptor and an alkyl nitrite.[29] Their modified procedure avoids isolating the shock sensitive inner salt. In the presence of excess furan, they were able to isolate 7-oxabenzonorbornadiene in 88% yield. By employing 5-bromoanthranilic acid and anthracene as benzyne trap, 2-bromo-triptycene was isolated in 75% yield.

Klanderman (1965) utilized the method of Friedman and Logullo to study the reactions of benzyne and substituted anthracenes.[26] In an extremely important observation, Klanderman observed a preference for benzyne trapping by the more electron-rich diene system. Heaney and Marples (1968) modified this method to prepare tetrachlorobenzyne for preparation of modified triptycenes.[30]

Gompper, Seybold, and Schmolke (1968) investigated the synchrony of benzyne genesis from benzenediazonium-2-carboxylate.[68] Their mechanistic investigation included considering both synchronous (concerted) and asynchronous (stepwise) elimination of nitrogen and carbon dioxide gases. Their study entailed the room temperature reaction of benzenediazonium-2-carboxylate in mixtures of furan, acetonitrile, and H_2O or MeOH. In both cases 7-

oxabenzonorbornadiene was the major product, but the nature of side products suggested the intermediacy of initial dediazoniation followed by subsequent decarboxylation. In aqueous reaction, salicylic acid was the major side product while phenol was not detected. In methanolic reaction mixtures, methyl salicylate was the major side product and small amounts of anisole were detected. While their experiments in no way excluded the operation of synchronous benzyne formation from benzenediazonium-2-carboxylate, the functionality of an asynchronous mechanism was strongly suggested by dependence of the product distribution upon H_2O or MeOH concentration.

Freidman and Logullo (1969) published a summary of their investigations into benzyne generation from benzenediazonium-2-carboxylates generated *in situ*.[69] Browne, Wright, Deadman, Dunnage, Baxendale, Turner, and Ley (2002) developed the continuous production and thermolysis of benzenediazonium-2-carboxylate in an on-line mass spectrometry flow system. This engineering feat resulted in the optimization of parameters which increased the efficiency of benzyne production and allowed for probing of side reactions while completely mitigating the hazardous handling of shock-sensitive energetic intermediates.[70]

Miller and Stiles (1963) reported on the reaction of benzyne produced from thermolysis of benzenediazonium-2-carboxylate in benzene or naphthalene suspension.[71] Thermolysis is the modern term for what was dubbed "*mild pyrolysis (30–60 °C)*" and like the terminological demarcation between oligomer and polymer there is considerable overlap in the usage of thermolysis and pyrolysis. In an article with the same submission date, Stiles, Miller, and Burckhardt elaborated on the reactions of benzyne intermediates in non-basic media by employing thermolysis of benzenediazonium-2-carboxylate.[72] The term thermolysis will be used to describe "*mild pyrolysis*" throughout this work. Their work culminated in the preparation of iodo-, fluoro-

, and nitrobenzynes from their parent anthranilic acids. They noted regiochemical preferences dictated by the inductive effect of substituent groups upon benzyne.

Buxton, Fensome, Heaney, and Kenneth (1995) reinvestigated the stepwise decomposition of benzenediazonium-2-carboxylate.[73] They concluded that multiple mechanism were likely occurring simultaneously and that benzyne formation was favored by halogenated solvents since any reactive free radicals in solution tended to facilitate radical dediazoniation. Under those conditions benzyne formation occurred by concerted dediazo-decarboxylation. The addition of silver ion to a reaction mixture containing wet furan dramatically altered the amount of phenol observed in the product mixture. It seems likely that benzyne rapidly added hydrated silver which increased its electrophilicity at the expense of its dienophilicity since the total isolated 7-oxabenzonorbornadiene was reduced.

5.1.2.2. Alternative Thermolysis Techniques

Le Goff (1962) reported the aprotic generation of benzyne from thermolysis of bench-stable diphenyliodonium-2-carboxylate.[74] Diphenyliodonium-2-carboxylate is a considerably more stable inner salt (melting point is greater than 220 °C) compared with benzenediazonium-2-carboxylate and thus also escaped hazards associated with the shock sensitivity of benznediazondium-2-carboxylate. The synthesis of diphenyliodonium-2-carboxylate begins with 2-iodobenzoic acid which is about one hundred times more expensive than anthranilic acid from commercial sources. Anthranilic acid can actually serve as the starting material for preparation of 2-iodobenzoic acid *via* Sandmeyer chemistry.

The iodine atom must be oxidized (with Oxone also known as potassium peroxymonosulfate) in concentrated sulfuric acid and quenched with benzene. The preparation must then be worked up with base to neutralize the molecule. Logoff noted that the inner salt is

somewhat soluble in chloroform and can also be recrystallized from H_2O. Gavina, Luis, Costero, and Gil (1986) adopted this procedure for the preparation of polymer supported benzyne while studying the lifetime of such intermediates.[75]

Baigrie, Cadogan, Mitchell, Robertson, and Sharp (1972) reported a simple, convenient, and direct conversion of anilines and anilides into arynes.[76] Nakayama, Yoshida, and Simamura (1973) described a reaction of benzyne generated from 1-(2-Carboxyphenyl)-3,3-dimethyltriazene with benzaldehyde and some other carbonyl compounds.[77] Fleming and Mah (1976) described the preparation of benzyne from phenyl benzenesulfonate.[78]

5.1.2.3. Potential for Benzyne's Biorenewability

Preparation of benzyne from the decomposition of diazotized anthranilic acid provides the key to accessing a premier reactive intermediate from renewable sources. The synthetic route towards that platform chemical [anthranilic acid] entails reaction of petroleum-derived phthalic anhydride with ammonia, followed by oxidative rearrangement mediated by the action of hypochlorite.[79-82] One of the most promising routes towards renewable terephthalic acid involves the thermal rearrangement of phthalic anhydride which was in turn prepared by an aromatic upgrading strategy from the products of furfural biorefinery: furan and maleic anhydride by cycloaddition.[83-86] This strategy has been employed in multiple past research endeavors for the preparation of highly substituted benzynes,[87] or the preparation of benzynes which would not tolerate the harsh conditions of organometallic reaction media.[30, 88]

5.1.3. Benzyne Structure & Reactivity

Due to the development of benzyne generation techniques in different media under vastly disparate conditions, Huisgen and Knorr (1963) asked "*are the benzynes from various provenance identical*?".[89] Their conclusion was that the benzyne generated from various methods appeared to

have the same reactivity. After examining many more benzyne generating reactions, Klanderman and Criswell (1969) responded to the question by stating "*for a number of precursors the benzyne formed has identical properties, but that it may appear to be different due to the nature of the reactants and the reaction conditions*".[90]

The biradical behavior of 1,2-benzyne has been investigated in relation to 1,3- and 1,4-dehydrobenzenes which cannot form traditional bonds. Understandably, 1,2-benzyne was found by Sakai (2005) to have the greatest aromaticity by an index of relative aromaticity.[19, 91-93] Wilhite and Whitten (1973) conclusively predicted a singlet ground state for *o*-benzyne by *ab initio* self-consistent-field and configuration-interaction methods.[94] In his compendium on the subject of 1,2-dehydrobenzene, Reinhard Hoffmann describes three major classes of aryne reactions.[8] These are: (1) radical reactions, (2) polar additions, and (3) nonpolar additions. As illustrated in the early case of Wurtz-Fittig coupling, benzyne is reactive radical acceptor.[20]

5.1.3.1. Benzyne from Photolysis

Photolysis of phthaloyl peroxide and of bis-*o*-iodophenylmercury was reported to afford 1,2-dehydrobenene by Wittig and Ebel (1961).[95] While these synthetic routes were expected to afford a reactive intermediate with biradical character such as free phenylene, 1,2-dehydrobenzene prepared by photolysis was trapped by tetracyclone in a Diels-Alder reaction. Maitland and DeCamp (1971) extended the study of photolytic generation benzyne from phthaloyl peroxide to include acetone cosolvent for the purpose of solubilization.[96]

They hoped to detect reaction products from either a triplet or singlet excited state. Discordantly, their system reacted as if it had the same symmetry as ground state benzyne prepared by traditional methods. The reactions were stereospecific for [4+2] cycloadditions, which indicated a concerted reaction. Whereas there was no stereospecificity in [2+2] cycloadditions,

which indicated a nonconcerted reaction mechanism and excluded operation of a thermally forbidden synchronous [2+2] cycloaddition. The thermal pathway of cycloadditions formally forbids synchronous [2+2] cycloadditions from the ground state while those proceeding from an excited state as is the case for photochemical reactions are allowed.

Polar additions to 1,2-dehydrobenzene encompass all of the early work in which alkali amides were used to determine the intermediacy of arynes. These reactions are rather underrepresented until modern synthetic methodologies introduced regioselective transformations which could overcome the equalization of positions one and two of 1,2-dehydrobenzene's structure. All polar reactions in question rely on the easy polarization and therefore ready action of arynes as electrophiles. Even weak nucleophiles such as tertiary alcohols have been used to attack the strained unsaturation.[72] The term polar additions must also include dipolar cycloadditions, towards which 1,2-dehydrobenzene is extremely reactive

Nonpolar additions to 1,2-dehydrobenzne are the major component of all reported aryne chemistry. The explanation of this phenomenon lies in appreciating the extreme dienophilicity of arynes due to the weakness of the bonding character of the highest occupied molecular orbital, and the relief of ring strain when the aryne is destroyed. In the absence of dienophile traps or nucleophiles, 1,2-dehdrobenzne will readily trap itself to form the highly strained but isolable biphenylene (which can be isomerized into biphenyl).

5.1.3.2. Strain Distortions Explain the Reactivity of Benzyne

Kukolich, McCarthy, and Thaddeus (2004) determined the molecular structure of *o*-benzyne by microwave spectroscopy (Fig. 5.3).[97] Their results were fairly consistent with theoretical parameters derived by Moskaleva, Madde, and Lin (1999) by high level molecular-orbital calculations.[98] The structure of benzyne contains a bond between C1-C2 which in slightly

elongated for a triple bond (~1.20 Å) but clearly shorter than typical carbon–carbon double bond (~1.34 Å) and much shorter than the antipodal bond between C4-C5 (1.40 Å). The C1-C2-C3 dihedral angle (126°) appears wider than the ideal 120° (found in benzene) at the expense of the C2-C3-C4 dihedral angle (111°) which is significantly constricted.

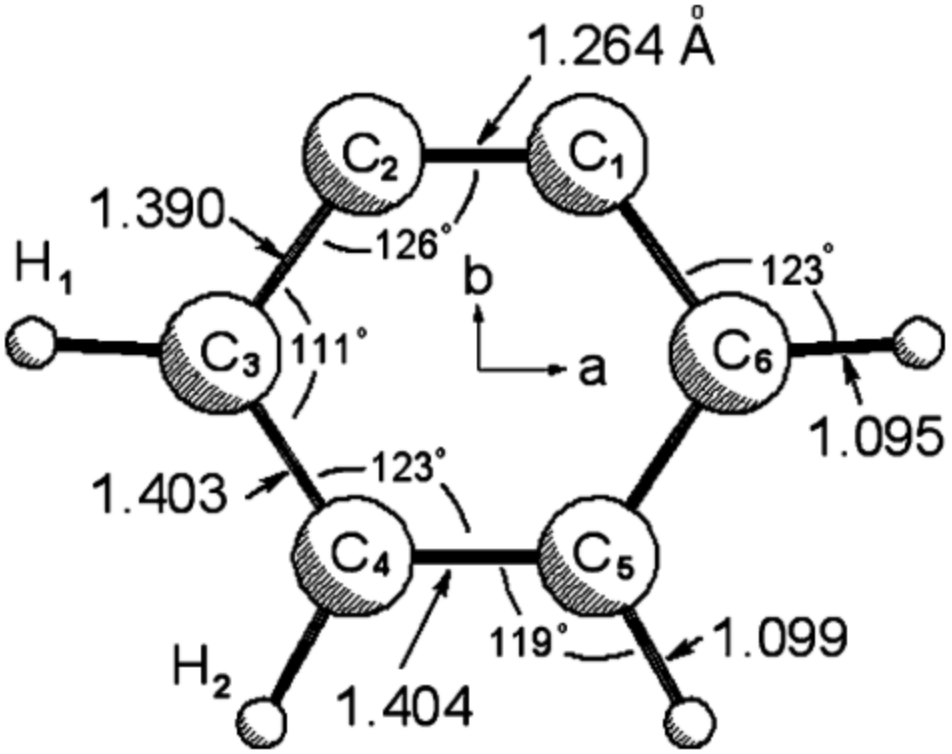


Fig. 5.3. Structure ortho-benzyne, showing the atom-numbering scheme and many of the measured structural parameters
Reprinted with permission from Kukolich, S. G.; McCarthy, M. C.; Thaddeus, P., Molecular Structure of *o*-Benzyne from Microwave Measurements. J. Phys. Chem. A **2004**, 108 (14), 2645–2651. Copyright 2004 American Chemical Society.

The reactivity of benzyne can be traced to its abnormal π-bond. Wittig (1962) wrote in reference to small rings with triple bonds:[7] "*failure to isolate these compounds is a consequence of the extremely high strain exerted on the ring by sp-hybridization of the σ-bonds*," and so the structure of benzyne is dominated by a struggle between the orthogonal π-bond as it deforms the aromatic system to approach a typical *sp*-bond (in dihedral angles and interatomic distances).

Conversely, the aromatic system would be at a minimum energy only when all centers of the system were sp^2-hybridized. The stabilization energy of the aromatic system mostly prevails, leading to a diffuse highest occupied molecular orbital (HOMO) which is only weakly bonding in character. Being that the bond is quite weak, it is easily polarized and voraciously seeks out partners for pericyclic reactions as a dienophile or for arylations as an electrophile. While the HOMO is comparable with an unstrained alkyne, the strain imparted by the fused aromatic system of an aryne significantly perturbs the lowest unoccupied molecular orbital (LUMO) which can be used to rationalize the exemplary dienophilicity and which has been realized by to its widespread employment in cycloadditions.

Rondan, Domelsmith, Houk, Bowne, and Levin (1979) reported their exploration of the relative rates of electron-rich and electron-deficient alkene cycloadditions with benzyne.[2] They concluded the enhanced electrophilicity of benzene relative to 2-butyne was a consequence of alkyne bending distortions (Fig. 5.4). By modeling the HOMO–LUMO energy gap of 2-butyne as it was constrained in sequentially more distorted forms gaining a resemblance to the bond-lengths and dihedral angles found in benzyne, they predicted a decrease in the gap energy primarily as a consequence of LUMO perturbation. While the HOMO of their distorted 2-butyne was perturbed slightly—*it was actually calculated to be higher than the HOMO of benzyne*—the effect was minor in comparison to the lowering of the LUMO.

The abnormal reactivity of benzyne is therefore due to significant distortion strain.[2, 7, 99] Rondan *et al.* reported "*experimental rates of [2+2] cycloadditions of a series of alkenes to benzyne, which reinforce the generalization that the electrophilic reactivity of benzyne is enhanced more than the nucleophilic reactivity as compared to that of unstrained acetylenes*" (1979).[2] The combined effect is a system with considerable nucleophilicity on par or slightly above that of 2-

butyne, and with extremely enhanced electrophilicity much greater than that of 2-butyne. That enhanced electrophilicity translates directly into superior dienophilicity and ready reaction by normal electron-demand Diels-Alder reactions.[26, 100]

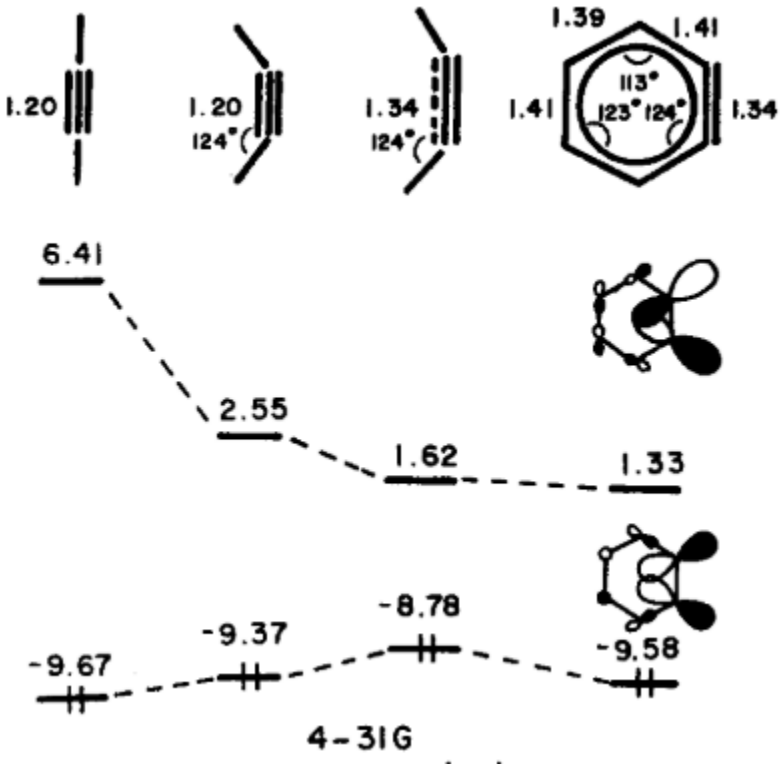


Fig. 5.4. Frontier orbitals and energies (eV) for 2-butyne models and benzyne
Taken with permission from Rondan et. al., Tetrahedron Letters, **1979**, 20 (35), 3237–3240.
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The strain-driven dienophilicity of small carbocyclic alkynes (such as cycloheptyne, cyclohexyne, and cyclopentyne) was critical to identification of their short-lived existences as they could be trapped irreversibly by 2,5-diphenyl-3,4-benzofuran (2,5-diphenylisobenzofuran).[7] In such a series of cycloalkynes, the yield of Diels-Alder adducts decreases with decreasing ring size which indicates access to a greater number of competitive side reactions. As the strain-energy contained in a molecule increases, the life-span of the intermediate and therefore likelihood of

survival till [2+4] adduction decreases. The notably longer lifetime of arynes greatly tempers them for cycloaddition.

In cases of reactions with substituted arynes, the *Aryne Distortion Model* described by Medina, Mackey, Garg, and Houk is best suited for predicting and rationalization of the reactions wherein "*common explanations, such as steric and electronic factors, do not suffice*" (2014).[1] The model predicts nucleophilic attack at the side of the arynic bond which contains a dihedral angle closest to linear. In the cases of substituents with powerful inductive effects (such as fluoro or methoxy) reacting with benzylazide in [3+2] dipolar cycloadditions, extreme regioselectivities are observed which cannot be completely explained by other models.

5.1.3.3. Quantification of Benzyne's Electrophilicity

Huisgen and Sauer (1960) wrote that "*intermediate arynes are strong electrophilic agents that can be considered as the most potent arylating agents after the aryl cations*".[101] Benzyne has been described as a "*soft*" electrophile by Klanderman (1965).[26] Gavina and Cosero (1986) investigated the substituent effect upon dehydrobenzene's trapping by polymer-supported dienes.[75] Substituted benzynes were generated from polymer-bound diaryliodonium-2-carboxylate precursors. Solution lifetimes were assessed.

Nathel, Morrill, Mayr and Garg asked: "*Just how electrophilic is benzyne*?" (2016).[102] They relied on a diffusion clock-method to determine electrophilicity parameters for several substituted benzynes and the parent compound "*for additions of nucleophiles to the triple bond that proceed with rate-determining formation of one new σ-bond*": -1 for benzyne, 3-methoxybenzyne, and 6,7-indolyne while 3-fluorobenzyne was determined to be 5 orders of magnitude greater than benzyne (electrophilicity parameter was ~4)! Whereas rate constants for cycloadditions or ene-reactions can analogously be determined by the diffusion-clock method described herein, these rate

constants will not follow the equation: log k(20 °C) =sN(N+ E), a prerequisite for the use of the electrophilicity parameters E. This was a significant advancement since the elusive and fleeting nature of aryne intermediates had always precluded evaluation and comparison with classical electrophiles on a logarithmic scale (Fig. 5.5).

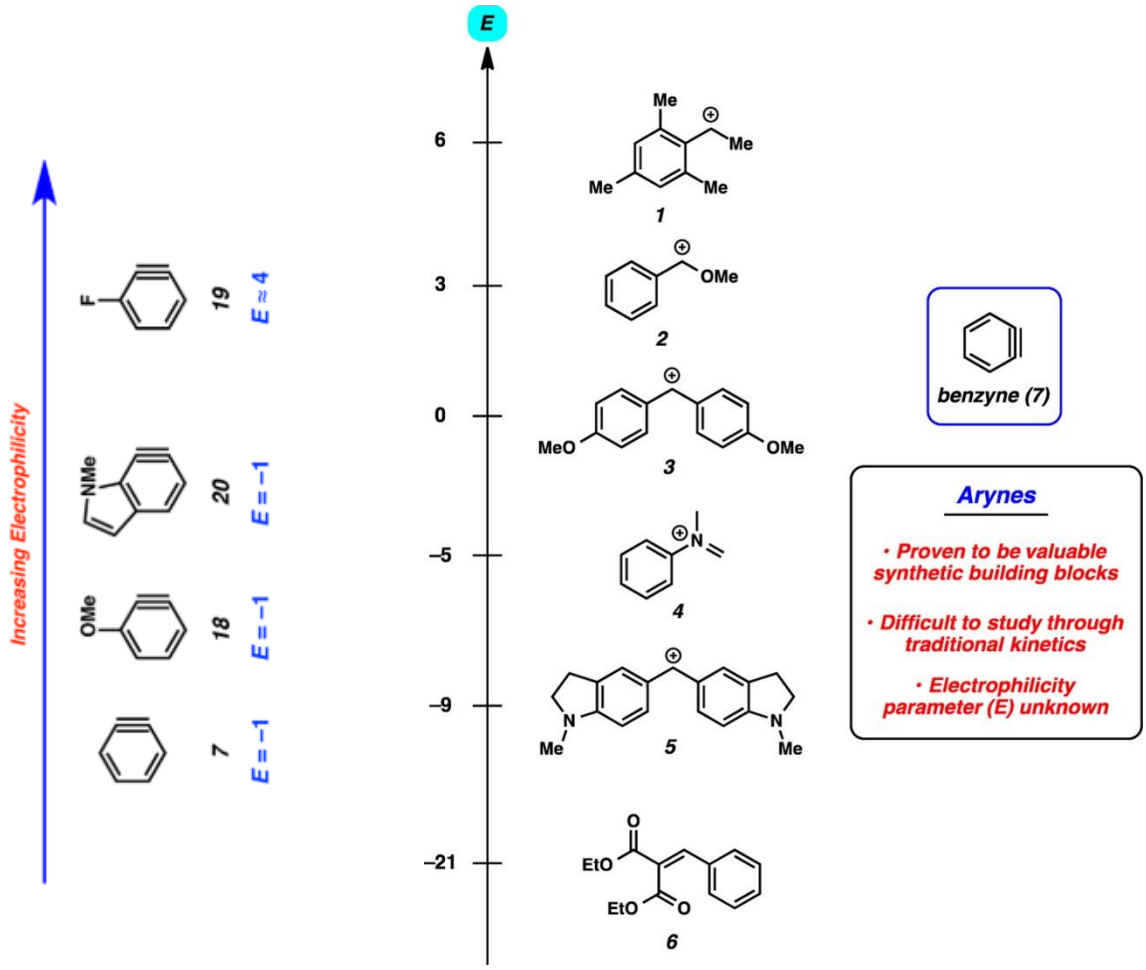


Fig. 5.5. Sampling of the benzhydrylium-based electrophilicity scale showing established electrophiles and benzyne
Reprinted with permission from Fine Nathel, N. F.; Morrill, L. A.; Mayr, H.; Garg, N. K., Quantification of the Electrophilicity of Benzyne and Related Intermediates. J. Am. Chem. Soc. **2016**, 138 (33), 10402–10405. Copyright 2016 American Chemical Society.

To quote Rondan *et al.*: "*Benzyne reacts more rapidly with electron-rich alkenes than electron-deficient alkenes, a result of the abnormally low energy LUMO of benzyne, which results from the acetylene bending enforced by the benzyne geometry*"(1979).[2] They utilized the method

described by Dittmer and Whitman for benzyne generation.[103] Relative reactivities of various mono- and 1,1-disubstituted olefins with benzyne without stereospecificity were experimentally determined. In reference to their findings the authors noted: "*there seems to be a trend toward higher reactivity with decreasing IP [ionization potential] (i.e., increasing nucleophilicity) of the alkene, and, most importantly, very electron-deficient alkenes cannot compete with the dimerization of benzyne*" (presumably into biphenylene).[2]

The reaction of benzyne—*prepared from thermolysis of benzenediazonium-2-carboxylate*—in phenylacetylene. and acetylenic compounds was reported by Stiles, Burckhardt, and Haag (1962) but no [2+2] cycloadducts were observed.[104] Instead, they isolated of 5,6-diphenyldibenzo[*ae*]cycloöctatetraene and phenanthrene (29% and 8% yield respectively). The major product was posited to arise from dimerization of benzocyclobutadienes formed from the [2+2] cycloaddition of benzyne and electron-rich alkyne. Surprisingly, "ethoxyacetylene reacted with benzyne to produce a 37% yield of 2-ethoxyphenylacetylene".[104] They determined the reaction to be nonstereospecific.

Gassman and Benecke (1969) elegantly collected "evidence for the formation of diradical intermediates in the [2+2] addition of benzyne to olefins" during the reaction of benzenediazondium-2-carboxylate with both *trans*- and *cis*cyclooctene.[105] Benzyne was trapped by *trans*cyclooctene to afford benzocyclobutene products but not in stereospecific fashion. Notably missing, no products of the Alder-ene reaction were observed. Conversely, benzyne was trapped by *cis*cyclooctene primarily as the ene adduct. Modifying the polarity of the reaction medium did not alter the *cis*- and *trans*benzocyclobutene product distribution which strongly indicated against a dipolar intermediate.

Leitich (1980) elaborated the work of Gassman and Benecke by examining the relative reaction rates of benzyne—*prepared by the thermolysis of benzenediazonium-2-carboxylate*—in aprotic solvent at 50 degrees C. with *cis,trans*- and *cis,cis*-1,5-cyclooctadiene, *trans*- and *cis*-cyclooctene and supported the proposed diradical intermediates.[106] Jones and Levin (1969) wrote "orbital symmetry considerations predict that the symmetric benzyne will undergo a nonconcerted [2+2] cycloaddition while the [2+4] reaction should be stereospecific" and tested that hypothesis by reacting benzyne with both *cis*- and *trans*-1,2-dichloroethylene with as well as with the dimethyl ester of *trans,trans*-muconic acid.[107]

Satoshi and Fukui (1973) applied *frontier molecular orbital theory*[108] to the [2+2] cycloadditions of benzyne. They were inspired by similarities between singlet oxygen and ethylene which do not occur *via* a traditional concerted cycloaddition process.[109] In their novel mechanism, the benzyne molecule is oriented perpendicular to the plane of ethylene with maximum overlap between ethylene's HOMO and the symmetry allowed lobe of benzyne's LUMO.

Dittmer and Whitman attempted the preparation of adducts from thiobenzophenone and benzyne by the thermolysis of benzenediazonium-2-carboxylate (1969); benzenediazonium-2-carboxylate was in turn generated in situ from reaction of benzenediazonium-2-carboxylate hydrochloride and propylene oxide in refluxing 1,2-dichloroethane.[103] Instead they observed products derived from dediazoniation and subsequent capture of the thiocarbonyl as 2,2-diphenyl-3,1-benzoxathian-4-one. They interpreted their result as supportive of the stepwise generation of benzyne from benzenediazonium-2-carboxylate.[68]

5.1.3.4. Augmenting the Electrophilicity of Benzyne by Complexation to Lewis Acids

Friedman (1967) described the effect of silver ion on the reaction between benzyne and benzene.[110] He noted that the distribution of products in the reaction between benzyne and benzene

differed vastly depending on whether benzyne came from thermolysis of benzenediazonium-2-carboxylate prepared *in situ*[29] or from the isolated inner salt which had been liberated of chloride by treatment with silver oxide.[71, 72] It was supposed by Friedman that residual silver ion contamination could be catalytically modifying the reactivity of benzyne through the formation of a silver(I)-benzyne complex with enhanced electrophilicity. Other cations (thallium(I), copper(I), copper(II), dimercury(II), and mercury(II)) completely failed to modify the reactivity of benzyne.

Churchill and Youngs (1979) have been able to isolate organometallic complexes of benzyne and acquire crystallographic data.[111] They observed a small decrease in the inter atomic distance between C1 and C2 in benzyne isolated as a tantalum complex. This observation supports extension of the Robinson benzene formalism—*the illustration of a benzene ring as a hexagon enclosing a circle indicating complete delocalization of pi-electrons*—to the depiction of arynes and extends the possibility of benzyne reactivity modulation by complexation.

5.2. Biorenewable 7-Oxabenzonorbornadienes

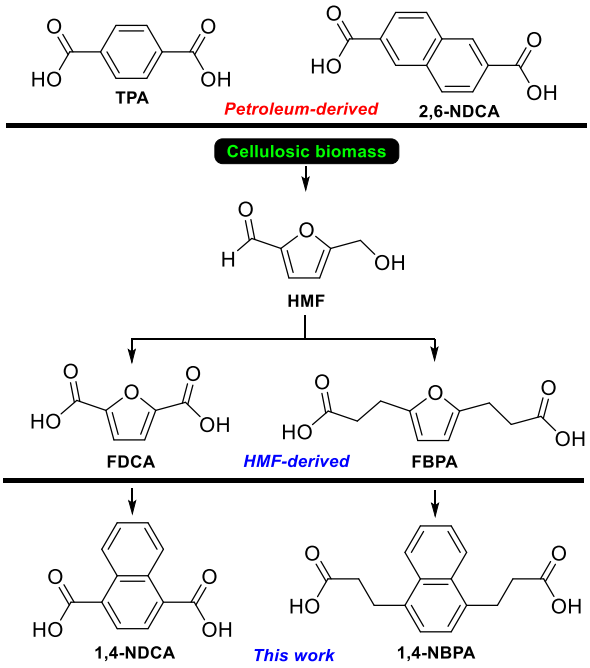
Woodward (1942) described the "*usual case of the Diels-Alder reaction*" which "*involves, on the one hand, a substance, e. g., a diene of relatively low ionization potential and, on the other, a molecule of high electron affinity, e. g., an α,β-unsaturated carbonyl compound*" in a short note.[100] This note was released before the concerted synchrony of many cycloadditions had been established[112] as evidenced by description of the Diels-Alder reaction containing a reversibly formed "*intermolecular semi-polar bond*" substantiated by many observed phenomena. Defining the unique mechanistic aspects of [4+2] cycloaddition as understood at that time illustrated the shifting focus towards a modern understanding of organic chemistry in which benzyne and the Diels-Alder reaction would become finely intertwined.

Benzyne reactions with electron-rich furans have been reported in the literature[113-117] as have their conversion to naphthalenes by various routes. In contrast, there are only a few examples of reactions between benzyne and heavily oxidized furans.[118] Benzyne has been shown to trap even furancarboxylate monoesters.[119] Biomass-derived 5-(hydroxymethyl)-2-furancarboxyaldehyde along with derivatives of FDCA[120] have potential for redox-efficient transformation into benzenoids *via* cycloaddition followed by aromatization. However, the electronic demands of the Diels-Alder reaction have led to an impasse which has been met mainly by redox-inefficient use of alkyl-substituted furans and in some cases by use of alkoxyfuranoates prepared *via* chemoselective oxidation of HMF;[121, 122] no direct synthesis of terephthalic acid has been reported from FDCA or its esters.

Pacheco and Davis (2014) explored the electronic limitations of a cycloaddition strategy—*employing ethylene and derivatives of HMF*—at varying oxidation states. The rate of adduction between ethylene and derivatives of FDCA were deemed not synthetically useful even at 200 °C (Scheme. 5.11).[121] Pacheco, Labinger, Sessions, and Davis (2015) successfully elaborated upon those findings by examining reactions between ethylene and compounds of intermediate oxidation state between HMF and dimethyl 2,5-furandicarboxylate: compounds such as methyl 5-methyl-2-furancarboxylate and methyl 5-(methoxymethyl)-2-furancarboxylate.[122]

Ogunjobi, Farmer, McElroy, Breeden, Macquarrie, Thornthwaite, and Clark (2019) directly prepared diethyl terephthalate from the reaction of diethyl 2,5-furandicarboxylate in one reactor over a montmorillonite clay into which had been exchanged aluminium (III) cations.[123] Their work was based on a detailed analysis of the patent literature and employed high pressures of ethylene gas and high reaction temperatures to overcome the low yields previously reported. Those low yields had been attributed to operation of an inverse electron demand Diels-Alder

cycloaddition mechanism. This reaction between an electron-deficient diene and mildly electron-rich dienophile has been conjectured to occur by an inverse electron demand mechanism wherein the HOMO of ethylene reacted with the LUMO of diethyl furan-2,5-dicarboxylate. The high temperatures employed in their reaction were not to surmount any barrier to the highly reversible inverse electron-demand Diels-Alder reaction, but instead were to facilitate ring-opening and subsequent dehydration over the aluminium (III) montmorillonite catalyst surface while thereby driving the reaction towards completion by the law of mass action.



Scheme 5.11. Strategies for aromatic upgrading of cellulosic biomass derived platform chemicals FDCA and FBPA

Understanding the superior dienophilicity of benzyne compared with either ethylene or acetylene, a cycloaddition strategy was devised which would surmount the normal electron demand reaction barrier with dimethyl 2,5-furandicarboxylate in a direct access strategy to afford dimethyl naphthalene-1,4-dicarboxylate with 7-oxabenzonorbornadienes and 7-oxabenzonorbornenes as intermediates (Scheme 5.11). This strategy will allow complete

realization of the potential latent in all furanic compounds and contribute to an acceleration of research into the novel structures and chemistries available from biorenewable precursors.

Although the benzyne Diels-Alder reaction with furan-dienes was established over 60 years ago by Wittig and Pohmer (1956),[51] excluding our own works, there have been no reported preparations of dimethyl 7-oxabenzonorbornadienyl-1,4-dicarboxylate from dimethyl 2,5-furandicarboxylate or any other source. An attempt by Wong (1989) to adduct dimethyl 2,5-furandicarboxylate with dibenzofused cycloocteneyne was unsuccessful.[124]

The resistance to catalytic hydrogenation considered a hallmark of aromaticity and the reactivity of ring-strained olefins combine to make chemoselective reactions with benzyne Diels-Alder adducts as substrates highly efficient. For example, the preparation of dimethyl 7-oxabenzonorbornene-1,4-dicarboxylate with greater than 95% isolated yield and catalyst loadings less than 1 mol% (Pd-C) has been included herein. The strategy which can surmount the reaction barrier between cycloaddition of benzyne and electron deficient dienes such as FDCA was also determined suitable for application to more traditional furan-dienes.

In example, a diacid containing naphthalenic core structure was prepared by application of this strategy (Scheme 5.11) to dimethyl 3,3'-(2,5-furandiyl)dipropionate which afforded 3,3'-(2,5-furandiyl)dipropionic acid. Investigations into applying the benzyne cycloaddition strategy for biomass-derived furan valorization has led to the discovery of some boundaries: cycloadducts from dimethyl 3,3'-(2,5-furandiyl)dipropenoate) could not be accessed due to side reactions between benzyne and the multiply olefinated 7-oxabenzonorbornadiene; additionally, DFF failed to afford any evidence of cycloaddition with benzyne.

While exploring the influence of furanic oxidation state on the outcome of the benzyne-Diels-Alder reaction, we also were interested in preparing terephthalic acid analogs on multigram

scale. This goal set a constraint on the possible routes for benzyne generation; the method had to be scalable by design. Two methods of benzyne generation were investigated by the Sibi research group,[3] with the thermolysis of benzenediazonium-2-carboxylate chosen for continued investigation.[4]

5.2.1. Overview of Furan-dienes

The reactivity of "*five-membered aromatic heterocycles as dienophiles in Diels-Alder reactions*" has been investigated by Wenkert, Moeller, and Piettre (1988) with a strong emphasis placed on reactions with furan, pyrrole, and indole.[125] Furan-dienes were used as substrates to probe the electronic requirements of the Diels-Alder reaction to illuminate the difficulties encountered in the pursuit of directly accessing biomass-derived terephthalic acid and analogous structures. Benzyne was generated by thermolysis of benzenediazonium-2-carboxylate and employed as a potent dienophile which was trapped by all the dienes studied. Good yields of the 7-oxabenzonorbornadiene adducts were isolated when hydroxyl and aldehyde moieties were protected.

Furan-diesters (dimethyl 2,5-furandicarboxylate, dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate, dimethyl 3,3'-(furan-2,5-diyl)dipropionate and furan-2,5-diylbis(methylene)diacetate) with potential for aromatic upgrading to benzenoids were compared with the xylene precursor (2,5-dimethylfuran) as targets for conversion to naphthalenes. A series of differentially disubstituted precursors—methyl 5-(acetoxymethyl)-2-furancarboxylate, ethyl 5-(acetoxymethyl)-2-furancarboxylate, methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-furancarboxylate, and methyl 5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-2-furancarboxylate—were compared with those symmetrically disubstituted furan-dienes. The range of furan-dienes illuminated several reaction constraints throughout the course of study.

The focus of this work was direct access to value added products from furandicarboxylic acids. Desired products such as 1,4-NDCA could become part of a renewable technology portfolio if this technology is implemented. However, the extreme reactivity of benzyne makes side reaction with acids[72, 126] problematic. During the benzyne-Diels-Alder reaction, primary hydroxyl groups can undergo redox reaction with benezenediazonium-2-carboxylate which destroys both reactive-intermediate-precursor and substrate.[72, 73] We therefore required protection of those moieties. Diesters provided an excellent alternative owing to their extensive use in poly(transesterification) reactions. Diesters are also known for the ease of their purification as compared to corresponding diacids.

Dimethyl 2,5-furandicarboxylate was prepared by esterification of crude FDCA with MeOH; pure dimethyl 2,5-furandicarboxylate was isolated by solid-phase extraction and recrystallization in 93% yield. Diethyl 2,5-furandicarboxylate was similarly prepared in ethanolic solution. Dimethyl 3,3'-(furan-2,5-diyl)(2E,2'E)-diacrylate was prepared from 5-(hydroxymethyl)-2-furandicarboxaldehyde in three steps with an overall yield of 78%. Dimethyl 3,3'-(furan-2,5-diyl)dipropionate was prepared by selective reduction of dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate in 93% yield. Furan-2,5-diylbis(methylene)diacetate was prepared by sodium borohydride reduction of 5-(hydroxymethyl)-2-furancarboxaldehyde in EtOH followed by DMAP catalyzed acetylation with acetic anhydride. The commercially available control (2,5-dimethyl furan) can be prepared from selective reduction of renewable CMF as discussed in Chapter 4 of this document.

The preparation of AB type furan-dienes from 5-(hydroxymethyl)-2-furancarboxylic acid was also detailed in Chapter 4; such preparations began by chemoselective Fisher esterification.[127] Methyl 5-(acetoxymethyl)-2-furancarboxylate and ethyl 5-(acetoxymethyl)-2-furancarboxylate

were prepared from DMAP catalyzed acetylation with acetic anhydride with their respective antecedents. Methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-furancarboxylate, and methyl 5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-2-furancarboxylate were prepared from methyl 5-(hydroxymethyl)-2-furancarboxylate by reaction with *tert*-butyldimethylsilyl chloride and 2,3-dihydropyran respectively. Complete procedures of the furan syntheses have been compiled in the experimental section of Chapter 4 of this dissertation.

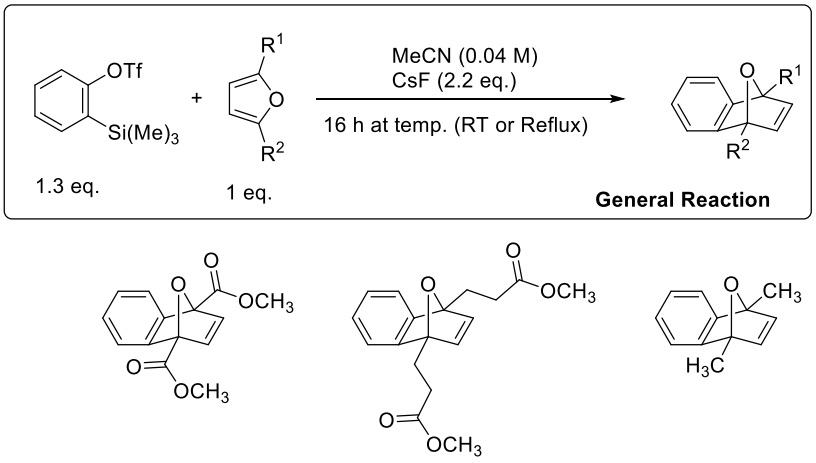
5.2.2. Screening Benzyne Trapping by Renewable Furan-Dienes

Two strategies of benzyne generation have been explored by the Sibi research group: (1) desilylation of trimethylsilyl-2-phenyltrifluoromethanesulfonate,[3] and (2) thermolysis of benzenediazonium-2-carboxylate.[3, 4] Desilylation provided proof of concept by affording adducts of benzyne and furan-dienes under finely controlled reaction conditions. These experiments were critical to establish the feasibility of benzyne trapping by such electron-deficient furan-dienes as dimethyl 2,5-furandicarboxylate (Scheme 5.11). Thermolysis of benzenediazonium-2-carboxylate was then methodically investigated by EMS to achieve economically scalable access to renewable 7-oxabenzonorbornadienes (also known as 1,4-epoxynaphthalenes). The effectiveness of furan-dienes to trap benzyne under variable conditions such as addition rate, reaction medium, temperature, and stoichiometry was evaluated.

5.2.2.1. Desilylation of trimethylsilyl-2-phenyltrifluoromethanesulfonate

Trimethylsilyl-2-phenyltrifluoromethanesulfonate undergoes fluoride-induced desilylation followed by elimination of triflate to form benzyne.[53] The desilylation protocol tightly controls solution concentrations of benzyne independent of temperature and dependent on fluoride concentration. The feasibility of trapping benzyne with dimethyl 2,5-furandicarboxylate (electron deficient) as compared with dimethyl 3,3’-(furan-2,5-diyl)dipropionate and 2,5-dimethylfuran

(electron rich) was carried out by postdoctoral researchers in the Sibi research group (Sermadurai Selvakumar Ph. D. and Nicolas Zimmermann Ph. D.) (Scheme 5.12). The results indicated the relative benzyne trapping ability of furan-dienes to afford 1,4-epoxynaphthalenes or 7-oxabenzonorbornadienes.[3]



temp.	dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate	dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)dipropionate	1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalene
RT	38%	97%	97%
Reflux	84%	na	na

Scheme 5.12. Benzyne by desilylation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate Carried out by postdoctoral researchers in the Sibi research group (Sermadurai Selvakumar Ph. D. and Nicolas Zimmermann Ph. D.).

While dimethyl 2,5-furandicarboxylate required refluxing in acetonitrile to achieve a reasonable conversion, efficient trapping by alkyl-substituted furans at room temperature was observed. No difference between the sterically more hindered dimethyl 3,3’-(furan-2,5-diyl)dipropionate versus 2,5-dimethylfuran was observed. Overall, implementation of the desilylation protocol was easy and provided 7-oxabenzonorbornadienes in good yield while indicating a normal electron demand Diels-Alder reaction since there was a thermal barrier for reaction with electron-deficient furan-dienes but not for electron-rich furan-dienes. In addition, these early experiments served as a proof of concept for the direct access strategy of Diels-Alder

adducts from benzyne and 2,5-furandicarboxylates. Unfortunately, there are severe economic limitations to the scalability and implementation of such a protocol as well as ecological concerns surrounding the generation of fluorinated wastes. A scalable method for benign benzyne generation was required to access practical quantities of bicyclic furan adducts and their derivatives.

5.2.2.2. Diels-Alder Reaction with Benzenediazonium-2-carboxylate Method Screen

The original method for benzyne preparation in non-basic media [65] was investigated to contrast the desilylation protocol with a cheap, benign, and thereby potentially scalable alternative. When first introduced, the thermolysis of benzenediazonium-2-carboxylate provided significant advantages over the organometallic protocols prevalent in the 1960s. The study of diazotized anthranilic acids greatly increased the types of benzyne which could be prepared under neutral conditions as well as expanded the scope of benzyne reactivity. Despite initial widespread implementation of this protocol, interest in benzenediazonium-2-carboxylate as a benzyne precursor was partially stymied by concerns revolving around its established shock sensitivity—*when isolated*.[66, 67]

Critically important to the future development of diazotization strategies, a method of safely employing the reactive intermediate (benzenediazonium-2-carboxylate) has been established on the analytical scale using flow chemistry.[70] Flow methods may attenuate dangers associated with harsh reaction conditions or reactive intermediates while providing a linearly scalable platform for organic synthesis. Consider the potential for biobased anthranilic acid technologies (*vide supra*), in conjunction with the advent of flow technology, which may together lead to reanimation of aryne research based upon diazotization of anthranilic acids.

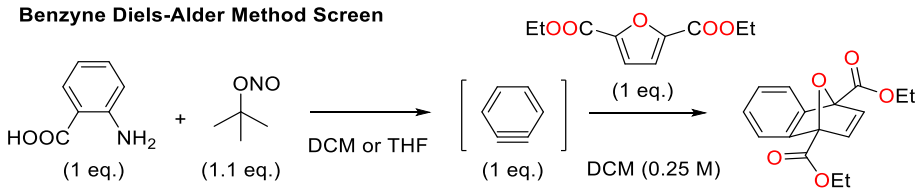
Prior to the development of benzyne by desilylation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate,[53] procedures had been developed to manage hazards associated with handling of benzenediazonium-2-carboxylate which were adequate for their safe-use by skilled technicians. They were: (1) addition of an anthranilic acid solution to the reaction mixture at reflux,[69] or (2) partial isolation of the inner salt without allowing it to dry. Both methods were investigated and have been described herein (*vide infra*). By adopting an *in situ* generation strategy, exposure to the hazardous intermediate—*benzenediazonium-2-carboxylate*—would be limited. By modifying a partial isolation protocol[63] for thermolysis of benzenediazonium-2-carboxylate, the excess furan usually required for effective benzyne trapping could also be significantly reduced to stoichiometric equivalents.

The furan-diene selected for preliminary screening of methodologies was diethyl 2,5-furandicarboxylate because of its superior separation from diethyl 7-oxabenzonorbornadienyl-1,4-dicarboxylate as compared with the ante-homologous set of methyl esters. A double drip experiment was devised based upon the methods described by Friedman and Logullo,[29, 69] then explored (Table 5.1, entries 1 and 2) in juxtaposition to combination of diazotization reaction mixtures (Table 5.1, entries 3 and 4) as well as isolated[23] benzenediazonium-2-carboxylate (Table 5.1, entries 5 and 6). Isolated yields were based on furan-diene as were calculations of recovered substrate. This consideration of furan-dienes was in contrast to many descriptions of benzyne research wherein the benzyne precursor was considered precious while the furan-dienes are typically supplied in super-stoichiometric excess or even used as solvent.

DCM was chosen as reaction solvent due to its low boiling point—*we were interested in exploring the thermal barrier for Diels-Alder reactions between benzyne and furan-dienes*—and the superior performance of halogenated solvents in the selective formation of benzyne from

benzenediazonium-2-carboxylate; as established by Buxton, Fensome, Heaney, and Mason (1995) during their investigation of the stepwise decomposition of benzenediazonium-2-carboxylate the superior performance of halogenated solvents has been attributed to the loss of reactive radical species to the solvent in favor of relatively stable halogen radicals.[73] Also of note, Buxton *et al.* relied on the same method of partially isolating benzenediazonium-2-carboxylate as reported by Logullo and Friedman (1968)[23] as was followed during the latter entries of Table 5.1. The identity of organic nitrite selected (*tert*-butyl) was strategic to avoid redox side reactions between lower alcohols and the diazo-moiety contained in benzenediazonium-2-carboxylate—*a potential issue relayed by Stiles, Miller, and Burckhardt (1963).*[72]

Table 5.1. Benzenediazonium-2-carboxylate thermolysis and trapping with diethyl 2,5-furandicarboxylate Diels-Alder method screen



Entry	Isolated Yield (%)	Substrate Recovered (%)	Stoichiometry	Method
1[a]	27	60	1:1	Double Drip 1 h
2[a]	47	36	1:1	Double Drip 10 h
3[b]	27	62	1:1	Single-shot 1 h
4[c]	27	63	1:1	Single-shot 1 h
5[d]	38	58	1:1	Single-shot 1 h
6[d]	58	35	2:1	Single-shot 1 h

a: solution of anthranilic acid in THF and solution of *tert*-butyl nitrite were mixed above the reaction mixture containing furan-diene and DCM as they were added by syringe pump; b: 3.75 h diazotization reaction; c: 1.5 h diazotization reaction catalyzed by trifluoroacetic acid (5 μM); d: tan colored benzenediazonium-2-carboxylate was isolated after 2.5 h diazotization reaction including trifluoroacetic acid (5 μM). *Detailed description of protocol employed may be found in the experimental section of this document.*

Between entries 1 and 2 (Table 5.1), the advantage conferred by extending the time interval of continuous addition can be observed. Significant improvement in the isolated yields (47% in entry 2 from 27% in entry 1) was likely due to a lower instantaneous concentration of benzyne-precursor during the course of the reaction. As a corollary to that lower solution concentration of benzyne, there would have been diminished opportunity for benzyne to benzyne as well as benzyne to benzyne-precursor side reactions. A semiquantitative evaluation of the stability of the substrate and product during the reaction was made by assessing the fraction of recovered substrate afforded by each method.

The percent isolated yield and percent recovered substrate could be summed to calculate a mass balance which is directly related to selectivity for the desired reaction. While many side reactions of benzyne and its precursor are known, the mechanism of decomposition would not be revealed by this method of mass balance calculation. The mass balance was practically unchanged in both double drip experiments (87% for entry 1 and 83% for entry 2) but could hint at instability of the system under prolonged heating while implying unaccountable consumption of furan-diene or adduct thereof in both cases.

In entries 3 and 4 (Table 5.1), the diazotization of anthranilic acid was carried out in THF solvent, following which the entire diazotization reaction mixture was added to a stirred solution of diethyl 2,5-furandicarboxylate in DCM as a single-shot whereupon the combined mixture was heated to reflux. THF was employed for the diazotization reaction since DCM was wholly unsuitable for dissolving anthranilic acid at ambient temperature. In one case (entry 3, Table 5.1)—*when the diazotization reaction was uncatalyzed*—it took almost four h to lose the brick red color attributed to the triazene adduct of anthranilic acid and benzenediazonium-2-carboxylate.[23] In another case (entry 4, Table 5.1), the loss of triazene was facilitated by addition of a catalytic

quantity of trifluoroacetic acid so that the diazotization reaction required only 90 min—*at room temperature*—to lose all brick-red color. In both cases wherein a single-shot addition of the entire diazotization reaction mixture was made (entries 3 and 4, Table 5.1), the results were practically indistinguishable from each other or from entry 1 in terms of isolated yield or mass balance.

Since addition of trifluoroacetic acid was beneficial to reducing the diazotization reaction time without deleterious outcome, it was employed in the isolation experiments (entries 5 and 6, Table 5.1). The diazotization reaction in these cases (entries 5 and 6) were extended to 2.5 h to ensure complete diazotization at ambient temperature followed by chilling in an ice bath and isolation of tan benzenediazonium-2-carboxylate by suction filtration through qualitative filter paper in a Hirsh funnel. The tan filter-cakes were rinsed with DCM until the filtrate ran colorless. Special care was taken to avoid ever completely drying the benzenediazonium-2-carboxylate, which was transferred to a volumetrically calibrated round bottom flask containing furan-diene with the aid of DCM from a wash bottle before the benzenediazonium-2-carboxylate suspension in furan-diene-DCM solution was heated to reflux.

The isolated yield of the isolation-procedure with equivalent amounts of benzenediazonium-2-carboxylate and furan-diene (entry 5, Table 5.1) was superior to the 60-min double drip experiment (entry 1, Table 5.1) and both of the single-shot experiments (entries 3 and 4, Table 5.1), while it was surpassed by the 10 h double drip experiments (entry 2, Table 5.1). In all cases, the isolation of benzenediazonium-2-carboxylate provided cleaner reactions with fewer side products as indicated by the superior mass balance (96%).

The isolation of benzenediazonium-2-carboxylate was repeated and decomposed in DCM suspension with dissolved diethyl 2,5-furandicarboxylate, this time with benzyne precursor in stoichiometric excess (entry 6, Table 5.1). The consequence of this excessive supply of benzyne

precursor was a greater isolated yield of diethyl 7-oxabenzonorbornadienyl-1,4-dicarboxylate (compared with entry 5, Table 5.1) while maintaining a high mass balance (93%). These results exhibited the potential for diazotized anthranilic acid as benzyne precursor in the Diels-Alder reaction with electron deficient furan-dienes.

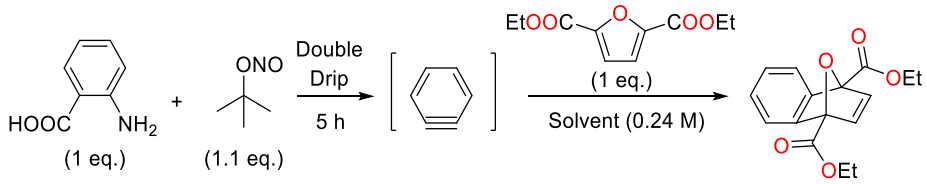
5.2.2.3. Diels-Alder Reaction with Benzenediazonium-2-carboxylate: Solvent Screen

The role of solvent in the double drip experiment was further investigated (Table 5.2). Ethereal solvents capable of completely dissolving anthranilic acid at ambient temperature were first probed (entries 1, 2, 3, and 4 Table 5.2) by concurrent addition of anthranilic acid solution and *tert*-butyl nitrite solution to the refluxing solution of diethyl 2,5-furandicarboxylate over 10 h. There was no trend in isolated yield which could be correlated with the boiling point of the solvent. Instead, the biomass-derivable solvent (2-methyltetrahydrofuran)[128] led to significantly greater isolated yield (35% for entry 2 *versus* 22% for entry 1 and 20% for entry 3) and mass balance (91% for entry 2 *versus* 67% for entry 1 and 63% for entry 3).

The best ethereal solvent investigated was 1,4-dioxane (54% isolated yield, 84% mass balance, entry 4, Table 5.2). The best two performing ethereal solvents (2-methyltetrahydrofuran and 1,4-dioxalane) both are known to form positive azeotropes with H_2O. To compare with the solvent employed in the desilylation of trimethylsilyl-2-phenyltrifluoromethanesulfonate, acetonitrile was investigated with mediocre results (28% isolated yield, 73% mass balance, entry 5, Table 5.2). A series of halogenated solvents were then investigated, but DME was used to dissolve the anthranilic acid: DCM (entries 6 and 7, table 5.2), chloroform (entry 8, table 5.2) and 1,2-dichloroethane (entries 9 and 10, Table 5.2). DCM under these conditions afforded a disappointing isolated yield and mass balance (10% isolated yield, 44% mass balance, entry 6, Table 5.2).

Table 5.2. Benznediazonium-2-carboxylate thermolysis and trapping with diethyl 2,5-furandicarboxylate. Diels-Alder solvent screening: double drip

Benzyne Diels-Alder Solvent Screen Double Drip 5 h



Entry	Yield (%)	Recovered Substrate (%)	Solvent	Boiling Point (°C)
1	22	45	THF	66
2	35	56	2-MeTHF	79
3	20	43	DME	85
4	54	30	1,4-dioxane	101
5	28	45	MeCN	81
6	10	34	DCM	40
7[a]	20	30	DCM	40
8	37	53	$CHCl_3$	61
9	18	71	DCE	84
10[b]	3	85	DCE	84

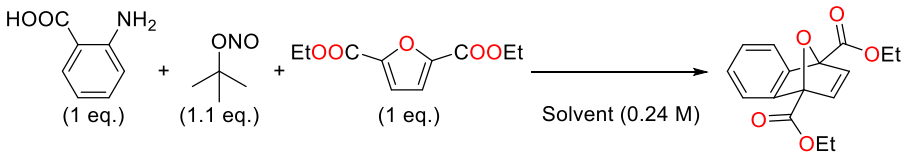
a: reagents dripped in over 20 h; b: reagent drips were allowed to mix on the inner wall of the West condenser rather than independently dripping into the reaction from just above the surface of the reaction mixture. *Detailed description of protocol employed may be found in the experimental section of this document.*

When the addition time was extended to 20 h, the reaction performed slightly better (20% isolated yield, 50% mass balance, entry 7, Table 5.2). Chloroform was an outstanding solvent for this reaction (37% isolated yield, 90% mass balance, entry 8, Table 5.2) and was only outperformed by 1,4-dioxane. Surprisingly, 1,2-dichloroethane afforded only 18% isolated yield but with an improved mass balance of 89% (entry 9, Table 5.2) which made it comparable to DME or the DCM (20 h drip) experiments but superior to DCM in a 10 h drip. It was thought that premixing the anthranilic acid and tert-butyl nitrite solutions above the reaction mixture would

afford improved yields; this was not the case as can be seen in entry 10 (Table 5.2) wherein only 3% of the desired bicyclic product was isolated.

Table 5.3. Benznediazonium-2-carboxylate thermolysis and trapping with diethyl 2,5-furandicarboxylate Diels-Alder solvent screening: single-shot

Benzyne Diels-Alder Solvent Screen Single Shot: Minimal Latent Period



Entry	Yield (%)	Recovered Substrate (%)	Solvent
1[a]	(0) 45	54	(Et_2O/DCM
2	9	89	THF
3	14	73	2-MeTHF
4	17	69	DME
5	20	63	1,4-dioxane
6	3	65	acetone
7	2	55	EtOAc
8	17	68	MeCN
9	34	47	DCM
10	62	36	$CHCl_3$
11	58	43	DCE

a: following 24 h of refluxing in Et_2O, the reaction mixture contained a great deal of tan solid, so the mixture was diluted with DCM and the temperature of the oil bath was increased to 50 °C and the mixture began to evolve gas and formed a red solution within 90 min. *Detailed description of protocol employed may be found in the experimental section of this document.*

Given some of the parallels observed in Table 5.1, the role solvent played in determining the outcome of benzyne generation from benzenediazonium-2-carboxylate and its trapping by diethyl 2,5-furandicarboxylate was extended to the single-shot of non-isolated diazotization reaction mixtures. Contrary to the methods explored in Table 5.1, the anthranilic acid was suspended in a solution of diethyl 2,5-furandicarboxylate, and *tert*-butyl nitrite was added by

syringe. This experimental protocol avoided all transference of the diazotization reaction mixture once the components were united.

The exploration of ethereal solvents was extended to include diethyl which resulted in a most curious outcome (entry 1, Table 5.3); refluxing ethoxyethane allowed formation of benzenediazonium-2-carboxylate but was unsuitably cool such that 24 h after reflux was first initiated, tan solid could still be observed in the reaction medium. Since 36 °C failed to completely decompose the benzyne precursor, DCM was added, the heat was raised, gas was evolved, and a red solution resulted in 90 min. From that mixture was isolated 45% yield of diethyl 7-oxabenzonobornadienyl-1,4-dicarboxylate with a mass balance of 99%! THF was an inferior solvent for this method in terms of isolated yield (9%), but again a great mass balance was observed (98%, entry 2, Table 5.3).

Other ethereal solvents performed in similar fashion with a slightly increasing trend in yield (14–20% isolated) corresponding to increasing boiling point (entries 3, 4, and 5, Table 5.3); however, 1,4-dioxane failed to afford the comparatively high yield observed in Table 5.2 and all the mass balances were in the eighties. Alternative solvents considered green including acetone (3% isolated yield, entry 6, Table 5.3) and EtOAc (2% isolated yield, entry 7, Table 5.3) were completely unsuitable for this method. Surprisingly in light of the results compiled int Table 5.1, acetonitrile (17%, entry 8, Table 5.3) performed similarly to DME in these experiments (entry 4, Table 5.4) even in terms of mass balance.

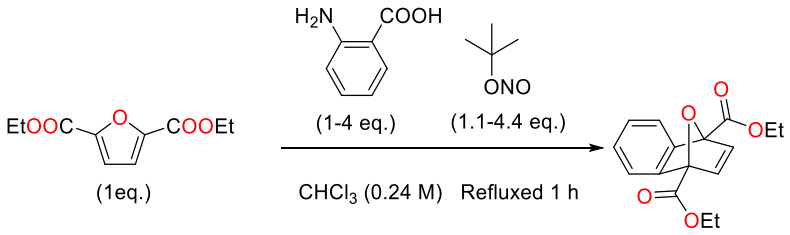
As expected, halogenated solvents provided superior access to benzyne furan-diene Diels-Alder adducts (entries 9, 10, and 11, Table 5.3) and all outperformed their counterpart experiments from Table 5.2. DCM afforded 34% isolated yield with 81% mass balance (entry 9, Table 5.3). Chloroform (62% isolated yield, 98% mass balance, entry 10, Table 5.3) and 1,2-DCM (58%

isolated yield, 101% mass balance, entry 11, Table 5.3) performed similarly and both could be favorably compared to the 55% yield of 7-oxabenzonorbornadiene

recovered from the decomposition of pure benzenediazonium-2-carboxylate in furan solution (boiling point of 33 °C) reported by Stiles and Miller (1960).[65] The result of a mass balance greater than 100% such as in the case of entry 11 (Table 5.3) is indicative of contamination of the isolated substrate or product with unidentified material.

5.2.2.4. Diels-Alder Reaction with Benzenediazonium-2-carboxylate: Stoichiometry Screen

Table 5.4. Benznediazonium-2-carboxylate thermolysis and trapping with diethyl 2,5-furandicarboxylate chloroform single-shot stoichiometry screen



Entry	Yield (%)	Recovered Substrate (%)	Anthranilic Acid (eq.)
1[a]	62	36	1.0
2	81	17	1.5
3	85	14	2.0
4	91	8	3.0
5	89	9	4.0

a: data taken from entry 10, Table 5.3. *Detailed description of protocol employed may be found in the experimental section of this document*.

Since the single-shot results with chloroform were so favorable (entry 10, Table 5.3), those conditions were utilized to examine the relationship between benzyne-precursor stoichiometry compared to equivalents of diethyl 2,5-furandicarboxylate as furan-diene in terms of isolated yield and mass balance (Table 5.4). Table 5.1 (entries 5 and 6) might lead a careful reader to predict

mild, stepped increases in the yield with large jumps of excess benzyne precursor. Increasing the stoichiometric excess of anthranilic acid and tert-butyl nitrite resulted in increased isolated yields of diethyl 7-oxabenzonorbornadienyl-1,4-dicarboxylate only to a limited degree.

Even a small increase in anthranilic acid and *tert*-butyl nitrite excess led to drastic improvements in the isolated yield while preserving the high mass balance (81% isolated yield, 98% mass balance, entry 2, Table 5.4). Further increases in benzyne-precursor stoichiometry afforded only minor increases in isolated yield (entries 3 and 4, Table 5.4). Four equivalents of anthranilic acid actually resulted in a slight decrease in the isolated yield compared to the maximum and could be evincing the potential of even these electron-deficient C1,C4-disubstituted 7-oxabenzonorbornadienes to engage in cycloaddition reactions as has been reported for simple 1,4-epoxynaphthalenes.[129, 130]

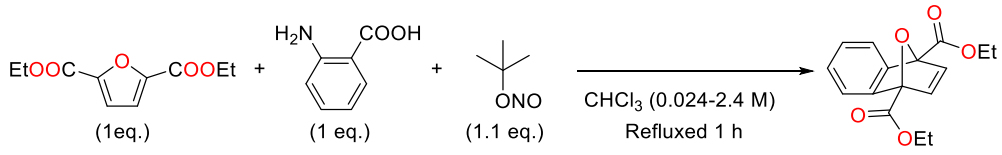
5.2.2.5. Diels-Alder Reaction with Benzenediazonium-2-carboxylate Concentration Screen

Concentration of furan-diene in the reaction medium was varied (Table 5.5). Extreme dilution (0.024 M) negatively impacted the isolated yield of Diels-Alder adduct (35%, entry 1, Table 5.4). A broad range of concentrations from 0.1 M to 1.1 M were tolerated (entries 2, 3, and 5, Table 5.5), while higher concentrations began to show deleterious effect (entry 5, Table 5.5). The negative impact of greater concentration was likely due to increasing side reactions between benzyne, and or benzenediazonium-2-carboxylate, and or anthranilic acid in light of the results of Table 5.4.

To rationalize these results, first consider the desirable reactions occurring in solution and their requirements for success: (1) diazotization of anthranilic acid—*benefits from high concentration,* (2) thermolysis of benzenediazonium-2-carboxylate—*independent of concentration*, and (3) benzyne trapping by furan-diene—*benefits from high concentration*. Now

consider the major known competing reactions and the conditions required to mitigate them: (1) dediazoniation of benzenediazonium-2-carboxylate to afford inert benzoic acid—*complicated but may be related to acid concentration*, (2) benzyne [2+2] cycloaddition with benzyne—*certainly is inversely related to the solution concentration of benzyne*, and (3) reactions of benzyne as a nucleophile or electrophile in addition reactions—*inversely related to the solution concentration of reactants*. Consequently, the formation if benzyne and its trapping by furan-dienes is facilitated at high concentration but must be balanced against the destruction of benzyne and its precursor by various routes which is also enhanced at higher concentration. So, the lifetime of benzyne in solution will be truncated if the concentration is too high. While amalgamation of diazotization reagent with anthranilic acid will suffer if their concentrations are too low, thereby circumventing benzyne formation.

Table 5.5. Benznediazonium-2-carboxylate thermolysis and trapping with diethyl 2,5-furandicarboxylate chloroform single-shot concentration screen

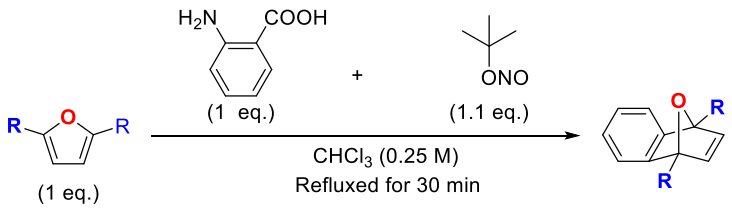


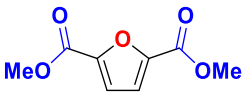
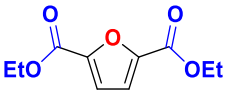
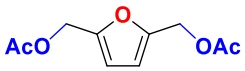
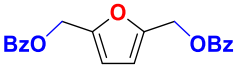
Entry	Yield (%)	Recovered Substrate (%)	[Substrate] (M)
1[a]	35	--	0.024
2	54	34	0.10
3[b]	62	36	0.24
4	56	39	1.1
5	43	49	2.4

a: the fractions containing the recovered substrate were spilled; b: data taken from entry 10, Table 5.3. *Detailed description of protocol employed may be found in the experimental section of this documen*t.

5.2.2.6. Diels-Alder Reaction with Benzenediazonium-2-carboxylate Substitution Effects

Table 5.6. Benznediazonium-2-carboxylate thermolysis and trapping chloroform single-shot substrate screening



Entry	Isolated Yield (%)	Substrate
1	47	
2	50	
3	65[a]	
4	66	

a: refluxed for 60 min, isolated yield was 64%. *Detailed description of protocol employed may be found in the experimental section of this document.*

A simplified experiment was devised which utilized the superb performance and facility of combining substrate and reagents in chloroform suspension-cum-solution followed by a brief—30 min—reflux followed by immediate workup. A minor but definite difference could be discerned in the reactivity of C2,C5-dicarboxylate substituted furan-dienes and C2,C5-dioxymethylene substituted furan-dienes (Table 5.6). Under these conditions, there was no discernable difference in the reactivity of furanic esters based on bulk (entries 1 and 2 together and entries 3 and 4 together, Table 5.6). The reactions had afforded red solutions following 30 min of reflux which was interpreted as the consumption of all anthranilic acid, and this was verified by extending the

reflux period to 60 min for 2,5-di(benzoyloxymethyl)furan with no change in the outcome (entry 3, Table 5.6).

Overall, this method was suitable for rapid screening of substrates and gave fairly consistent and reproducible results. These results also clearly showed a preference for benzyne-trapping by the more electron rich furan-dienes thereby providing additional support for a normal electron demand Diels-Alder reaction mechanism. However, the wasteful trapping of only half of the benzyne theoretically produced by the anthranilic acid consumed in these strategies required further optimization to achieve a practical level of sustainability.

5.2.3. Benzyne from 2,2'-(1-Triazene-1,3-diyl)bis(benzoic Acid)

Triazene adducts of benzenediazonium-2-carboxylate and secondary amines such as pyrrole were investigated as safer—*stabilized*—precursors for benzyne by Buxton and Heaney (1995).[131]

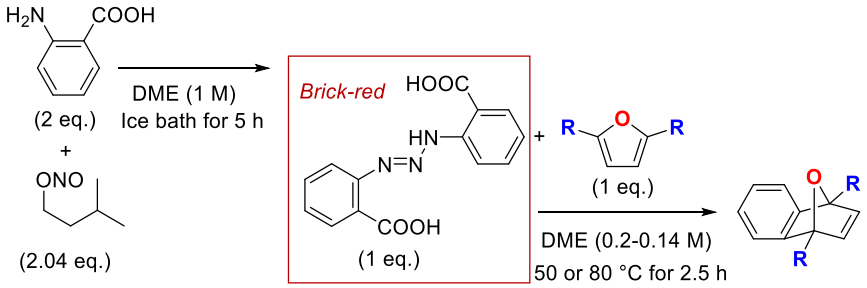
5.2.3.1. Intermediacy of 2,2'-(1-Triazene-1,3-diyl)bis(benzoic acid)

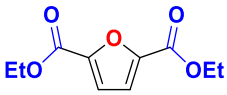
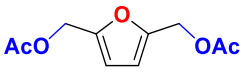
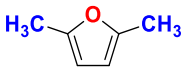
Additionally, the formation a triazene from anthranilic acid and benzenediazonium-2-carboxylate—*2,2'-(1-triazene-1,3-diyl)bis(benzoic acid), CAS# 29772-37-0*—at ice bath temperatures was described by Logullo, Seitz, and Friedman during their preparation of biphenylene (1968).[23] It was supposed that formulation of the reaction mixtures to rely on one molar equivalent of preformed 2,2'-(1-triazene-1,3-diyl)bis(benzoic acid) with enough excess organic nitrite to further convert the residual anthranilic acid could serve as a safe and time delayed benzyne delivery method.

This method was investigated, and the results have been summarized in Table 5.7 with furan-dienes listed in ascending electron-richness. A general trend for increased yield could be predicted by considering the normal electron demands of the Diels-Alder reaction; an electron-

deficient furan-diene afforded mediocre yields (42% and 45%, entry 1, Table 5.7), while oxyalkyl substitution afforded moderate yields of 7-oxabenzonorbornadiene products (65% and 62 %, entry 2, Table 5.7) and alkyl (74%, entry 5, Table 5.7).

Table 5.7. Benznediazonium-2-carboxylate-anthranilic acid triazene adduct thermolysis and trapping multiple shot method screening (1)



Entry	Substrate	Yield (%) 50 °C	Yield (%) 80 °C
1		--	44
2		64	64
3		--	44[a]
4		--	60[b]
5		63	74

a: 1.0 eq. of anthranilic acid, 1.1 eq. of isoamyl nitrite; b: diazotization mixture contained HCl(aq) (0.036 M). *Detailed description of protocol employed may be found in the experimental section of this document.*

Also, these reactions were carried out in DME which was not a superior solvent for single-shot experiments but has been used widely in literature for benzyne-trapping reactions. One of the major factors which had a positive impact on the outcome of these reactions was the preformation of triazene in a diazotization reaction mixture combined with its portion wise addition to a refluxing solution of furan-diene. This strategy circumnavigated the quandary presented by the

concentration screening experiments (Table 5.4) by performing the diazotization in a separate flask at relatively high concentration followed by small additions of that mixture to the preheated reaction mixture which strictly controlled the reaction solution's concentration of benzyne.

The temperature of the reaction mixture likely played a role in several chemical reactions within each reaction mixture such as: (1) the rate of bezenediazonium-2-carboxylate liberation from 2,2'-(1-triazene-1,3-diyl)bis(benzoic acid), (2) the rate of benzenediazonium-2-carboxylate thermolysis to afford benzyne, (3) the rate of benzyne trapping by furan-diene, and (4) the rates of benzyne side reactions. Depression of the reaction temperature in the case of 2,5-bis(acetoxymethyl)furan (entry 2, Table 5.7) made no significant difference to the outcome of the Diels-Alder reaction with benzyne, whereas an improvement of 11% isolated yield was the consequence in the case of 2,5-dimethylfuran (entry 5, Table 5.7). Since the trajectory of the reaction towards the desired bicyclic product was differentially affected by shifts in temperature (compare entries 2 and 5 from Table 5.7) as a result of those and other competing processes, it is likely that the optimization of any particular benzyne trapping reaction with bioderived furan-dienes would be required for process scale-up.

When the stoichiometric excess of anthranilic acid parameter was reduced, the excess of isoamyl nitrite was also limited to 1.1 equivalents. Those reactions were carried out at 80 °C, and there was a precipitous drop in the isolated yield of 1,4-bis(acetoxymethyl)-7-oxabenzonorbornadiene (43% and 45%, entry 3, Table 5.7). These results indicated that the anthranilic acid thusly treated was not as prone to afford benzyne amenable for trapping by furan-dienes as compared with simply mixing the reagents (entry 3, Table 5.6).

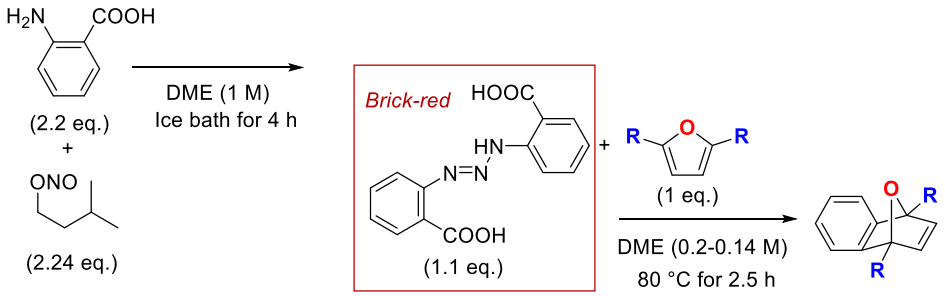
When a catalytic amount of aqueous hydrogen chloride was added to the diazotization reaction mixture, it had a slightly negative impact on the isolated yield of 1,4-di(acetoxymethyl)-

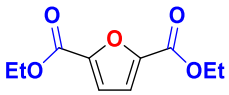
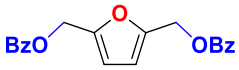
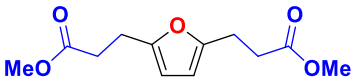
7-oxabenzonorbornadiene (entry 3, Table 5.7). That small amount of aqueous acid did not change the composition of the reaction mixture from the brick red of 2,2'-(1-triazene-1,3-diyl)bis(benzoic acid) to the light tan of benzenediazonium-2-carboxylate. The negative of the aqueous acid was likely due to the increased solution concentration of benzenediazonium-2-carboxylic acid which may not readily undergo simultaneous elimination of carbon dioxide and nitrogen to afford benzyne.

Given the established sensitivities of amyl nitrite,[132] its concentration in the reaction mixture made available for diazotization of the anthranilic acid released by dissociation of 2,2'-(1-triazene-1,3-diyl)bis(benzoic acid) was in question. The results with three furan-dienes containing representative electronic substitution—*carboxy, oxyalkyl, and alkyl*—have been summarized and showed improved yields of 7-oxabenzonorbornadienes (compare Table 5.7 to Table 5.8) with the latent time allowed for the diazotization reaction reduced to four h and the concentration of the reaction mixture slightly less (0.2 M to 0.4 M). As may be expected from the stoichiometry screening summarized in Table 5.4, even small changes in the excess of benzyne precursor could have a dramatic impact upon the outcome of the reaction (78% *versus* 67% entry 1, Table 5.8 and compared with 45%, entry 1, Table 5.7).

The electronically intermediate furan-diene, 2,5-bis(benzoyloxymethyl)furan, provided the highest yields of Diels-Alder adduct with benzyne (88% and 82%, entry 2, Table 5.8). As could be predicted by consideration of the results from the stoichiometry screening experiments (Table 5.4) in combination with the expectation of a normal electron demand Diels-Alder reaction mechanism, the alkyl substituted substrate—*dimethyl 3,3'-(2,5-furandiyl)dipropionate*—actually afforded the lowest yields of Diels-Alder adduct (entry 3, Table 5.8). This was taken as an indication of greater benzyne generation efficiency by this protocol.

Table 5.8. Benznediazonium-2-carboxylate-anthranilic acid triazene adduct thermolysis and trapping multiple shot method screening (2)



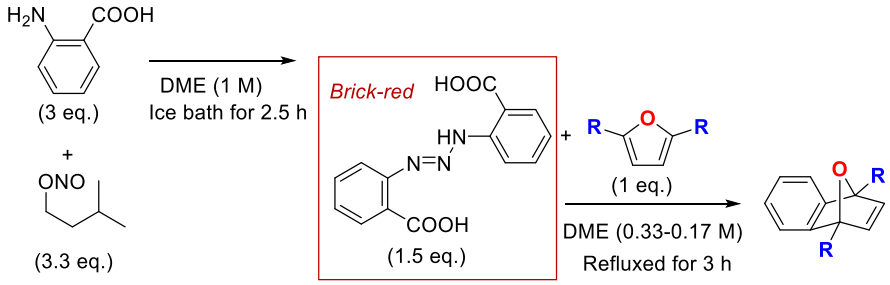
Entry	Substrate	Isolated Yield (%)
1		78
2		67[a]
3		88, 82
4		60
5		49[a]

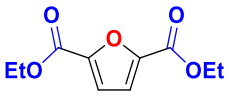
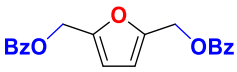
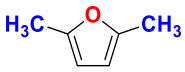
a: 2 eq. anthranilic acid, 2.1 eq. isoamyl nitrite. *Detailed description of protocol employed may be found in the experimental section of this document.*

The benzyne was disproportionately trapped by the more electron rich furan-dienes thus leading to higher solution concentrations of 7-oxabenzonorbornadienes earlier in the course of the reaction. These then could be trapped by benzyne in an overreaction proportional to the solution concentrations of benzyne and Diels-Alder adduct. The benzoyloxymethyl group was the optimal substrate for these conditions with a predicted intermediate propensity to trap benzyne combined with sterically bulky benzoyloxymethyl moieties to partially block the strained olefin contained in its 7-oxabenzonorbornadiene core. As implicated by entry 3 (Table 5.8), even the application of slightly lower stoichiometric excess of benzyne precursors would lower the yield predictably as seen in entry 1 (Table 5.8). Possibly, the greater steric bulk of 3-substituted methyl propionates

makes it a poor substitute or 2,5-diemthylfuran in comparing their reactivity in the Diels-Alder reactions. These observations reinforce the need to individually optimize the reaction conditions to afford any given furan-diene-benzyne adduct for a targeted application.

Table 5.9. Benznediazonium-2-carboxylate-anthranilic acid triazene adduct thermolysis and trapping multiple shot method screening (3)



Entry	Substrate	Isolated Yield (%)
1		89
2		75
3		76
4		72[a]

a: 3.3 eq. *tert*-butyl nitrite used rather than *iso*-amyl nitrite. *Detailed description of protocol employed may be found in the experimental section of this document.*

These results illustrate some of the limitations encountered in pursuing model studies in some of these cycloaddition strategies due to the severe consequences of minor alterations to reaction conditions. To flush out such sensitivities further and following the trends from Table 5.7 and 5.8, the excess of diazotization mixture containing 2,2'-(1-triazene-1,3-diyl)bis(benzoic acid) in proportion to furan-diene was increased, the latent period for diazotization was decreased, and the concentration of the benzyne Diels-Alder reaction was further reduced (0.33 M to 0.17 M

during the reaction); the results have been compiled in Table 5.9. The workup of these reactions was modified to include partitioning of the reaction mixture's concentrate between EtOAc and aqueous ammonia. The dual roles of the ammonia were to ionize any residual anthranilic acid to the very H_2O soluble ammonium carboxylate salt and to neutralize any residual diazotizing reagent.

The results of this method were quite good and consistent for the electron deficient furan-diene, dimethyl 2,5-furandicarboxylate (90% and 87% yield, entry 1, Table 5.9). For 2,5-di(benzoyloxymethyl)furan, the results were fairly consisted and predictably lower than observed in Table 5.8 when considering the paradigm of benzyne over reaction (72–77%, entry 2, Table 5.9). Consideration of possible partial benzoate ammonolysis cannot be excluded and could explain the wider variance in those results. When examining the results of benzyne trapping by 2,5-dimethyl furan, wildly inconsistent results were obtained (71%, 71%, and 85%, entry 3, Table 5.9) which were more or less replicated upon substitution of *iso*-amyl nitrite with *tert*-butyl nitrite (71%, 78%, and 62%, entry 3, Table 5.9). The lower average yield for 2,5-diemthylfuran does not preclude the overreaction with benzyne hypothesis and the relative agreement between the two sets of triplicate experiments (entry 3, Table 5.9) illustrates the inconsequential substitution of nitrite reagent. While the portion wise addition of 1.5 molar equivalents of 2,2'-(1-triazene-1,3-diyl)bis(benzoic acid) to refluxing solutions of furan-diene afforded high yields of electron withdrawing substituted 7-oxabenzonorbornadienes, the process was still deemed unsustainable due to the wasted anthranilic acid and nitrite precursors.

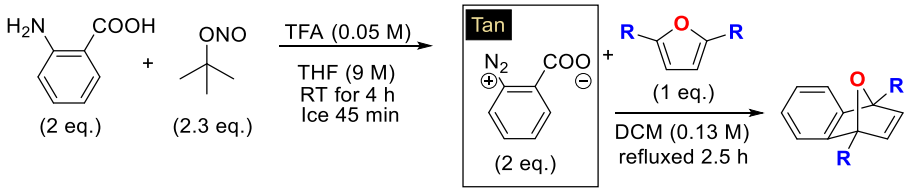
5.2.4. Benzyne from Benzenediazondium-2-carboxylate

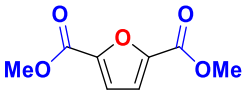
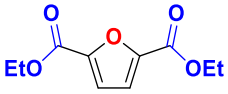
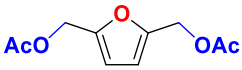
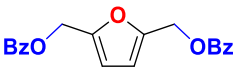
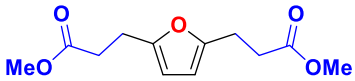
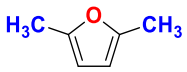
5.2.4.1. Diels-Alder Reaction with Isolated Benzenediazondium-2-carboxylate (1)

To begin investigation into a more efficient route towards benzyne from anthranilic acid, a partial isolation protocol was developed. Wherein, the diazotization mixture was treated with catalytic amounts of trifluoracetic acid (a parameter which was investigated) at room temperature to facilitate dissociation of 2,2'-(1-triazene-1,3-diyl)bis(benzoic acid) to allow complete conversion of anthranilic acid to benzenediazonium-2-carboxylate.[23] The benzenediazonium-2-carboxylate was isolated from the reaction mixture by suction filtration but never allowed to completely dry. When this tan solid was added to a calibrated flask containing furan-diene and DCM, thermolysis could be induced by refluxing the slurry. By this method consistently higher yields of 7-oxabenzonorbornadienes could be collected while wasting less anthranilic acid (Table 5.10). The handling of energetic intermediates required in the portion wise addition experiments was also dispelled by returning to the single-shot method.

Dimethyl 2,5-furandicarboxylate was isolated in 84% yield by this protocol (entry 1, Table 5.10) which required consumption of 2 equivalents of anthranilic acid. Increased trifluoracetic acid in the diazotization mixture combined with extended DCM washing to remove said acid resulted in mediocre and inconsistent yields (70%, entry 2, Table 5.10).

Table 5.10. Isolated benznediazonium-2-carboxylate thermolysis and trapping substrate screening



Entry	Substrate	Isolated Yield (%)
1		84
2		70[a]
3		91[b]
4		78[a,c]
5		88
6		83
7		88[a]
8		77
9		76[a]
10		68
11		69[a]

a: TFA concentration in the prereaction was increased to 0.19 M and the prereaction was shortened to 2.5 h, b: 4% recovered substrate, c: 4% recovered substrate. *Detailed description of protocol employed may be found in the experimental section of this document.*

Diethyl furan-2,5-dicarboxylate afforded an even greater yield under the standard conditions (91%, entry 3, Table 5.10) which could be indicative of the steric protection from over-reaction with benzyne conferred to diethyl 7-oxabenzonorbornadienyl-1,4-dicarboxylate by the

bulkiness of the ethyl *versus* methyl carboxylate moieties. Duplicate experiments with extra trifluoracetic acid were very inconsistent (66% and 89%, entry 3, Table 5.10), which lent credence to the belief that inconsistent washing with DCM was removing significant amounts of benzenediazonium-2-carboxylate and that the shortened prereaction (2.5 h) did not necessarily lead to lowered yields.

The oxyalkyl substituted furan-2-dienes were intermediate performers with 2,5-bis(acetoxymethyl)furan resulting in a relatively high yield (88%, entry 5, Table 5.10) and with 2,5-bis(benzoyloxymethyl)furan affording scattered but fair yields; 83% by standard experiment (entry 6, Table 5.10) and again inconsistent yields were obtained with shorter reaction time and greater acid concentration (76%, and 99%, entry 7, Table 5.10). The trapping with carboxyalkyl substituted dimethyl 3,3'-(2,5-furandiyl)propionate resulted in fair yields which were consistent (77% and 76%, entries 8 and 9, Table 5.10) and higher than those observed from 2,5-dimethylfuran (68% and 69% entries 10 and 11, Table 5.10). This trend in lower yields corresponding with greater electron richness in the furan-diene has been incorrectly interpreted by some as evidence of an inverse electron demand Diels-Alder reaction. However, it is merely an artifact of broadly applying the optimized super stoichiometric reaction conditions for electron deficient furan-dienes.

5.2.5. Probing the Over-reaction Hypothesis

The over-reaction hypothesis states: the results from Table 5.10 are explained by an initial normal electron demand Diels-Alder reaction followed by subsequent over-reaction between benzyne and the strained olefin of 7-oxabenzonorbornadienes—prepared *in situ*—in an asynchronous [2+2] cycloaddition. While the strained olefins are expected to be universally reactive across these substrates chiefly due to strain imparted by the benzo-fused bicyclic ring system, furan-dienes which are better benzyne traps—*electron rich*—led to a higher solution

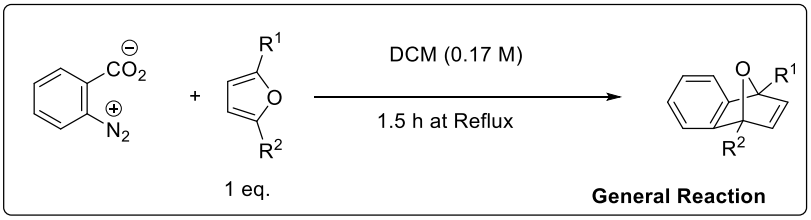
concentration of 7-oxabenzonorbornadiene earlier in the reaction. Since the concentration of benzyne is self-limiting—*by biphenylene formation*—the solution concentration of that reactive intermediate is roughly at a steady state during the course of the portion wise addition reactions such that the concentration of 7-oxabenzonorbornadiene scaled by time spent in solution is the greatest determining factor in a second reaction with benzyne.

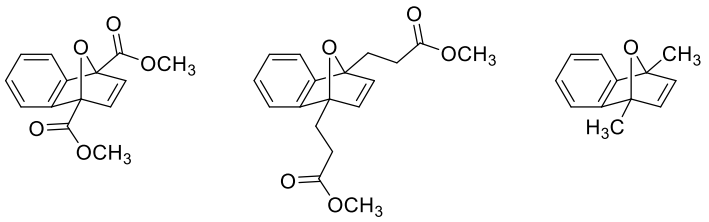
In this hypothesis, is expected that any of the [4+2] cycloadditions will be faster than subsequent [2+2] cycloadditions such that over-reaction does not become a competitive process until the reaction medium becomes starved for furan-diene. The implication being that sluggish benzyne traps—*electron deficient*—provide a protective influence during the course of a standard reaction by dint of their comparatively higher concentration throughout. A second route towards over-reaction could also explain the reversal of the trend expected for a normal electron demand Diels-Alder reaction: a subsequent strain-driven Diels-Alder reaction—[4+2] cycloaddition—between 7-oxabenzonorbornadiene (as the dienophile) and furan-diene. This process would be expected to differentially affect change in the product distribution only with electron rich furan-dienes since it would also be a normal electron demand Diels-Alder reaction.

5.2.5.1. Diels-Alder Reaction with Isolated Benzenediazondium-2-carboxylate (2)

An extenuation of the experiments summarized in Table 5.10 was made by increasing the ratio of *iso*-amyl nitrite added to the diazotization reaction mixture (Scheme 5.13). The use of isopentyl nitrite as opposed to *tert*-butyl nitrite (sometime used in the literature) was made since the reaction of anthranilic acid and isopentyl nitrite is faster. Therefore, the latent time before the reaction was minimized. This resulted in a significant decrease in the time spent with shock sensitive material on the bench and thereby mitigated some of the hazards associated with a shock sensitive intermediate. Since some questions have been raised by the previous results regarding

the delivery of benzyne by the thermolysis approach, a series of experiments was performed under more strictly controlled conditions with no aqueous workup.





Benzyne eq.	dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate	dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)dipropionate	1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalene
1.0	42%	56%	70%
1.4	80%	82%	85%
2.0	91%	91%	67%

Scheme 5.13. Benzyne by thermolysis of benzenediazonium-2-carboxylate

Furan-dienes—dimethyl 2,5-furandicarboxylate (electron deficient) as compared with dimethyl 3,3’-(furan-2,5-diyl)dipropionate and 2,5-dimethyl furan (electron rich)—smoothly transformed to 7-oxabenzonorbornadienes (dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate, dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)dipropionate, and 1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalene) (Scheme 5.13: *procedural details are included in the experimental section of this document*). The combination of electron-rich with sterically minimal substitution resulted in much greater benzyne trapping efficiency by 2,5-dimethylfuran (70%) contrasting with electronic-deficient dimethyl 2,5-furandicarboxylate (42%) or sterically hindered dimethyl 3,3’-(furan-2,5-diyl)dipropionate (56%). This indicated that 40 °C was sufficient to induce thermolysis while also overcoming the thermal barrier for trapping with electron-deficient furan-dienes and was the first time the role played by the steric environment of the furan-diene could be directly observed.

Further experiments (Scheme 5.13) explored the role of initial stoichiometric ratios between benzenediazonium-2-carboxylate and furan-diene; the results showed approximately 60% of benzyne generated by this thermolysis method was trapped by the furans studied except for the very efficient furan-diene (2,5-dimethylfuran). The result utilizing 1:1 stoichiometry (molar equivalents, eq.) of benzenediazonium-2-carboxylate to dimethyl 2,5-furandicarboxylate actually contained a crude mass corresponding to 68% isolated yield but was corrected when the NMR analysis indicated significant (~20%) concentration of epoxidized 7-oxabenonorbornadiene. Importantly, these reactions had not been protected by exclusion of atmospheric oxygen.

Those results indicated that degradation of Diels-Alder adducts was observed when reactions were not protected from oxygen and residual nitrites; the nitrogen dioxide–catalyzed epoxidation[133] of 7-oxabenzonorbornadienes on the bench had not otherwise been reported. The strained olefin could be seen to completely epoxidize in some of the samples stored in an NMR tube over the course of several weeks. The product was confirmed by reaction of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate with *meta*-chloroperoxybenzoic acid (*m*CPBA) and subsequent comparison of ^{1}H NMR spectra as well as HRMS. Likely, some alkyl nitrite or other nitrogenous oxide coeluted with the product which formed nitrogen dioxide in solution upon reaction with atmospheric oxygen. This presented an entirely new facet of the observed trend in yield isolation, since increasing benzyne equivalents also corresponded to greater equivalents of diazotization reagent. This interesting phenomenon does not account for the total reversal of yield trend observed at higher reaction stoichiometries (Scheme 5.13).

Twofold excess of bezenediazonium-2-carboxylate led to isolated yields above 90% of Diels-Alder adducts (dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate and dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)dipropionate). Even at that super stoichiometry, some dimethyl 2,5-

furandicarboxylate was recovered (6%). The reaction of dimethyl 2,5-furandicarboxylate and benzenediazonium-2-carboxylate was safely scaled up to 98 mmol and resulted in 91% isolated yield of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate which afforded a low-melting crystalline solid which existed as a brown oil at room temperature. This scaled up experiment actually allowed for the eventual isolation of a derivative product from [benzyne+7-oxabenzonorbornadiene], [2+2], cycloadditions following hydrogenation and acid catalyzed dehydration.

Notably, use of excess benzenediazonium-2-carboxylate led to a decreased yield of 1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalene**.** The results of screening reaction stoichiometry succeeded in differentiating the dialkylfuran substrates by their steric qualities and indicated at least one degradation pathway which disproportionately predated upon sterically vulnerable olefins composing 7-oxabenzonorbornadienes. Following the general procedure described for Scheme 5.13, 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate was employed as benzyne trapping agent. The benzyne by thermolysis reaction mixtures typically become so red as to appear black. However, this preparation was a lighter red color and solid precipitated upon cooling. This indicated that the excess benzyne was consumed in some manner other than that color-forming process and likely led to lower rates of self-adduction. That solid was relatively insoluble in acetone. The material was partially purified by flash chromatography; the center fraction of the major eluate peak was analyzed by ^{1}H NMR (Fig. 5.6). Many new aromatic peaks along with new aliphatic signals were observed in ^{1}H NMR. This indicated that dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate was an effective diene but that over-reaction between benzyne and olefins challenges the efficiency of this process. Some residual starting material (pure form overlaid in red) was detected, which indicated that a side reaction engaging benzyne and the first adduct was

proceeding faster than the Diels-Alder reaction with dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate. Some 7-oxabenzonorbornadiene was detected, which was likely a consequence of benzyne depletion towards the end of the reaction.

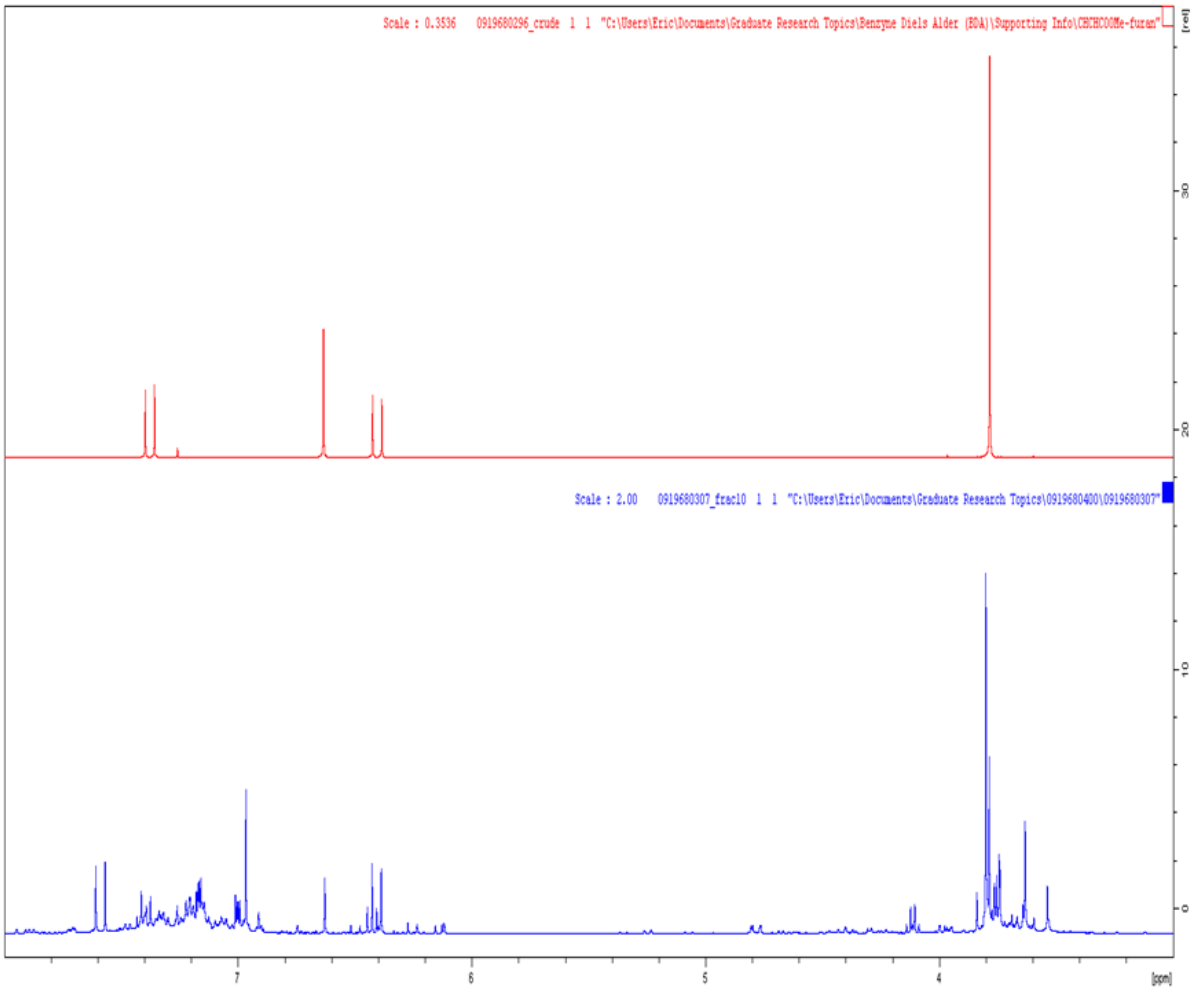
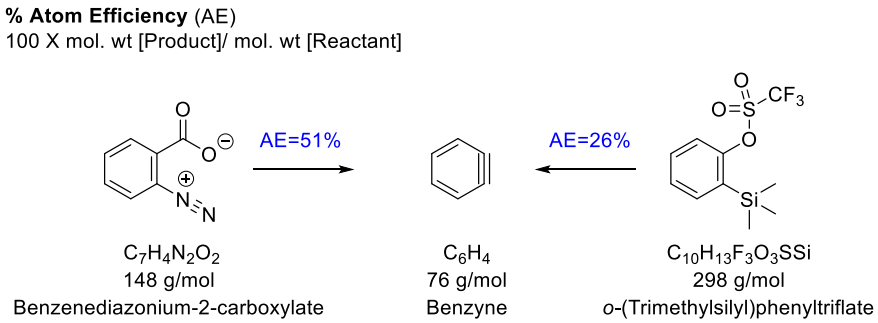


Fig. 5.6. Results of ^{1}H NMR analysis (bottom blue) following Diels-Alder reaction between benzyne and dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate (DMFBA) (top red)

In summary, under thermolysis conditions, each furan-diene trapped benzyne with general uniformity (Scheme 5.13). However, dimethyl 3,3'-(furan-2,5-diyl)(2*E*,2'*E*)-diacrylate did not cleanly transform to dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)(2*E*,2'*E*)-diacrylate (or 7-oxabenzonorbornadiene-1,4-diacrylate). Only some adduct could be detected in the reaction along with residual starting material.

5.2.6. Discussion of Metrics for the Benzyne Diels-Alder Reaction



Scheme 5.14. Atom efficiency of benzyne formation by two routes

While atom efficiency is among the most preliminary of metrics,[134] it provides optimal information to guide the initial stage of process development and scale-up when implementing design thinking to consider the maximum efficiency offered by a given process as described by Sheldon (2007) wherein the relationship between atom efficiency and theoretical environmental factor was derived.[135] In the course of the following analysis, the atom economy equation was slightly modified to include the reagent stoichiometries of the standard experimental reaction conditions so as not to unduly bias one technique over another. For reference the percent atom efficiency was calculated for the simple process of benzyne generation from benzenediazonium-2-carboxylate (51%, Scheme 5.14) and from 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (26%, Scheme 5.14).

Diels-Alder reactions on the other hand have inherent potential for perfect atom efficiency by incorporation of all atoms from the diene and dienophile into an adduct. However, since benzyne must be generated *in situ* from a precursor such as 2-(trimethylsilyl)phenyl trifluoromethanesulfonate or benzenediazonium-2-carboxylate, there will be some discarded atoms. These two methods were compared with emphasis on assessing their respective atom efficiency (also known as atom economy), nature of side products, and intensity of preparation.

The atom efficiencies corresponding to both benzyne Diels-Alder methods were calculated for dimethyl 2,5-furandicarboxylate since it embodies the direct-access strategy for aromatic upgrade from heavily oxidized, renewable furanics. For desilylation, a modified atom efficiency of 29% describes the synthesis of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate as compared with 60% when the thermolysis protocol was employed in a 1:1 stoichiometry and 38% atom efficiency when a 2:1 anthranilic acid: furan-diene stoichiometry was used. There is significantly greater efficiency potential for the thermolysis approach.

In a systems thinking exercise, please consider the type of waste developed in each reaction. When the nature of the side products is considered, nitrogen and carbon dioxide would clearly be preferable to trimethylsilyl fluoride and cesium triflate as environmental waste. Preparation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate from readily available starting materials is also much more intensive than preparation of benzenediazonium-2-carboxylate. However, the shock sensitivity of benzenediazonium-2-carboxylate requires extreme care and precautions for its safe handling. Halogenated solvents are strictly considered hazardous[136] and recommended for replacement;[137] but they provide a superior reaction medium for the selective conversion of benzenediazonium-2-carboxylate to benzyne.[73]

Since isolation of the shock-sensitive benzenediaznium-2-carboxylate is diametrically opposed to the principles of green chemistry, the many advantages of this otherwise benign technology are inversely proportional to the isolation of that reactive intermediate. For the sake of reducing the process intensity while limiting exposure to hazards associated with benzenediazonium-2-carboxylate, the method of reaction was modified. The inner salt was prepared ahead of the reaction in contrast to double drip methodologies wherein alkyl nitrite and

anthranilic acid are added concurrently in solution by syringe or to the isolation protocol utilized in Scheme 5.13.

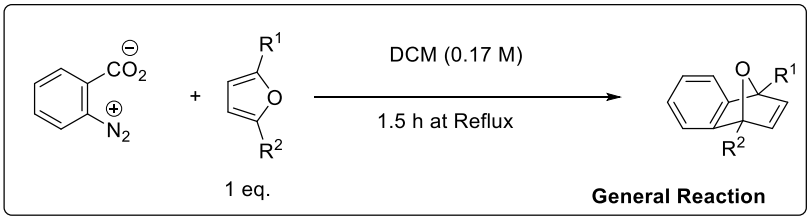
Furan-dienes (dimethyl 2,5-furandicarboxylate and dimethyl 3,3'-(furan-2,5-diyl)dipropionate**)** were employed to determine the feasibility of flow methods by approximation. Thermolysis was expected to proceed at 40 °C as with isolated benzenediazonium-2-carboxylate. The diazotization mixture was composed of light tan solid slurried with deeply red solution. When the slurry was used in a single-shot without partial isolation, predictably inferior yields were observed. However, when a flow system was approximated, by injecting aliquots of diazotization mixture into a refluxing benzyne DAR mixture, commensurate yields to the isolation protocol were obtained! Thus, the hazard associated with handling benzenediazonium-2-carboxylate can be circumvented by engineering a delivery system which only prepares small quantities of reactive intermediate immediately prior to thermolysis.

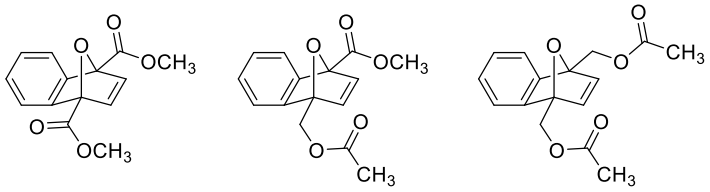
5.2.7. Expansion of Technology to AB Type Furan-dienes

The established protocol (Scheme 5.13)[3] for cycloaddition with benzyne was slightly modified and applied to methyl 5-(acetoxymethyl)furan-2-carboxylate. In this series of experiments, variation upon the stoichiometric excess of anthranilic acid was further explored to test the normal electron demand Diels-Alder hypothesis (Scheme 5.15). A greater excess of benzenediazonium-2-carboxylate (2 eq.) gave good yield (89%) of methyl 4-(acetoxymethyl)-1,4-epoxynaphthalene-1-carboxylate.

To frame contribution of methyl carboxylate *versus* acetoxymethyl substituents in an AB type furan-diene, AA type furan-diene (dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate, 86%, Scheme 5.15) and BB type furan diene (1,4-epoxynaphthalene-1,4-diyl)bis(methylene) diacetate, 92%, Scheme 5.15) were also subjected to the cycloaddition with 2 eq. benzenediazonium-2-

carboxylate. The results seemed comparable under those reaction conditions, but the slightly lower yield of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate in Scheme 5.14 (86%) compared with the results from Scheme 5.13 (91%) may be indicative of less benzyne delivery to the reaction by this modified protocol.



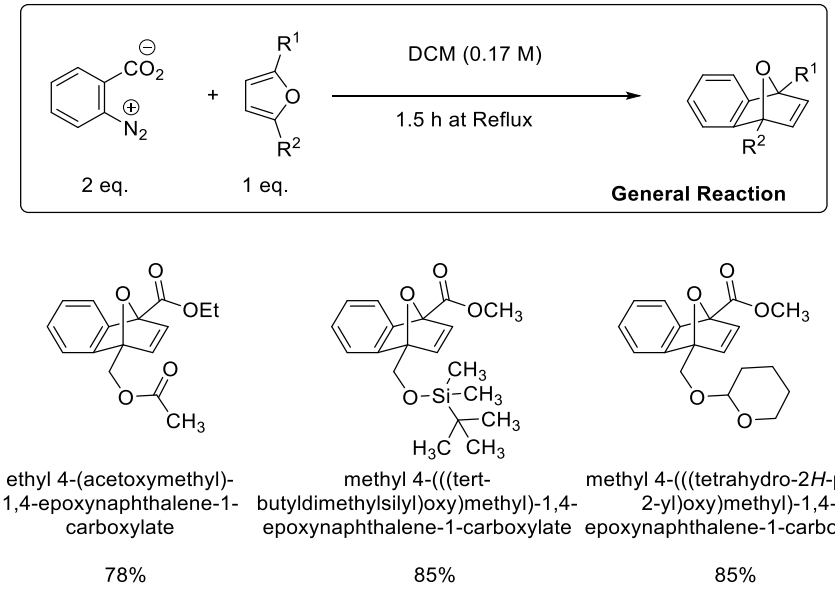


Benzyne eq.	dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate	methyl 4-(acetoxymethyl)-1,4-epoxynaphthalene-1-carboxylate	(1,4-epoxynaphthalene-1,4-diyl)bis(methylene) diacetate
1.0	na	na	63%
1.5	na	72%	85%
2.0	86%	89%	92%

Scheme 5.15. Benzyne by thermolysis. AB type furan-dienes (1)

The relationship between reaction stoichiometry and adduct yield with the optimal substrate (furan-2,5-diylbis(methylene) diacetate) was further explored (Scheme 5.15). A distinct trend in benzyne trapping was observed. As expected, at 1:1 stoichiometry the isolated yield of 7-oxabenzonorbornadiene product was around 60% and a 3:2 benzyne-precursor to furan-diene ratio led to an isolated yield of 85%. When a 3:2 benzyne-precursor to furan-diene ratio was employed with methyl 5-(acetoxymethyl)furan-2-carboxylate, an isolated yield of 72% was observed. The results from these studies suggest that the reaction outcome of the benzyne-Diels-Alder cycloaddition was largely ruled by the influence of a deactivating—*electron deficient*—group contained in a differentially substituted furan-diene. This was consistent with the strain-driven

benzyne reactivity model and leads to extreme dienophilicity under conditions of normal electron demand.



Scheme 5.16. Benzyne by thermolysis. AB type furan-dienes (2)

The thermolysis protocol with 2:1 reaction stoichiometry was extended to ethyl 4-(acetoxymethyl)-1,4-epoxynaphthalene-1-carboxylate (78%, Scheme 5.16) and resulted in more side products than the methyl 4-(acetoxymethyl)-1,4-epoxynaphthalene-1-carboxylate (Scheme 5.15). The substrate scope and substituent-effects were further investigated by carrying out reactions with methyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,4-epoxynaphthalene-1-carboxylate (85%) and methyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1,4-epoxynaphthalene-1-carboxylate (85%) (Scheme 5.16); greater steric bulk in the hydroxyl protecting group had a slight negative impact upon the yield of 7-oxabenzonorbornadienes.

5.3. Applications of Strained 7-Oxabenzonorbornadienes

Electron-rich adducts described in the previous chapter were readily prepared from reduced cellulose biorefinery platform chemicals and resembled those previously described in the chemical literature. Conversely electron-deficient 7-oxabenzonorbornadienes were starkly contrasted as a

new class of stained bicycles which were stabilized by a high barrier to ring opening reactions involving development of positive charge character in the transition state. As opposed to ring opening reactions mediated by expensive silane reagents, a cheap and practical two-step strategy replaced the one-step trimethylsilyl iodide mediated deoxyaromatization. Since the production of these potential platform molecules does not contain many steps and since each of the two steps proceeded with much greater economy taken together as compared with the single step approach, this was an example of counter-step-economy. This served as another clear example for the need to apply multivariate consideration to a synthetic optimization. The two steps were catalytic hydrogenation of the strained-olefin contained in 7-oxabenzonorbornadiene systems followed by acid mediated ring-opening and dehydration. The two-step approach was effective in aromatizing both electron rich and electron poor substrates, although a clear difference in mechanism was discovered by noting the different acid concentrations required for the reaction.

Owing to the high energy of the reactive intermediate benzyne, 7-oxabenzonorbornadienes do not suffer from facile retro-Diels-Alder reaction.[138-145] Electron rich varieties may be readily deoxygenated by various methods to afford naphthalene derivatives as part of an aromatic upgrade strategy.[146-149] The 7-oxabenzonorbornadienes contain a reactive-strained-internal olefin and strained ethereal-bridge which elects them exquisite targets for isomerization into naphthols,[150] photorearrangement,[151] chiral derivatization agents,[152] formal aryne polymerization,[153] ring opening polymerization,[154, 155] cyclopropanation,[156, 157] epoxidation,[158-161] 1,3-dipolar-cycloaddition,[162] [2+2] cycloaddition,[163-168] [4+2] cycloaddition,[169-175] oxidative ring-opening reactions,[176] and functionalization by various nucleophilic ring-opening reactions.[177-181]

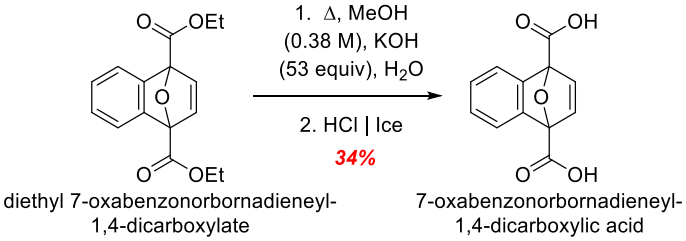
The parent ring system—*norbornene*—can undergo homopolymerization by four mechanisms to afford three distinct polymers: (1) ring opening polymerization, (2) cationic or free

radical addition polymerization, and (3) vinyl type metathesis polymerization.[182] Ring strain in 7-oxabenzonorbornadienes has been harnessed to drive ring-opening polymerization.[155] The sensitivity of those polymers to oxidation has been addressed by blocking the allylic/benzylic bridgeheads with alkyl substitutions;[183] presumably carboxy substitutions would also be quite effective while affording additional opportunity for network connectivity with potential application in the preparation of novel thermosetting materials. The rich chemistry of 7-oxabenzonorbornadienes has led to their use in developing previously unobtainable polymers as aryne surrogates in the preparation of (*o*-arylenes).[153]

5.3.1. Preparation of 7-Oxabenzonorbornadiene Monomers

Manipulation of various hydroxyl masking groups led to the preparation of multiple new bioderivable monomers.

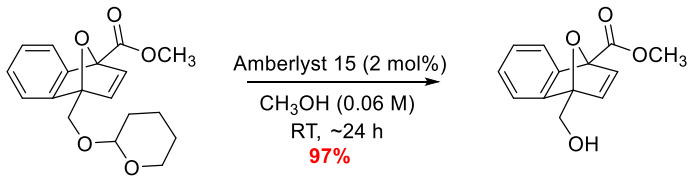
5.3.1.1. Preparation of a Bicyclic AA Type Monomer



Scheme 5.17. Alkaline hydrolysis of diethyl 7-oxabenzonorbornadienyl-1,4-dicarboxylate

In order to further characterize this new class of electron-deficient 7-oxabenzonorbornadienes, and to evaluate the likelihood that they would survive polyester or nylon synthesis, diethyl 7-oxabenzonorbornadiene-1,4-dicarboxylate was subjected to harsh-alkaline hydrolysis (Scheme 5.17). While the yield was low, isolating any of the desired bicyclic diacid product was promising.

5.3.1.2. Preparation of a Bicyclic AB Type Monomer



methyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1,4-epoxynaphthalene-1-carboxylate

methyl 4-(hydroxymethyl)-1,4-epoxynaphthalene-1-carboxylate

Scheme 5.18. Preparation of methyl 4-(hydroxymethyl)-1,4-epoxynaphthalene-1-carboxylate

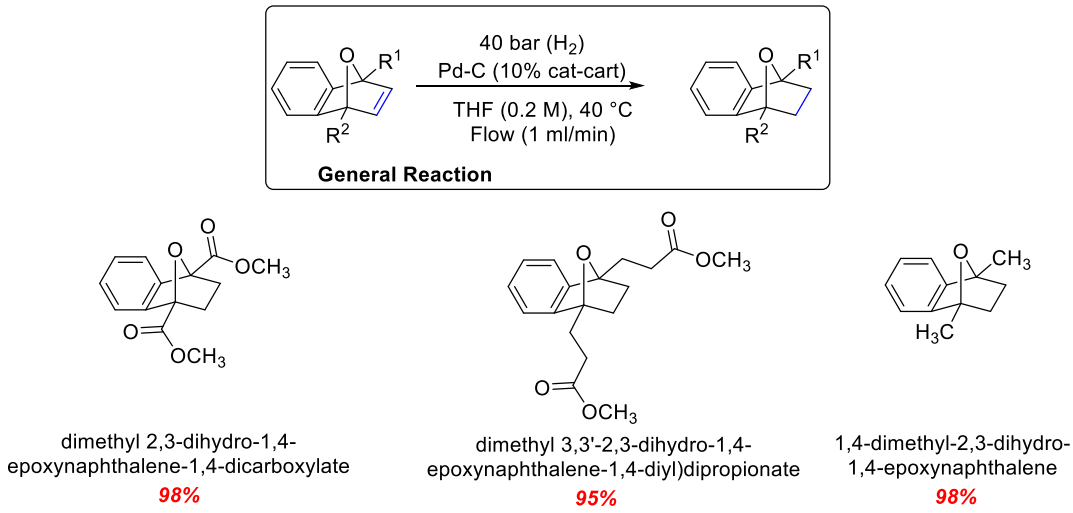
To achieve access to a series of biosourced hydroxyester AB type monomers, it was important to define conditions which could selectively unmask the hydroxyl substituent from protected bicyclic intermediates. Inspired by facile deprotection of tetrahydropyranyl ethers with mild Dowex resin,[184] methyl 4-(hydroxymethyl)-1,4-epoxynaphthalene-1-carboxylate was procured following acidic methanolysis of methyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1,4-epoxynaphthalene-1-carboxylate (Scheme 5.18). Facile isolation required filtration to remove the Amberlyst 15[185] resin and concentration under reduced pressure to remove solvent and volatile 2-methoxytetrahydropyran in excellent yield (97%).

5.3.2. Biorenewable 7-Oxabenzonorbornenes

A redox-neutral dehydroaromatization has been inspired by Wittig and Pohmer's original report of naphthalene synthesis from furan and benzyne.[51] A series of biorenewable 7-oxabenzonorbornadienes have been hydrogenated using a flow system in preparation for a study aimed solely at investigating this reaction. One advantage to the employment of a flow system is its linear scalability and small reaction volume which mitigates many of the hazards endemic to the handling of dangerous intermediates like hydrogen saturated transition metal catalysts. In theory a similar system[70] could be designed in which the Diels-Alder reactions could occur in one

loop without requiring isolation of the benzyne precursor (shock sensitive) followed by a pass through a hydrogenation loop.

Ring-strain can increase the reactivity of olefins. Enhanced reactivity was observed especially in catalytic hydrogenation reactions. The olefin-reactivity of 7-oxabenzonorbornadienes (dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate, dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)dipropionate, and 1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalene) is independent of substitution at the bridgehead. An aromatization strategy that selectively targets reduction apart from the ring-opening reaction offers potential to maximize the efficiency of the furanic aromatic upgrade strategy while affording another class of bicyclic derivatives. Uniformly efficient catalytic hydrogenations using a flow system were observed and excellent yields were achieved with little reaction optimization (Scheme 5.19);



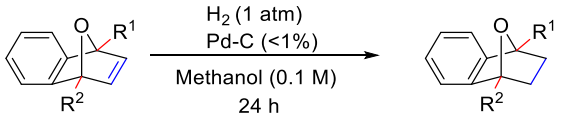
Scheme 5.19. Preparation of 7-oxabenzonorbornenes by flow catalytic hydrogenation

The diesters were crystalline solids with elevated melting points compared to 7-oxabenzonorbornadienes (dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate, and methyl 4-(acetoxymethyl)-1,4-epoxynaphthalene-1-carboxylate). Hydrogenation blocked many degradation pathways by removing the reactive olefin from these bicycles. Hydrogenated DAAs

(dimethyl 2,3-dihydro-1,4-epoxynaphthalene-1,4-dicarboxylate and dimethyl 3,3'-2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)dipropionate) were bench stable for over a year with no observable change in appearance or spectrum; liquid 1,4-dimethyl-2,3-dihydro-1,4-epoxynaphthalene did slowly yellow over time even upon storage in the freezer under inert atmosphere.

Table 5.11. Catalytic hydrogenation: preparation of 7-oxabenzonorbornenes

General Reaction



	Substrate		Product		
Entry	R^1	R^2	R^1	R^2	Yield[a]
1					94
2					97
3					96
4					98
5					95
6					94

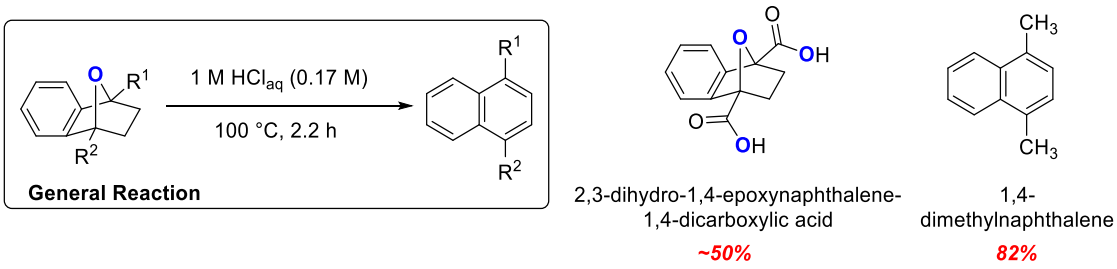
a; isolated yield (%).

Reaction description: 7-oxabenzonorbornene substrate and Pd-C (<1 mol%) were combined under argon. The flask was evacuated, charged with MeOH (0.1 M), covered with hydrogen, and stirred for 24 h at room temperature. The product was isolated in pure form following suction filtration through a pad of Celite and subsequent concentration.

Since symmetrically disubstituted 7-oxabenzonorbornadienes are known to undergo efficient catalytic hydrogenation at ambient temperature and pressure with min palladium catalyst

loadings.[3] A series of novel 7-oxabenzonorbornenes was prepared (Table 5.11) in excellent yield (>90%).[4] In a delightful turn of events, methyl 4-(hydroxymethyl)-3,4-dihydro-1,4-epoxynaphthalene-1-carboxylate was isolated from the hydrogenation mixture of methyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1,4-epoxynaphthalene-1-carboxylate also in excellent yield (98%, Table 5.11, entry 4).

5.3.2.1. Selective Hydrolysis of AA Type 7-Oxabenzonorbornene



Scheme 5.20. Hydrochloric acid (1 M) mediated hydrolytic aromatization

Dimethyl 2,3-dihydro-1,4-epoxynaphthalene-1,4-dicarboxylatewas treated with 1 M HCl at elevated temperature, and the major component of the isolate was a partial hydrolysis product with an intact oxygen-bridge: 7-oxabenzonorbornyl-1,4-dicarboxylic acid (~50%); The same conditions afforded 1,4-dimethylnaphthalenewith complete conversion and 82% isolated yield (Scheme 5.20). This was taken as strong indication of different ring-opening aromatization mechanisms.

5.4. 1,4-Disubstituted Naphthalenes

While 2,6-NDCA is considered a high performance alternative to TPA,[186] comparable polyesters derived from 1,4-NDCA have been classified as amorphous.[187] The drastic difference in these two naphthalenedicarboxylic acids is likely due to *peri* interactions[188] which cause the carboxy moieties to exist in noncoplanar conformations.[189] This unique attribute has been used to create integral plasticization of insoluble ridged rod polymers by creating kinks.[190] This has the

effect of improving their solubility and processability;[191] notably, 1,4-NDCA was used to prepare an electrochromic polyamide with good solubility and great potential for use in optoelectronics applications.[192]

Aromatic diacids [1,4-NDCA and TPA] appear prominently in hybrid organic/inorganic materials such as coordination polymers with diverse applications including chemo sensation of nitro-explosives[193] and light-triggered release of adsorbed molecules.[194] Often, 1,4-NDCA serves as a spacer in metal organic frameworks (MOFs) and allows for the tuning of structural properties.[195-197] Metal-organic gels (MOGs) are important for their application in catalysis,[198] gas adsorption, and as chemical sensors. Notably, 1,4-NDCA was used in a MOG to assiduously remove arsenic from aqueous solution; the π–π stacking of the naphthyl ring was credited as driving nanosheet genesis.[199]

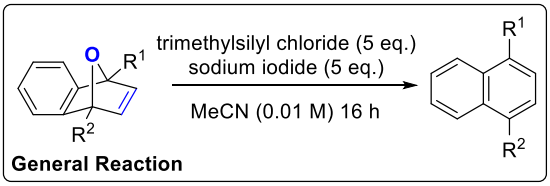
Sources of singlet oxygen in solution have been developed from 1,4-disubstituted naphthalenes upon their cycloaddition to said reactive species.[200-203] Naphthalene-1,4-endoperoxides have been derivatized to afford substituted 2,3-epoxynaphthalene 1,4-endoperoxides[204] in similar fashion to the generation of anti-1,2: 3,4-naphthalene dioxide with *meta*-chloroperoxybenzoic acid.[205]

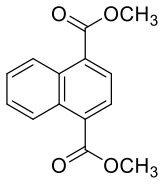
5.4.1. Aromatization of Benzyne-Furan-Diene Diels-Alder Adducts

The action of acid upon substrates, such as invert sugar, capable of acid mediated dehydrative aromatization was studied by M. M. Harrison (1914) by observing decreasing percentages of plane polarized light passing through the optically active sugar solutions during the course of the reaction.[206] It was concluded that acid concentration, identity, and temperature were capable of modulating the selectivity between aromatized products such as HMF, oligomeric

derivatives thereof, and later formation of oxidatively ring-opened products (levulinic acid and formic acid).

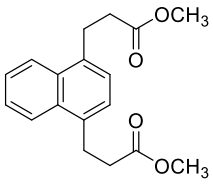
5.4.2. Reductive Aromatization by Action of Trimethylsilyl Iodide





dimethyl naphthalene-1,4-dicarboxylate

25% at reflux



dimethyl 3,3'-(naphthalene-1,4-diyl)dipropionate

98% at room temp

Scheme 5.21. Deoxygenation by trimethylsilyl iodide generated *in situ*
Carried out by postdoctoral researchers in the Sibi research group (Sermadurai Selvakumar Ph. D. and Nicolas Zimmermann Ph. D.).

In a process termed deoxyaromatization of 7-Oxabenzonorbornadienes, a one pot procedure was applied by our hardworking postdoctoral scholars (Sermadurai Selvakumar and Nicolas Zimmermann). With benzyne–Diels-Alder viability established, DAAs (dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate, and dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)dipropionate) were treated with trimethylsilyl iodide by postdoctoral researchers in the Sibi group (Sermadurai Selvakumar Ph. D. and Nicolas Zimmermann Ph. D.). The reaction afforded dimethyl naphthalene-1,4-dicarboxylate and dimethyl 3,3'-(naphthalene-1,4-diyl)dipropionate by deoxyaromatization (Scheme 21).[207] Electron-deficient dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate showed no reaction at room temperature and required elevated reaction temperature to undergo deoxygenation to afford poor yield of dimethyl naphthalene-1,4-dicarboxylate (25%).

Whereas alkyl-substituted dimethyl 3,3'-(1,4-epoxynaphthalene-1,4-diyl)dipropionate readily aromatized at ambient temperature (98%). When the stoichiometric excess of trimethyl silyl chloride and sodium iodide were reduced to three molar equivalents each and the reaction

was increased in concentration to 1.5 M in treatment of 1,4-dimethyl-1,4-dihydro-1,4-epoxynaphthalene, a good yield of 1,4-dimethyl naphthalene was observed (92%).

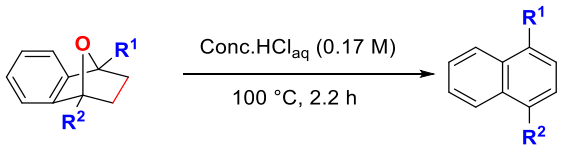
The novelty of bicycle dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate lies not only in its preparation but also in its resistance to ring opening. The stabilizing influence of electron-withdrawing groups at both bridgehead positions may be rationalized by considering the relative stabilities of the tertiary-allylic-benzylic carbenium intermediates developed by spontaneous ring opening. The action of trimethylsilyl iodide likely entails the initial formation of a silyloxonium intermediate. Formation of that intermediate should be irreversible under these conditions due to the comparative bond strengths of Si-O versus Si-I. To probe the observed stability of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate, its robust diethyl ester homolog was prepared and subjected to aggressive alkaline hydrolysis. The diester was treated with potassium hydroxide in boiling hot MeOH, then neutralized with concentrated hydrochloric acid on ice. The major product was 7-oxabenzonorbornadiene-1,4-dicarboxylic acid (33% yield). The deoxyaromatization step (Scheme 5.21), which converts our 7-oxabenzonorbornadienes into biorenewable naphthalenes is the least efficient in our series and would present the greatest hurdle to development of bulk materials from this technology.

5.4.3. Acid Mediated Dehydrative Aromatization of 7-Oxabenzonorbornenes

A new synthetic approach to fluorescent-brightening dye precursors—*namely 1,4-naphthalenedicarboxylic acid*—was reported by Um, Kang, Ham, Yang, and Lee (2000)—*translated into English by Eungyo Hong, an undergraduate research assistant in the Sibi research group*.[208] Such materials are required by textile and paper industries since bleaching technologies are effective in removing many of the brown colors associated with biomass derived materials but are ineffective in completely removing trace yellow-colored impurities. Dyes which absorb no

visible light, but which emit light in the 400–500 nm range effectively rebalance the color spectrum in combination with the reflected yellow light. The same emissive properties which make a good fluorescent brightener also make 1,4-napthalenedicarboxylic acid a poor candidate for food packaging since thin films of said compound will appear translucent when absorbing UV-light. Compared to the refined four-step synthesis from 1-methyl naphthalene described by Um *et al.*, the perfect regioselectivity set by the regiochemistry of cellulose derived furans (CDFs) during the benzyne cycloaddition valorization strategy—*three steps from dimethyl 2,5-furandicarboxylate*—may improve accessibility to these interesting materials. Direct access to cellulose derived naphthalenes (CDNs) can thereby play a pivotal role in adding value to poly(ethylene 2,5-furanoate) production- as well as packaging-waste- streams while contributing to sustainable practices in some large scale biobased materials industries.

Table 5.12. Dehydrative-aromatization with concentrated HCl(aq)



Entry	Substrate	Product	Yield (%)[a]
1	COOMe	COOH	91
2	COOEt	COOH	86
3	CH_2OAc	CH_2Cl	89
4	CH_2OBz	CH_2OBz	75
5	CH_2CH_2COOMe	CH_2CH_2COOH	72
6	CH_3	CH_3	84

a: isolated yield

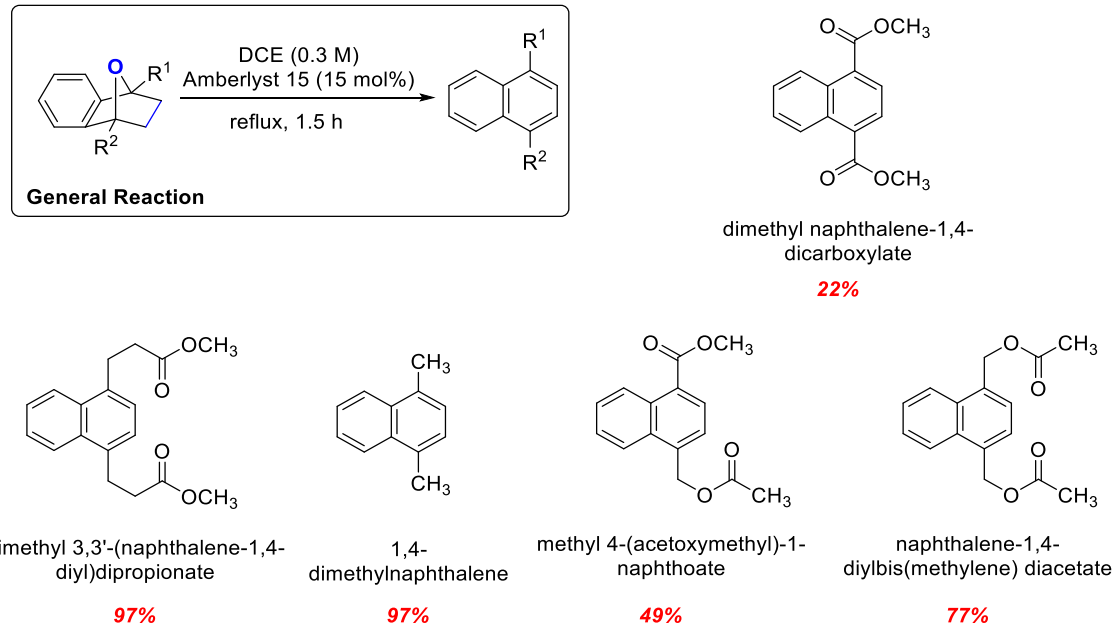
To afford naphthalenedicarboxylic acids directly, dimethyl 2,3-dihydro-1,4-epoxynaphthalene-1,4-dicarboxylate and dimethyl 3,3'-2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)dipropionate were treated with concentrated hydrochloric acid at 100 °C (0.17 M concentration of substrate) (91 and 86%, Table 5.12, entries 1 and 2 respectively). The differences in acid lability between benzoyloxymethyl and acetoxymethyl moieties were delineated by this set of experiments (Table 5,12, entries 3 and 4); while 1,4-bis(benzoyloxymethyl)-2,3-dihydro-1,4-epoxynaphthalene transformed into 1,4-bis(benzoyloxymethyl)naphthalene under these conditions (77%, entry 3), 1,4-bis(acetoxymethyl)-2,3-dihydro-1,4-epoxynaphthalene transformed into 1,4-bis(chloromethyl)naphthalene (entry 4, 89%).

Despite instances of chlorodehydration, this protocol led to the isolation of hydrolyzed naphthalenes with good yields by suction filtration. Likely due to its greater H_2O solubility, 3,3'-(naphthalene-1,4-diyl)dipropionic acid was isolated in lower yield under the unoptimized conditions. Alkyl substituted substrate, 1,4-dimethyl-2,3-dihydro-1,4-epoxynaphthalene, was converted to 1,4-dimethylnaphthalene isolated by extraction in only moderate yield (Table 5.12, entry 6, 84%). This could have been due to polymerization of the product and starting material as the color of the reaction mixture darkened.

5.4.3.1. Amberlyst 15 Mediated Dehydrative Aromatization of 7-Oxabenzonorbornenes

A selective method for dehydrating 7-oxabenzonorbornenes (dimethyl 2,3-dihydro-1,4-epoxynaphthalene-1,4-dicarboxylate, dimethyl 3,3'-2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)dipropionate, 1,4-dimethyl-2,3-dihydro-1,4-epoxynaphthalene, methyl 4-(acetoxymethyl)-3,4-dihydro-1,4-epoxynaphthalene-1-carboxylate and (2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)bis(methylene) diacetate) was explored (Scheme 5.22). Amberlyst 15 was chosen as a

reusable and highly active acid catalyst for dehydration reactions under nonaqueous conditions. Prevention of ester hydrolysis was a primary concern.



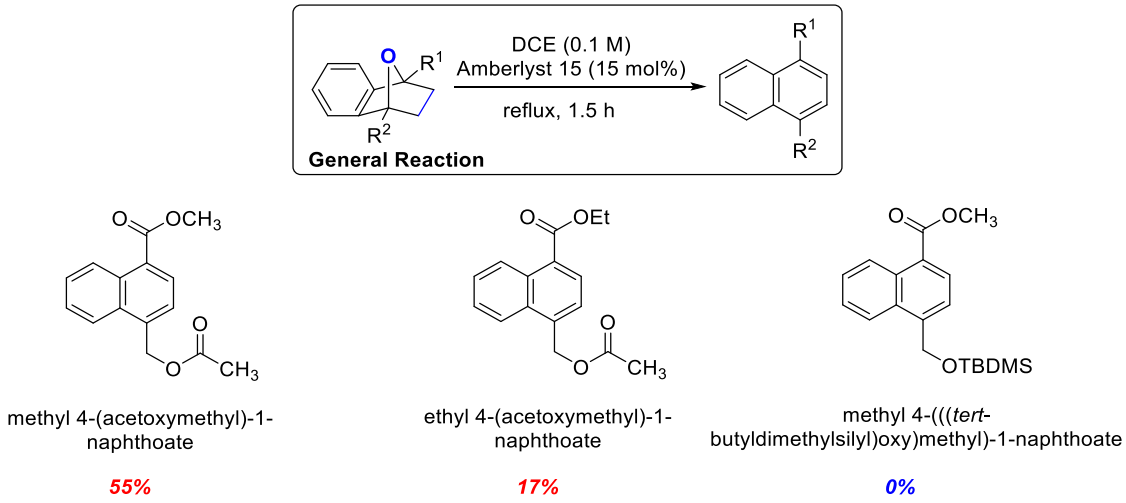
Scheme 5.22. Amberlyst 15 mediated dehydroaromatization (0.3M)

As expected by the previously observed resistance to ring-opening reactions (Table 5.11), dimethyl 2,3-dihydro-1,4-epoxynaphthalene-1,4-dicarboxylate converted to dimethyl naphthalene-1,4-dicarboxylate in low yield (Scheme 5.22, 22%) under conditions which completely converted alkyl-substituted substrates such as dimethyl 3,3'-2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)dipropionate and 1,4-dimethyl-2,3-dihydro-1,4-epoxynaphthalene in high yield (Scheme 5.22, 97% in both cases). This comparison highlights the astoundingly enhanced stability of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate was conserved in methyl 4-(acetoxymethyl)-3,4-dihydro-1,4-epoxynaphthalene-1-carboxylate.

The implication is that these novel oxygen-bridged bicycles may lead to the development of new classes of biomass-derived polymers. It also clearly shows that catalytic processes can

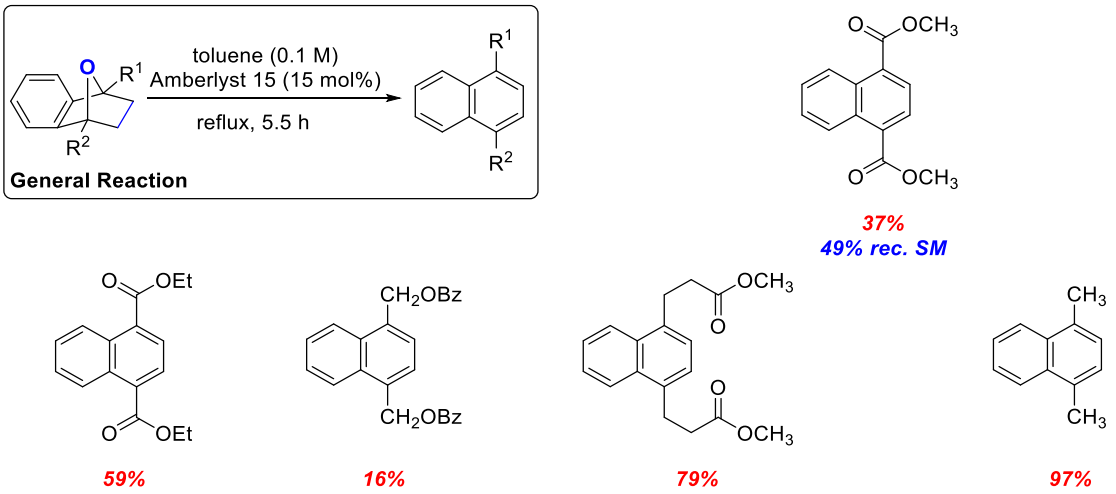
replace stoichiometric reagents in the aromatization of furan-derived [2.2.1] oxygen-bridged bicycles. Catalysis affords significant improvement to the economy of the overall approach.

For the deoxyaromatization of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate, an atom efficiency of only 16% was calculated owing to the use of a super-stoichiometric ring-opening/reducing agent. Catalytic hydrogenation and catalytic dehydration in the case of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate to methyl 4-(acetoxymethyl)-3,4-dihydro-1,4-epoxynaphthalene-1-carboxylate to dimethyl naphthalene-1,4-dicarboxylate shows more promise for development into an efficient and benign technology.



Scheme 5.23. Amberlyst 15 mediated dehydroaromatization (0.1 M)

Amberlyst 15 mediated dehydrative aromatization of 7-oxabenzonorbornenes[3] is facilitated by substituents with increasing aptitude to stabilize a developing positive charge at bridgehead positions.[3] Surprisingly, this technique (Scheme 5.22) was not particularly amenable to obtaining oxymethyl substituted naphthalenes. Concentration seemed to have little effect on the reaction outcome (compare Scheme 5.22 to Scheme 5.23). Steric bulk and hydrolytic infirmity (Scheme 5.23) both negatively affected the reaction's outcome.

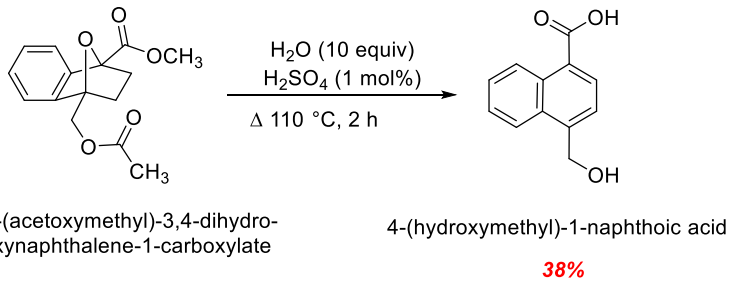


Scheme 5.24. Amberlyst 15 mediated dehydroaromatization in toluene (0.1 M)

In some cases, a large amount of the mass balance was recovered starting material. Silyl ether substrates afforded neither product nor recovered substrate. In the case of (2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)bis(methylene) diacetate, which contained small-stabilizing substitutions at both bridgeheads (Scheme 5.23), conversion of starting material was complete in 90 min. The low conversion and incomplete mass balance in reactions with dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate compared with the reaction of dimethyl 3,3'-(2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)dipropionate and 1,4-dimethyl-2,3-dihydro-1,4-epoxynaphthalene indicates that this reaction setup was not sufficiently removing the H_2O extruded in this reaction and that some hydrolysis of ester moieties was occurring.

The dehydration reaction of dimethyl 1,4-epoxynaphthalene-1,4-dicarboxylate (Scheme 5.24) was scaled up to 40 mmol. The reaction time was extended to 8 h. The reaction was sparged with nitrogen throughout the reaction to facilitate drying the reaction mixture. With those modifications, 74% of dimethyl naphthalene-1,4-dicarboxylate was isolated by flash column chromatography. Prior to separation, ^{1}H NMR indicated a contaminant of 1,4-naphthalene dicarboxylic acid with about 15% relative intensity compared with the desired diester product.

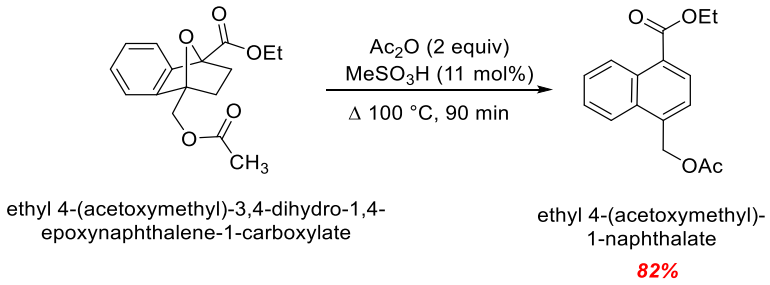
5.4.3.2. Preparation of an AB Type Monomer: 4-(Hydroxymethyl)-1-naphthoic Acid



Scheme 5.25. Preparation of 4-(hydroxymethyl)-1-naphthoic acid

A naphthalene analog of 5-(hydroxymethyl)furan-2-carboxylic acid was prepared (Scheme 5.25) by one pot deprotection and dehydroaromatization of methyl 4-(acetoxymethyl)-3,4-dihydro-1,4-epoxynaphthalene-1-carboxylate. The isolation of 4-hydroxymethyl-1-napthoic acid was simple; as the mixture cooled, light colored solid separated from the reaction mixture and was isolated by suction filtration. Supposing the low yield for the product was due to partial H_2O solubility, the filtrate was extracted repeatedly with EtOAc. Disappointingly, the extract was a mixture of oligomerized side products, not pure hydroxyacid.

5.4.3.3. Acetyl Methanesulfonate Mediated Dehydrative Aromatization of 7-Oxabenzonorbornenes



Scheme 5.26. Improved preparation of ethyl 4-(acetoxymethyl)naphthalene-1-carboxylate

Since polysulfonic acid containing macroreticular resin failed to afford high yields due to degradation of the benzylic oxymethylene moiety (Scheme 5.23), and since aqueous sulfuric acid also was inefficient (Scheme 5.25), another aromatization strategy was evaluated. Inspired by the

mixed anhydride dehydroaromatizations used in the preparation of phthalic anhydride,[83] ethyl 4-(acetoxymethyl)-3,4-dihydro-1,4-epoxynaphthalene-1-carboxylate was successfully converted to ethyl 4-(acetoxymethyl)-1-naphthoate in good yield (82%, Scheme 5.26). A similar reaction employed diacetate substrate (2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)bis(methylene) diacetate, and afforded naphthalene-1,4-diylbis(methylene) diacetate in 68% isolated yield. This set of reactions provided additional insight into the protective effect of incorporating electron withdrawing groups on the bridgeheads of 7-oxabenzonorbornenes.

5.5. Outlook

Synthesis of C1,C4-disubstituted 7-oxabenzonorbornadienes with electron withdrawing substituents could afford ready access to a currently obscure class of isobenzofurans such as dimethyl isobenzofuran-1,3-dicarboxylate[209] which are surprisingly stable; dimethyl isobenzofuran-1,3-dicarboxylate was isolated in 50% and 22% yield of the cis- and trans-isomers respectively. A melting point of 178–180 °C was reported. and could become uniquely important probes for the inverse electron-demand Diels-Alder reaction. Ready access to isobenzofurans from 7-oxabenzonorbornadienes could be achieved by a Diels-Alder/*retro*Diels-Alder strategy or by hydrogenation followed by flash vacuum pyrolysis.

We have developed a technology which employs the Diels-Alder reaction (DAR) between the super-dienophile, benzyne, and a series of cellulose derived furans (CDFs).[3, 4, 210] This work was initially inspired by attempts to prepare biomass-derived terephthalic acid (TPA) analogs, but has now developed into a rich platform for developing novel chemistries from renewable sources; the most noteworthy results to date can be illustrated by the power of this strategy to transform a single furanic-monomer of any type (AA, AB, or BB) into an entire family of monomers of the same type but with new skeletal structures.

The scope of this dissertation has been limited to experiments with the strain-driven-normal-electron-demand-super-dienophile, benzyne, and those promising results indicate potential opportunity to employ additional—*strain driven*—dienophiles in the near future. While benzyne is fine, all other attempts to utilize the DAR with FDCA or its derivatives have been met with diminutive yields following the natural reactivity trend of the DAR.[122] Benzyne, has been demonstrated to be less sensitive to the electronic demands of the DAR while still following the expected trend in reactivity also known as normal electron demand DAR. The waste-free process of pericyclic reaction between diene and dienophile has colloquially been termed adduction and the products are called adducts.

The Diels-Alder adducts (DAAs) formed from renewable furanic platform chemicals provide a route towards cellulose-derived naphthalenes (CDNs). They also have potential to provide the basis of a new family of polymers with novel structures. Since structure controls physical properties, we can expect to develop correspondingly novel properties. This technology provided the core of a funded ND-EPSCoR Doctoral Dissertation award from August 2016 till August 2018 and will hopefully continue to contribute to North Dakota's excellence in research.

That proposal outlined three enumerated tasks; (1) the design, synthesis and characterization of cellulose-derived poly[ethylene-1,4-napthalate] (1,4-PEN) including a side investigation into the properties of its copolymer with polyethylene-2,5-furanoate[120] (PEF) to quantify the expected property enhancement; (2) the preparation and evaluation of the DAAs from benzyne and CDFs as monomers in the synthesis of unsaturated polyesters and their copolymers; (3) a direct transformation from aromatic polyesters such as PEF into unsaturated polyesters akin to those in Task 2 by direct action of benzyne and other biomass-derived super-dienophiles upon solubilized PEF.

Many of the current trends in sustainable technology research can be described as attempts to exploit the novel properties of renewable chemicals with a focus on the valorization of biomass.[211] Motivation for these actions is commonly ascribed to the trending fears of an oil-supply-crash and the impact of this petroleum age upon the environment. In this dissertation and exemplified in this chapter an alternative and greater motivation can be tapped. There are enough exciting chemistries latent in biorenewable materials awaiting discovery to motivate pursuit of their applications in sustainable materials science.

The complementarity of fossil *versus* renewable structures emphasizes a point of economic importance which is a penultimate measure of sustainability. Consider a list of aromatic diacid (AA type monomers) used in the polyester industry; the list contains only one with potential for further aromatic upgrading. Only the biomass-derived FDCA contains a furanic core which is amenable to further functionalization by the DAR.

Unfortunately, 1,4-PEN is unlikely to compete with 2,6-PEN or PET in packaging polyesters due to *peri* interactions between carboxylate moieties. The electronic-field repulsion they experience being in close proximity to protons on the fused aromatic ring led to a distortion of their co-planarity and consequently their overlap with an extended π-cloud. This phenomenon provides a plasticizing effect by decreasing the rigidity of the system and actually sets 1,4-NDCA apart from every other aromatic diacid in common use; when possible aromatic diacids (terephthalic acid, isophthalic acid, 2,6-NDCA, and FDCA) are predicted to maximize orbital overlap between aromatic π-systems and carboxylate carbonyls which contributes to their crystallinity and rigidity.

When a strange property such as the relatively low melting point of 1,4-NDCA is observed in a trend of 1,3 or 1,4 or 2,5 disubstituted carboxylic acids, the aberration has got to be exploited!

In fact, 1,4-NDCA could be considered a privileged structure for use in preparing metal organic frameworks (MOFs). These polymeric materials are hybrids of organic and inorganic components and have a diverse range of ever-expanding applications. This range includes noteworthy examples such as methane fuel storage and release at safer operating pressures to remediation of biologically damaging chemical contaminants from soil or ground H_2O.

The reason for price disparity between 1,4-NDCA and 2,6-NDCA is likely due to a combination of scaling economics and the synthetic difficulty encountered in grafting both carboxy moieties onto the same ring when beginning with a petroleum feedstock. The development of a technology which can provide difficult or impossible substitution patterns [from petroleum] selectively from biomass stands a good chance of becoming commercially viable even in the face of any future oil-gluts.

Post Polymerization Modification

The same conditions required to affect the redox-neutral dehydrative aromatization could bring about polymerization by acid catalyzed transesterification in a tandem fashion. If this strategy proves feasible, then pure 1,4-PEN could be prepared on large scale for the first time and its physical properties determined. This would allow for a direct comparative study with PET, 2,6-PEN, and PEF as well as of their copolymer blends. That information is obviously lacking in the literature and could have a broad impact if it could establish a predictive model for the quantification of polyester property enhancement from blending expensive-high performance-polyesters with base materials. High-performance properties would be the economic key to commercialization of any new technology which finds itself in competition with the petroleum industry.

The DAAs themselves present a heretofore undeveloped area of polymer science. The DAAs are 1,4-dihydro-1,4-epoxynapthalenes which are ripe for ring opening polymerization techniques including ring opening metathesis polymerization (ROMP) which would be driven by the high degree of ring strain in the bridged cycle. The substituents on position 1 and 4 are the direct result of functional group manipulation of CDFs. The strained internal unsaturate is quite reactive under the many known transformations which use alkenes as. In the realm of materials science, unsaturated polyesters are a primary target since they may be processed as thermoplastics but cured like thermosets. The aromatic ring is expected to impart rugged physical properties when incorporated into a polymer backbone thereby improving the material's durability. The DAAs from CDFs and benzyne exist as meso forms (AA or BB type) and as diastereomeric pairs (AB type). This has a large impact on the potential utility of the material since highly crystalline polymers are tough but brittle. They are also unsuitable for many coating and packaging applications since the crystallites display a phenomenon known as total internal reflection (the same phenomenon which transforms a clear and colorless sugar or salt crystal into a lump of apparently white material) which makes them appear cloudy or turbid.

A novel scheme for the direct transformation of PEF and related polyesters into unsaturated polyesters by benzyne's attack upon the furanoate backbone has been devised. Since this strategy does not aim to produce an aromatic diacid from the DAR**,** the use of other biomass-derived-super-dienophiles such as maleic anhydride, maleimides, and dicarboxyacetylenes should be included as substrates to quantify the portion of property modulation which depends upon the nature of the dienophile. The CDFs represent a privileged class of feedstocks that are more readily prepared from renewable sources than from petroleum, and so demonstrate the wonderful new molecular architectures that await discovery and development for sustainable-materials-scientists.

5.5.1. Chapter Conclusions

This work demonstrates the valorization of cellulosic biomass-derived chemicals. This work has extended the range of functionalized monomers accessible from non-edible biomass and highlighted the utility of Diels-Alder cycloaddition for upgrading furanic platform chemicals. Importantly, chemoselective transformations yielding HMFA and ester derivatives enabled the synthesis of unsymmetrical monomers including hydroxyesters of interest for homopolymerization. 7-Oxabenzonorbornadienes and 7-oxabenzonorbornenes were obtained in good to excellent yields, and dehydroaromatization of the latter demonstrated the potential of this approach for accessing a variety of symmetrical (AA and BB type) as well as unsymmetrical (AB type) naphthalenic monomers from biomass.

The new furanic AA, BB and AB type monomers provided efficient access to oxabenzonorbornadiene and oxabenzonorbornene skeletons via a Diels-Alder cycloaddition with benzyne followed by hydrogenation. Systems thinking has been applied throughout and these efforts provide the basis for a new generation of novel materials by transformation of furanic core structures. The ability to shift the core structure of polyester precursors could create a pathway for the value-added recycling of future furanic packaging plastics.

Design thinking could facilitate future deployment and scaling of these novel technologies allowing for exploration of the materials properties of polymers derived thereof. Barriers to this type of future work include the high cost of most methods for the generation of benzyne, the typical use of super-stoichiometric amounts of furan-diene, and the purification profile of reactions which utilized super-stoichiometric amounts of benzyne. Many of these obstacles were investigated and have been detailed herein. Repeatedly in this study we found that the direction of benzyne research has been diverted towards more controlled generation under mild conditions and has focused

predominately on the use of electron rich dienes. Therefore, the most modern techniques were suitable for furanics with reduced substituents but not for the dicarboxylates. Conversely the older more general methods could be readily adapted for the purpose of scalable trapping by electron deficient furan-dienes with incipient potential for biorenewability.

The highly-oxidized nature of compounds such as HMF and FDCA seem uniquely suited to redox-efficient transformation into benzenoids of practical importance by cycloaddition and aromatization strategy. The development of a green Diels-Alder Reaction combines benzyne and biomass-derived-furan-dienes while requiring atom and redox economy to provide a route to the Diels-Alder adducts (1,4-disubstituted 7-oxabenzonorbornadienes) which themselves form a structurally diverse series of cellulose-derived-platform-chemicals. Valorization by cycloaddition strategy with AB type furanics derived from 5-(hydroxymethyl)furan-2-carboxylic acid prepared novel AB type monomers (mixed diesters, hydroxyesters or hydroxyacids), which are amenable to homopolymerization. The development of such monomers from readily available furanic-substrates should facilitate further developments in bio-based materials applications; the execution of polycondensation reactions using AB type monomers is simplified by the perfect reaction stoichiometry of pure samples. Valorization of a series of symmetrically and differentially substituted AA, AB, and BB type furan-dienes has been combined to form this chapter.

5.6. Experimental

5.6.1. General Procedures

Unless otherwise stated, all commercially procured materials were used as received without further purification. Melting points were determined on a REACH Devices RD-MP digital melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 MHz instrument and processed with Topspin software. Infrared spectra

were recorded with a Nicolet™ iS™ 10 Fourier transform infrared spectrometer using a diamond sample plate for attenuated total reflectance and processed using Omnic; the FTIR figures were prepared using Origin Pro. High resolution mass spectra were recorded on Waters Synapt G2-Si high definition mass spectrometer and were processed using MassLynx. Unless otherwise stated, all reactions were stirred magnetically by polytetrafluoroethylene coated magnetic spin-bars. All mention of silica gel refers to Sorbtech standard grade silica gel: 230-400 mesh.

Theoretical yields have been calculated in terms of the limiting reagent throughout this work.:

$$Theoretical\ Yield = 1\ Molar\ Equivalent = 1\ eq. \tag{5.1}$$

Yields have been calculated only with respect to the limiting reagent and are reported as percentages:

$$Yield\ (\%) = \frac{equiv.product\ isolated}{theoretical\ yield} \times 100 \tag{5.2}$$

Recovered substrate was calculated by considering the amount of substrate recovered from flash chromatographic purification in relation to the amount charged into a reaction flask:

$$Recovered\ Substrate\ (\%) = \frac{equiv.recovered\ substrate}{equiv.charged\ substrate} \times 100 \tag{5.3}$$

$$Mass\ Balance\ (\%) = \sum all\ characterized\ isolates = \ yield\ (\%) + recovered\ substrate\ (\%) \tag{5.4}$$

5.6.2. Synthesis of Benzyne Furan-Diene Diels-Alder Adducts

Benzenediazonium-2-carboxylate is known to be shock sensitive and may be easily detonated when dry. Strangely, there is also a greater danger of detonation when a slurry of benzenediazonium-2-carboxylate has been allowed to settle and especially when the diazotization mixture is stored in a freezer. Both factors seem to facilitate crystallization of the inner salt and lead to solvent exclusion with concomitant enhanced sensitivity. Do not use metal spatulas at any

time. Disposable polyethylene transfer pipettes were extremely useful for agitation and transfer of the slurry.

5.6.2.1. Procedure for 1 h Double Drip Experiment (entry 1, Table 5.1)

A 100 mL single neck round bottomed flask was charged with a spinbar, diethyl 2,5-furandicarboxylate (2.12 g, recrystallized from IPA for this study, 10 mmol, 1.0 eq.), DCM (20 mL) and the mixture was swirled into a complete and colorless solution. The mixture was warmed in a preheated thermoregulated oil bath (45 °C) beneath a Graham condenser sealed with a red rubber septum (plumbed with flexible tubing to a mineral oil bubbler). The mixture reached reflux and some bubbles escaped prior to equilibration. A Harvard syringe pump was used to simultaneously deliver a steady stream of *tert*-butyl nitrite (1.5 mL, 90% 11 mmol, 1.1 eq.) diluted to 10 mL with benchtop DCM and anthranilic acid (1.37 g, 10 mmol, 1.0 eq.) which had been taken up in THF (10 mL, HPLC grade).

The solutions were infused through the red rubber septum *via* long needles, and they dripped onto the very bottom of the coolant spiral inside the Graham condenser over the course of 1 h at a rate of 0.166 mL per min. This slowly led to the precipitation of some solid on the inner walls of the flask which could not be rinsed down with DCM. The mixture bubbled slowly throughout the infusion and stopped within 30 min of the completion of the addition.

The mixture was raised from the oil bath and allowed to cool to room temperature. Thin layer chromatographic (TLC) analysis indicated two motile spots in both 6:1 and 6:2 (Hex:EtOAc). There was a bright fluorescing spot near the baseline which was likely residual anthranilic acid and the lower of the two motile spots reacted with saturated aqueous potassium permanganate ($KMnO_4$ stain) which was indicative of an olefin such as the 7-oxabenzonorbornadiene product.

The spot looked very light in comparison with the substrate. The spin bar was pulled, and the dark-red-orange mixture was concentrated by rotary evaporation then adsorbed onto silica gel before being loaded onto a 75 g cartridge of 60 A amorphous silica gel above a 120 g column of the same. The cartridge was primed with Hex at 50 mL/min until it was completely wetted. The column was primed with 460 mL of Hex at 120 mL/min. A gradient was programmed which began at 0% EtOAc and reached 30% in 15 column volumes. The system was eluted on that gradient at 50 mL/min until column volume nine was reached at which time the flow rate was increased to 85 mL/min. The eluent peak centered around nine column volume marks where the darkest spot on the TLC plate had eluted and was identified as the starting material.

The underwhelming product eluate escaped the column just after the starting material had escaped and was identified as the diethyl 7-oxabenzonorbornadienyl-1,4-dicarboxylate. The respective fractions were combined and concentrated while the fractions which contained recovered starting material were also combined and concentrated. The concentrates were transferred into tared vials with the aid of a small amount of chloroform. The recovered material was then flushed with nitrogen in a fume hood to remove most of the residual solvent. The mass of product at that point was 1.13 g. The residue was then dried on the high vacuum line with warming from a heat gun to keep the viscous-oil fluid. Product mass was 0.78 g (2.7 mmol) of viscous red orange oil, 27% isolated yield. Recovered substrate was 1.27 g (6.0 mmol) of golden brown crystalline solid 60%. Mass balance: 87%.

5.6.2.2. Procedure for 10 h Double Drip Experiment (entry 2, Table 5.1)

Same as for entry 1, with the following exceptions: (1) the needles were adjusted so that their drops could mix before hitting the solution, but such that they would not be able to contact the side walls of the flask, (2) the addition rate was set to 1 mL per h so that the total addition

would take 10 h. Product mass was 1.35 g (4.7 mmol) of viscous red orange oil, 47%. Recovered substrate was 0.77 g (3.6 mmol) of brown crystalline solid 36%. Mass balance: 83%.

5.6.2.3. Procedure for SS Experiment (entry 3, Table 5.1)

A 100 mL single necked round bottomed flask was charged with anthranilic acid (1.37 g, 10 mmol, 1.0 eq.), THF (10 mL, HPLC grade inhibited with BHT). That mixture formed a colorless solution upon stirring at room temperature. Diethyl 2,5-furandicarboxylate (2.12 g, 10 mmol, 1.0 eq.) was added; the furan-substrate dissolved almost instantaneously. The mixture was diluted with DCM (20 mL), from a benchtop squirt bottle.

The room temperature solution was stirred as a solution of *tert*-butyl nitrite (1.5 mL of 90%, 11 mmol, 1.1 eq.) dissolved in DCM (10 mL) was added dropwise. The *tert*-butyl nitrite was a light-yellow color out of the reagent bottle, but it rapidly turned orange upon dripping into the reaction solution. The initial dissolution of the *tert*-butyl nitrite was endothermic, and the combination with the reaction solution did not seem to generate an exotherm. The mixture spontaneously generated a slurry which was light orange and transitioned to a brick red color which indicated formation of the triazene adduct of benzenediazonium-2-carboxylate and anthranilic acid.

The combination was stirred at room temperature for 3.75 h without losing its brick-red color. The mixture was fixed under a Dimroth condenser and lowered into an oil bath (45 °C); the evolution of gas was monitored by watching a gas bubbler which had been affixed to the top of the condenser. The product and recovered substrate were isolated as described above. Product mass was 0.77 g (2.7 mmol) of viscous red orange oil, 27%. Recovered substrate was 1.31 g (6.2 mmol) of golden brown crystalline solid 62%. Mass balance was 89%.

5.6.2.4. Procedure for SS Experiment (entry 4, Table 5.1)

A 100 mL single neck round bottom flask was charged with diethyl 2,5-furandicarboxylate (2.12 g, 10 mmol, 1.0 eq.), anthranilic acid (1.37 g, 10 mmol, 1.0 eq.), DCM (10 mL) and the mixture formed a white slurry which would not clear up upon stirring. THF (10 mL, HPLC) was added and a complete solution formed rapidly. The mixture was diluted with DCM (another 10 mL) and the solution persisted. At room temperature, trifluoroacetic acid (0.05 mL, 0.6 mmol, 0.6 eq.) was added to the mixture which gave no observable change.

tert-Butyl nitrite (1.5 mL, 90%, 11 mmol, 1.1 eq.) was diluted with DCM (10 mL) and added to the stirring reaction solution dropwise at first and finally in a steady stream. The mixture was bright orange, and then it became turbid. The mixture turned brick-red eventually and then slowly transitioned into a tan colored slurry suspended in dark-red solution. Following 1.5 h of stirring, the mixture was affixed to a Dimroth condenser and heated to reflux in an oil bath (45° C) for 1 h. The reaction was worked up as above. Product mass was 0.78 g (2.7 mmol) of viscous red orange oil, 27%. Recovered substrate was 1.35 g (6.3 mmol) of brown crystalline solid 63%. Mass balance: 90%.

5.6.2.5. Procedure for SS Experiment (entry 5, Table 5.1)

A 100 mL beaker was charged with anthranilic acid (1.37 g, 10 mmol, 1.0 eq.), THF (10 mL, HPLC grade) and a complete solution formed rapidly. At room temperature, trifluoroacetic acid (0.05 mL, 0.6 mmol, 0.6 eq.) was added to the mixture which gave no observable change.

Tert-butyl nitrite (1.5 mL, 90%, 11 mmol, 1.1 eq.) was diluted with DCM (10 mL) and added to the stirring reaction solution dropwise. The mixture was bright orange, and then it became turbid before it turned brick red. Following 2.5 h of stirring the mixture had become a tan slurry; the mixture was diluted with DCM which caused it to develop a reddish color. The mixture was

chilled in an ice bath, and carefully separated by suction filtration through a ceramic Hirsch funnel and qualitative filter paper (1 cm). The orange solid residue was rinsed with ice cold DCM.

Cold DCM was used to wash the residue through a polypropylene funnel into a 100 mL single neck round bottom flask which had been calibrated to 40 mL; the flask was charged with diethyl 2,5-furandicarboxylate (2.12 g, 10 mmol, 1.0 eq.), and a spin-bar then diluted to 40 mL with DCM. The flask was affixed to a Dimroth condenser heated to reflux in an oil bath (45° C) for 1 h. The reaction mixture was stirred for 60 min and was worked up as described above. Product mass was 1.10 g (38 mmol) of viscous golden oil, 38%. Recovered substrate was 1.24 g (58 mmol) of brown crystalline solid 58%. Mass balance: 96%.

5.6.2.6. Procedure for SS Experiment (entry 6, Table 5.1)

Same as entry 5 but the 100 mL round bottom flask was charged with less 2,5-furandicarboxylate (1.07 g, 5.0 mmol, 0.5 eq.). Product mass was 0.83 g (2.9 mmol) of viscous golden oil, 58%. Recovered substrate was 0.37 g (1.8 mmol) of golden brown crystalline solid, 35%. Mass balance: 93%.

5.6.2.7. General procedure for 5 h Double Drip Solvent Screening (Table 5.2)

A 50 mL single neck round bottom flask was charged with diethyl 2,5-furandicarboxylate (0.71 g, recrystallized from IPA, 3.3 mmol, 1.0 eq.), a spin-bar, and the desired solvent (4 mL). Anthranilic acid (0.46 g, 3.3 mmol, 1.0 eq.), was loaded into a breached polypropylene syringe (6 mL) which was secured to a long 18 gauge stainless steel needle through which was drawn up the desired solvent (to a volume of 4 mL) and the syringe was repeatedly inverted to form a solution. For the halogenated solvents (entries 6–10) which had difficulty dissolving the anthranilic acid, DME (2 mL) was first drawn up into the syringe and a solution was formed before dilution (to 4 mL) with the desired solvent. Another 6 mL disposable syringe equipped with a long 18-gauge

stainless steel needle was used to draw *tert*-butyl nitrite (0.5 mL, 90%, 3.6 mmol, 1.1 eq.), which was then diluted (to 4 mL) with the desired solvent and mixed to homogeneity by repeated inversion.

The substrate charged flask was affixed to a short West condenser which was sealed with a red rubber septum; a mineral oil gas bubbler ran to flexible tubing tipped with a cut-off syringe/disposable 18 g stainless steel needle which was inserted into the headspace of the reflux condenser through the septum. The reaction mixture was thermally equilibrated with an oil bath (preheated to 5 °C above the boiling point of the employed solvent). The syringes containing the benzenediazonium-2-carboxylate precursors were loaded into a dual delivery syringe pump (Harvard Apparatus) and their needles were inserted through the septum and down the inner wall of the West condenser to within 2 cm of the reaction mixture's surface.

The anthranilic acid and *tert*-butyl nitrite solution were delivered continuously over five h, the reaction was allowed to cool, concentrated by rotary evaporation under reduced pressure, adsorbed onto silica gel, and purified by flash chromatography using Hex and EtOAc as the mobile phase. The fractions containing recovered substrate and product were respectively combined, concentrated by rotary evaporation under vacuum, and dried to a constant mass on a high vacuum line.

5.6.2.8. General procedure for Single-shot Solvent Screening (Table 5.3)

A 50 mL single neck round bottom flask was charged with diethyl 2,5-furandicarboxylate (0.71 g, recrystallized from IPA, 3.3 mmol, 1.0 eq.), a spin-bar, and the desired solvent (14 mL), and anthranilic acid (0.46 g, 3.3 mmol, 1.0 eq.). *tert*-Butyl nitrite (0.5 mL, 90%, 3.6 mmol, 1.1 eq.) was added dropwise to the reaction mixture as it stirred above an oil bath preheated (to 5 °C above

the boiling point of the desired solvent). The mixture would transition from either a light slurry or colorless solution (depending upon the solubility of anthranilic acid in the studied solvent).

The flask was affixed to a tall West condenser which was sealed with a red rubber septum; a mineral oil gas bubbler was installed as described above. The reaction mixture was lowered into the oil bath within five min of the union of reagents and always appeared as a brick red slurry by that time. The reaction was stirred at 450 rpm and gently refluxed for 50 min; the reaction stopped evolving gas by that time. The reaction mixture was worked up as described above.

5.6.2.9. General procedure for (Table 5.4)

A 50 mL single neck round bottom flask was charged with diethyl 2,5-furandicarboxylate (2.2, 1.7, 1.1, or 0.8 mmol, 1.0 eq.), a spin-bar, anthranilic acid (3.3 mmol, 1.5, 2.0, 3.0, 4.0 eq.) and chloroform (enough to prepare a 0.24 M solution of substrate). To that stirring mixture (above an oil bath preheated to 65 °C) was added *tert*-butyl nitrite (0.5 mL, 90%, 3.7 mmol, 1.1, 1.8, 2.2, 3.3, 4.4 eq.) and within 5 min, the brick red reaction slurry was affixed to a tall West condenser outfitted with a mineral oil bubbler and lowered into the oil bath to reflux for one h. The reaction mixture was pulled from the oil bath and worked up as described above.

5.6.2.10. General procedure for (Table 5.5)

A 50 mL single neck round bottom flask was charged with diethyl 2,5-furandicarboxylate (3.3 mmol, 1.0 eq.), a spin-bar, anthranilic acid (3.3 mmol, 1.0 eq.) and chloroform (enough to prepare a 0.024, 0.10, 1.11, 2.4 M solution of substrate). To that stirring mixture (above an oil bath preheated to 65 °C) was added *tert*-butyl nitrite (0.5 mL, 90%, 3.7 mmol, 1.1 eq.) and within 5 min, the brick red reaction slurry was affixed to a tall West condenser outfitted with a mineral oil bubbler and lowered into the oil bath to reflux for one h. The reaction mixture was pulled from the oil bath and worked up as described above.

5.6.2.11. General procedure (Table 5.6)

A 50 mL single neck round bottom flask was charged with furan-substrate (2 mmol, 1.0 eq.), a spin-bar, anthranilic acid (2 mmol, 1.0 eq.) and chloroform (8 mL). To that stirring mixture (above an oil bath preheated to 65 °C) was added *tert*-butyl nitrite (0.3 mL, 90%, 2.2 mmol, 1.1 eq.) and after 5 min, the brick red reaction slurry was affixed to a tall West condenser outfitted with a mineral oil bubbler and lowered into the oil bath to reflux for 30 min. The reaction mixture was pulled from the oil bath and worked up as described above.

5.6.2.12. General Procedure (Table 5.7)

A 50 mL pear shaped flask was charged with a spinbar, anthranilic acid (1.37 g, 10 mmol, 2.0 eq.) and DME (10 mL, warm, freshly distilled off of sodium benzophenone ketyl). A lightly amber solution formed. The mixture was chilled in an ice bath and stirred as *iso*-amyl nitrite (1.5 mL, 11 mmol, 97% was added as a light-yellow liquid, 2.0 eq.). The nitrite addition caused the united solution to become orange, then light yellow, then rusty red colored as the mixture was stirred for 30 min on the ice. The mixture had formed a brick red slurry as it stirred for five h on ice.

A solution of furan substrate (5.0 mmol, 1.0 eq.) in dry DME (25 mL, 0.2 M) was warmed in an oil bath (50° C). The spin bar from the diazotization mixture was pulled and transferred to the stirring solution which was from then on stirred vigorously. The small amount of red slurry which had transferred became a colorless slurry upon thoroughly mixing with the furan-solution. A Pasteur pipette was used to draw up shots of the ice-cold-red-slurry and drip that mixture into the furan solution. Five min of latent time was afforded between each diazo-addition. In that five min, a solution would form, then the reaction would redden; the 80 °C reactions became amber solutions much faster in comparison. Additions were within two h and ten min of reaction time.

The mixture was stirred for twenty min and the heat was killed. The mixture was allowed to thermally equilibrate with ambient temperature overnight. The red solution was concentrated by rotary evaporation, adsorbed directly onto silica gel and purified by flash chromatography.

5.6.2.13. General Procedure: (Table 5.8)

A 50 mL round bottom flask was charged with anthranilic acid (1.37 g, 10 mmol, 2.2 eq.) a spin bar, and dry DME (10 mL). The mixture was stirred until a solution formed, then it was chilled in an ice bath before isoamyl nitrite (1.5 mL, 2.2 eq.) was added by syringe. The mix rapidly gave a brick red slurry, which was stirred for four h. An aliquot of the diazotization mixture was pipetted into a solution of furan substrate (4.6 mmol, 1 eq.) in dry DME (20 mL, 0.23 M solution) in a preheated oil bath (80 °C). Additions of the red slurry were made every five min and were completed within two h. The mixture was stirred for 30 min and then the heat was killed before the mixture was allowed to stir overnight. The mixture was concentrated, adsorbed onto silica gel and purified by flash chromatography.

5.6.2.14. General Procedure (Table 5.9)

A 20-dram sample vial was charged with anthranilic acid (1.37 g, 10 mmol, 3 eq.), and DME (5.0 mL freshly distilled off of sodium benzophenone ketyl) and a clear faintly yellow solution formed. The solution was chilled in a H_2O ice bath and sealed with a 14/20 red rubber septum. After fifteen min chilling, *iso*-amyl nitrite (1.52 mL, 11 mmol, 2.2 eq.) was added which immediately turned orange and began giving brick red precipitate within ten min. The mixture was stirred for three h after which the red solid was freed from the walls of the vials with the aid of a rubber policeman and diluted with additional DME (5.0 mL).

A solution was prepared in a 50 mL recovery flask, comprised of furan-substrate (3.33 mmol, 1 eq.) and DME (10 mL, 0.33 M). That furan solution was heated in an oil bath (90 °C) and

the benzenediazonium-2-carboxylate slurry was added to it dropwise (0.3 mL every three min) for 60 min. The clear colorless furan solutions became dark red to black as the additions continued. There was a period of 60 min of stirring in the oil bath (90 °C)—*following the first 60 min of additions*—wherein additions were not made. This was followed by a 30 min period of continued additions (same rate as before), and at the 30-min mark, all remaining slurry was added. The reaction was stirred for 30 min in that oil bath, lifted, allowed to cool, the stir bar was pulled, and the mixture was concentrated *in vacuo* by rotary evaporator.

The residue was partitioned between EtOAc (80 mL) and aqueous ammonia (20 mL of saturated aqueous ammonia diluted to 40 mL with DI H_2O). Both layers were very deeply red following the shakeup. The EtOAc solution was washed two more times with aqueous ammonia (2 × 10 mL of saturated aqueous ammonia diluted to 40 mL), and pre-dried with a saturated sodium chloride wash (40 mL). The extract solution was isolated and dried overnight ($N_{a2}SO_4$). The dried EtOAc solution was adsorbed upon silica gel with the aid of rotary evaporation and purified by flash chromatography (EtOAc and Hex).

5.6.2.15. General Procedure: (Table 5.10)

A 20 Dram vial was charged with anthranilic acid (0.907 g, 6.6 mmol, 2 eq.), 7 mL of HPLC grade THF (0.94 M solution) and the mixture was stirred; a complete solution formed rapidly. Trifluoroacetic acid was added (0.2 mL of a solution 1.87 M solution comprised of 1 mL TFA dissolved in 7 mL of HPLC grade THF) to prepare a 0.053 M solution; no change in appearance was observed. The mixture was placed into a room temperature H_2O bath and *tert*-butyl nitrite (1.0 mL, 90 %, 7.57 mmol, 2.3 eq.) was added dropwise by syringe. The mixture formed a cream-colored suspension, then thickened and turned brick red. The mixture was stirred at room temperature. The diazotization mixture had certainly begun to lose its red color on the

walls of the flask within 3 h. The diazotization mixture had lost all of its red color and had become tan within 4 h.

A Pasteur pipette was used to free the solid from the walls of the vial by gently taking up the slurry and jetting it into the walls. The room temp H_2O bath was traded for an ice bath. After 45 min the tan precipitate was diluted with a bit of DCM, isolated by suction filtration over a Hirsch funnel, rinsed heavily with DCM (circa 40 mL) and transferred to a pear-shaped flask which was calibrated with a 25 mL mark. The tan solid was never allowed to dry, and it was transferred to the flask with the assistance of a DCM squirt bottle. Furan substrate (3.3 mmol, 1 eq.) was added and the reaction volume was brought up to 25 mL with DCM. The flask was fitted with a short West condenser and lowered into an oil bath (48 °C). The mixture was refluxed (2.5 h), then adsorbed onto silica gel and purified by flash chromatography.

5.6.2.16. General Procedure (Scheme 5.13)

To a 6-dram sample vial was added anthranilic acid (4.9 mmol, 2, 1.5, or 1 eq.), DME (5 mL, stabilized with BHT), and the mixture was stirred to form a colorless solution. Trifluoroacetic acid (0.02 mL, 0.26 mmol) was added in two drops to the DME solution with no apparent change. While stirring vigorously at room temperature, ice cold *iso*-pentyl nitrite (1.2 mL, of 99% as light yellow solution, 8.8 mmol, 3.6, 2.7, or 1.8 eq.) was added rapidly and the reaction mixture quickly became turbid yellow and then transitioned to a brick red slurry; The reaction mixture was capped and stirred vigorously at room temperature for 90 min as the red color dissipated; room temperature stirring was required as the triazene is stable at ice bath temperatures. Periodically a rubber policeman was used to liberate the precipitate which clung to the walls of the vial. The reaction mixture was composed of cream colored solid and light orange solution at the completion of 90 min, and it was submerged in an ice bath.

A 50 mL single necked round bottomed flask was calibrated to 19 mL with DCM and charged with substrate (4.9, 3.5, or 2.45 mmol depending on the entry). The ice-cold benzenediazonium-2-carboxylate slurry was separated by pouring it into a 15 mL medium fritted glass Büchner funnel and careful application of suction by H_2O aspirator. The filtrate was deeply red, and the residue was cream colored solid stained with orange solution. The mixture was never allowed to dry. The stir bar was pulled, rinsed with DCM and added to the calibrated flask charged with substrate. The filter-cake was dispersed in DCM and stirred up with a rubber policeman repeatedly followed by careful suction; the total volume of the filtrate was circa 25 mL.

The cream-colored DCM slurry was transferred to the calibrated reaction flask—*charged with furan-diene*—by the aid of a plastic funnel and a stream of DCM from a wash bottle. The reaction mixture was diluted to the calibration mark and affixed to a West condenser plumbed with cold flowing tap H_2O. The reaction flask was lowered into a preheated oil bath (50 °C) and allowed to reflux for 90 min.

The reaction mixture was concentrated by rotary evaporation and purified by flash chromatography using EtOAc and Hex as elution solvent. The eluate fractions containing the 7-oxabenzonorbornadiene could be easily identified by staining the thin layer chromatography slide with potassium permanganate. The fractions containing the product were combined, concentrated by rotary evaporation and vacuum dried.

5.6.2.17. General Procedure (Schemes 5.14 and 5.15)

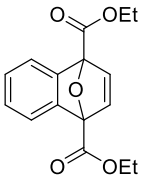
To a 1-dram sample vial was added: anthranilic acid (8, 0.274 g, 2.0 mmol, 2 eq.), DME (1.5 mL), and the mixture was stirred to form a colorless solution. While stirring vigorously at room temperature, isopentyl nitrite (0.34 mL, 2.5 mmol, 2.5 eq.) was added dropwise and the reaction mixture quickly became turbid yellow and then transitioned to a brick red slurry.

Trifluoroacetic acid (stock solution 1 g/10 mL DME, 0.06 mL, 0.05 eq.) was added to the diazotization mixture. The reaction mixture was capped and stirred vigorously at room temperature for 90 min as the red color dissipated; room temperature stirring was required as the triazene is stable at ice bath temperatures. The reaction mixture was composed of cream colored solid and light orange solution at the completion of 90 min.

A 10 mL single neck round bottom flask was charged with substrate (1.0 mmol, 1.0 eq.). The benzenediazonium-2-carboxylate slurry was separated by suction filtration through a Hirsch funnel (1 cm) and careful application of suction by H_2O aspirator. The filtrate was deeply red, and the residue was cream colored solid stained with orange solution. The mixture was never quite allowed to dry! The residue was rinsed with small amounts of DCM till the filtrate was colorless. The stir bar and tan filter cake were transferred to the calibrated flask charged with furan-diene substrate; the transfer was assisted by disposable plastic pipette by making little puffs of air.

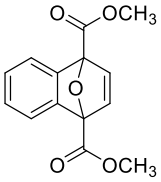
The reaction mixture was diluted with DCM (5 mL, 0.25 M). The reaction flask was lowered into a preheated oil bath (50 °C) and allowed to reflux for 90 min. The reaction mixture was concentrated by rotary evaporation and purified by flash chromatography using EtOAc and Hex as elution solvent. The eluate fractions containing the 7-oxabenzonorbornadiene could be easily identified by staining the thin layer chromatography slide with potassium permanganate. The fractions containing the product were combined, concentrated by rotary evaporation and vacuum dried to constant mass. The results have been compiled in Schemes 5.14 and 5.16 of this chapter.

5.6.2.18. Diethyl 7-Oxabenzonorbornadieneyl-1,4-dicarboxylate



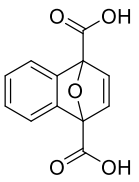
HRMS $[C_{16}H_{16}O_5Na]^+$ Calcd.: 311.0895, found: 311.0898;H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J*=3.0, 5.2 Hz, 1H), 7.11 (s, 1H), 7.03 (dd, *J*=3.0, 5.2 Hz, 1H), 4.44 (q, *J*=7.15 Hz, 2H), 1.39 (t, *J*=7.15 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 146.6, 143.4, 126.2, 120.5, 90.5, 62.5, 15.5; FTIR (Neat) cm^{-1} 3073, 2983, 2939, 2908, 1761, 1604, 1445, 1398, 1373, 1314, 1265, 1189, 1145, 1105, 1053, 997, 583, 759, 720, 695.

5.6.2.19. Dimethyl 7-Oxabenzonorbornadieneyl-1,4-dicarboxylate[3]



Viscous yellow oil; HRMS $[C_{14}H_{12}O_5Na]^+$ Calcd.:283.0583, found: 283.0577; H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J*=3.0, 5.2 Hz, 1H), 7.15 (s, 1H), 7.07 (dd, *J*=3.0, 5.2 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 146.3, 143.2, 126.2, 120.5, 90.4, 53.1; FTIR (Neat) cm^{-1} 3645, 3467, 3096, 3013, 2957, 2853, 1764, 1738, 1603, 1439, 1364, 1321, 1268, 1202, 1144, 1109, 1054, 966, 922, 805, 760, 694, 640, 552.

5.6.2.20. 7-Oxabenzonorbornadiene-1,4-dicarboxylic Acid[3]



Tan solid ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (dd, *J*=3.0, 5.2 Hz, 1H), 7.23 (s, 1H), 7.08 (dd, *J*=3.0, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 147.3, 143.8, 125.7, 119.9, 89.7; FTIR (ATR, neat) cm^{-1} 3458, 3079, 1916, 1732, 1449, 1357, 1254, 1205, 1155, 1080, 1007, 837, 756, 635, 443.

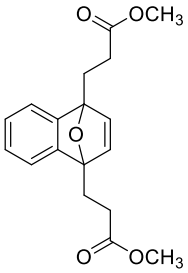
Represented in Scheme 5.17. A light-yellow oil, diethyl 7-oxabenzonorbornadiene-1,4-dicarboxylate (0.3355 g, 1.164 mmol 1 eq.) was diluted with MeOH (3 mL), and the mixture was warmed by submersion in a 65 °C oil bath. A solution of KOH (3.5 g, 62.5 mmol, 54 eq.) in H_2O (2.5 mL) was prepared and diluted to 7 mL with MeOH. The alkaline solution was added dropwise by Pasteur pipette into the stirring methanolic solution of diethyl 7-oxabenzonorbornadiene-1,4-dicarboxylate and the reaction mixture turned from light yellow to dark orange with the first drop's

contact. That mixture was stirred on the oil bath for 2 h and was then allowed to cool to room temperature.

Wet ice (100 mL) was combined with concentrated hydrochloric acid (6 mL) and the alkaline mixture was dripped into that acidic mixture with vigorous stirring provided by a glass rod. A light-yellow solution developed. The MeOH and all of the H_2O was removed by rotary evaporation to leave a white solid residue. That mixture was digested in boiling DCM and when all the DCM had escaped, the mixture was digested in warm EtOAc. Once the mixture had cooled to room temperature, it was gravity filtered through a plug of cotton and stored in a 250 mL Erlenmeyer flask with a little bit of sodium sulfate.

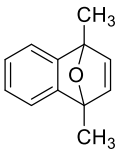
The EtOAc was concentrated by rotary evaporation under vacuum to afford a light brown oil which smelled faintly of acetic acid and was observed to crystallize upon standing. The white solid was determined to have a mass of 0.297 g. The mixture was triturated under diethyl ether and the ether was pipetted away and deposited on a watch glass. Upon drying, the brown ether solution had clearly deposited some crystalline material onto the watch glass. The residual light brown solid was flushed with nitrogen stream until the ether smell had dissipated. The mass of residual solid was 0.092 g, 34%.

5.6.2.21. Dimethyl 3,3'-(7-Oxabenzonorbornadienyl-1,4-dipropionate)[3]



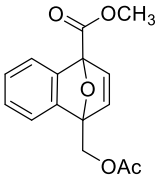
Light yellow oil; HRMS $[C_{18}H_{20}O_5Na]^+$ Calcd.: 339.1208, found: 339.1209; H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J*=3.0, 5.12 Hz, 1H), 6.97 (dd, *J*=3.0, 5.14 Hz, 1H), 6.74 (s, 1H), 3.70 (s, 3H), 2.79–2.50 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 151.6, 145.9, 125.0, 118.9, 91.2, 51.8, 29.5, 24.4; FTIR (ATR, neat) cm^{-1} 3354, 3069, 2951, 2849, 1732, 1437, 1321, 1265, 1169, 1088, 1023, 938, 886, 758, 695, 567.

5.6.2.22. 1,4-Dimethyl-7-oxabenzonorbornadiene[3]



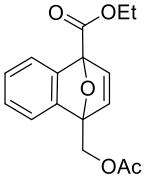
H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J*=3.0, 5.1 Hz, 1H), 6.98 (dd, *J*=3.0, 5.1 Hz, 1H), 6.79 (s, 1H), 1.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 146.8, 124.7, 118.3, 88.6, 15.3; FTIR (ATR, neat) cm^{-1} 3070, 2980, 2933, 2865, 1566, 1451, 1383, 1344, 1299, 1235, 1140, 1077, 1034, 1004, 888, 856, 767, 746, 694, 648, 605, 511, 433.

5.6.2.23. Methyl 4-(Acetoxymethyl)-7-oxabenzonorbornadienyl-1-carboxylate



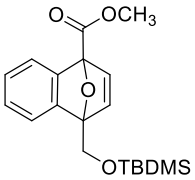
Brown viscous oil; HRMS $[C_{15}H_{14}O_5Na]^+$ Calcd.: 297.0739, found: 297.0737; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.32 (m, 1H), 7.18–7.16 (m, 1H), 7.13 (d, *J*=5.3 Hz, 1H), 7.03–7.01 (m, 2H), 6.89 (d, *J*=5.4 Hz, 1H), 5.01 (d, *J*=12.8 Hz, 1H), 4.84 (d, *J*=12.8 Hz, 1H), 3.96 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 168.1, 148.5, 146.8, 144.5, 142.8, 126.1, 125.8, 120.2, 120.0, 91.5, 90.4, 61.2, 53.1, 21.0; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2957, 1736, 1451, 1368, 1353, 1330, 1225, 1152, 104, 886, 759, 730, 695.

5.6.2.24. Ethyl 4-(Acetoxymethyl)-7-oxabenzonorbornadienyl-1-carboxylate carboxylate



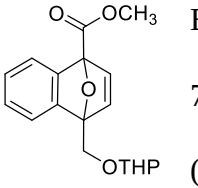
Brown viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 1H), 7.20–7.15 (m, 1H), 7.13 (d, *J*=5.2 Hz, 1H), 7.07–6.97 (m, 2H), 6.88 (d, *J*=5.4 Hz, 1H), 5.01 (d, *J*=12.8 Hz, 1H), 4.85 (d, *J*=12.8 Hz, 1H) , 4.45 (qd, *J*=7.14 Hz, *J*=0.9 Hz, 2H), 2.13 (s, 3H), 1.40 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 167.6, 148.7, 146.9, 144.6, 142.8, 126.1, 125.8, 120.2, 119.9, 91.4, 90.4, 62.4, 61.2, 21.0, 14.5; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2980, 1737, 1454, 1369, 1323, 1226, 1153, 1106, 1043, 955, 887, 854, 757, 729, 694, 648.

5.6.2.25. Methyl 5-(((tert-Butyldimethylsilyl)oxy)methyl)-7-oxabenzonorbornadienyl-1-carboxylate



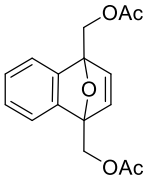
Cream colored solid, melting point range: 63–65 °C; HRMS $[C_{19}H_{26}O_4SiNa]^+$ Calcd.: 369.1498, found: 369.1499; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2H), 7.07 (d, *J*=5.3 Hz, 1H), 7.03 (d, *J*=5.3 Hz, 1H), 7.03–6.95 (m, 2H), 4.47 (d, *J*=10.9 Hz, 1H), 4.33 (d, *J*=10.8 Hz, 1H) , 3.95 (s, 3H) 0.94 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 148.9, 148.6, 143.9, 143.4, 125.9, 125.2, 120.5, 119.6, 92.8, 90.2, 77.5, 77.2, 61.5, 52.9, 18.5, -5.22, -5.24; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2954, 2929, 2856, 1767, 1741, 1452, 1354, 1327, 1249, 1196, 1151, 1101, 1053, 1005, 835, 777, 754, 728, 692, 641.

5.6.2.26. Methyl 4-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-7-oxabenzonorbornadienyl-1-carboxylate



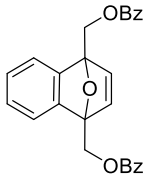
Brown viscous oil (*mixture of diastereomers*); ^{1}H NMR (400 MHz, CDCl3) δ 7.34–7.26 (m, 3H), 7.26–7.20 (m, 1H), 7.09 (d, *J*=5.3 Hz, 2H), 7.0–46.95 (m, 6H), 4.79 (ddd, J_1=J_2=3.5 Hz, J_3=9.6 Hz, 2H), 4.65 (d, *J*=11.5 Hz, 1H), 4.52 (d, *J*=11.2 Hz, 1H), 4.22 (d, *J*=11.2, 1H), 4.12 (d, *J*=11.4 Hz, 1H), 3.96–3.87 (m, 8H), 3.65–3.52 (m, 2H), 1.92–1.45 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 148.8, 148.7, 148.0, 147.9, 143.8, 143.7, 143.4, 125.9, 125.5, 125.3, 120.6, 120.0, 119.8, 119.7, 99.6, 99.4, 92.4, 92.1, 90.3, 64.8, 64.7, 62.6, 62.3, 52.9, 30.5, 30.4, 25.5, 19.5, 19.3; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2950, 2871, 1765, 1740, 1452, 1353, 1327, 1353, 1327, 1249, 1200, 1153, 1126, 1071, 1035, 961 ,904, 758, 694, 643.

5.6.2.27. 1,4-Bis(acetoxymethyl)-7-oxabenzonorbornadiene



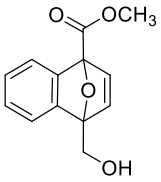
Cream colored crystalline solid recrystallized from IPA melting point range: 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, J_1=2.9 Hz, J_2=4.9 Hz, 1H), 7.00 (dd, J_1=3.0 Hz, J_2=5.2 Hz, 1H), 6.89 (s, 1H), 4.98 (d, J=12.7 Hz, 1H), 4.84 (d, J=12.7 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 148.9, 143.9, 125.5, 119.5, 90.9, 61.2, 20.9; FTIR (ATR, diamond, neat) cm^{-1} 3097, 2955, 1734, 1453, 1365, 1251, 1225, 1040, 982, 880, 854, 771, 747, 702, 650, 601, 467.

5.6.2.28. 1,4-Bis(benzoyloxymethyl)-7-oxabenzonorbornadiene



Off white crystalline solid; HRMS $[C_{26}H_{20}O_5Na]^+$ Calcd.: 435.1205, found: 435.1208; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dt, J_1=1.3 Hz, J_2=7.9 Hz, 2H), 7.56 (tt, J_1=1.2 Hz, J_2=7.4 Hz, 1H), 7.42 (t, J=7.9 Hz, 2H), 7.26 (dd, J_1=3.0 Hz, J_2=5.2 Hz, 1H), 7.02 (dd, J_1=3.0 Hz, J_2=5.2 Hz, 1H), 7.01 (s, 1H), 5.25 (d, J=12.6 Hz, 1H), 5.07 (d, J=12.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 149.4, 144.2, 133.5, 130.1, 129.8, 128.7, 125.7, 119.8, 91.3, 62.1; FTIR (ATR, diamond, neat) cm^{-1} 3046, 3008, 29945, 1718, 1600, 1582, 1452, 1395, 1315, 1303, 1271, 1230, 1178, 1143, 1122, 1105, 1067, 1043, 1025, 968, 938, 878, 856, 761, 710, 695, 660, 641.

5.6.2.29. Methyl 4-(Hydroxymethyl)-7-oxabenzonorbornadienyl-1-carboxylate



Brown viscous oil; HRMS $[C_{13}H_{12}O_4Na]^+$ Calcd.: 255.0633, found: 255.0627; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 1H), 7.22–7.18 (m, 1H), 7.12 (d, J=5.4 Hz,1H), 7.07–6.97 (m, 2H), 6.94 (d, J=5.4 Hz, 1H), 4.54–4.40 (m, 2H), 3.98 (s, 3H), 2.01 (t, J=6.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 149.0, 146.7, 144.5, 143.2, 126.1, 125.7, 120.2, 120.0, 94.3, 90.4, 60.3, 53.1; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 3444, 3072, 2955, 1740, 1452, 1330, 1249, 1194, 1154, 1106, 1052, 962, 849, 757, 695, 639, 546.

Corresponding to Scheme 5.18 of the manuscript, to a 250 mL single neck round bottom flask charged with a diastereomeric mixture of methyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1,4-epoxynaphthalene-1-carboxylate (0.842 g, 2.66 mmol) was charged with HPLC grade MeOH (50 mL, 0.5 M) and Amberlyst 15 hydrogen form C-null (0.009 g, 2 mol%). The headspace of the flask was flushed with argon and the mixture was stirred for 36 h at room temperature. The mixture was suction filtered through a pad of Celite, rinsed through with MeOH, concentrated by rotary evaporation under reduced pressure, and vacuum dried to constant mass of viscous brown oil: 0.610 g, 2.63 mmol, 99% of the theoretical maximum. The brown oil darkened upon standing. After two weeks, the compound was purified by flash chromatography to afford 0.498 g of yellow oil, a recovery of 82%.

Alternatively carried out by Anna Renner, based on the procedures of: (1) Ravindranath and Sharma,[212] (2) Elhalem *et al.*,[213] (3) Wang *et al.*,[214] a 250 mL round bottom flask containing methyl 4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-1,4-epoxynaphthalene-1-carboxylate (0.371 g, 0.0017 mol, 1.0 eq.) was charged with MeOH (4.8 mL). The flask was purged with argon, stirred at room temperature, and PPTS (0.031 g, 0.00012 mol, 11 mol%) was added. The reaction mixture was stirred overnight at room temperature.

A large pipette was packed with basic alumina (occupying about half the volume of the pipette body) between layers of cotton, and the resulting microcolumn was equilibrated with MeOH. The product mixture was pipetted into the top of the column and eluted with MeOH into a 250 mL round-bottomed flask. The eluate was concentrated *in vacuo*, and the resulting residue was orange-brown viscous oil. Crude ^{1}H NMR indicated residual pyridine.

Another micro column with silica gel stationary phase (occupying about half the volume of the pipette body) was equilibrated with 50:50 Hex/EtOAc. The product mixture was transferred

with 50:50 Hex/EtOAc to the top of the column and eluted with 50:50 Hex/EtOAc. Based on TLC analysis, select eluate, fractions were transferred with acetone and concentrated *in vacuo* affording a viscous yellow oil. Following vacuum drying, the mass of oil was determined to be 0.190 g (70% of the theoretical yield).

5.6.3. Hydrogenated Benzyne-Furan-Diene Diels-Alder Adducts

5.6.3.1. General Procedure (Scheme 5.18)

The H-Cube Pro was primed with HPLC-grade THF at 3 mL/min with 100% hydrogen generation; the reaction chamber was set to 40 bar H_2 pressure and set to 40 °C. A 0.2 M solution of pure 1,4-disubstituted-7-oxabenzonorbornadiene in HPLC-grade THF was prepared by stirring at room temperature, then eluted through a 30 mm Pd/C catalyst cartridge at a flow rate of 1 mL/min (40 °C). The eluting solution was concentrated to afford the 1,4-disubtituted-7-oxabenzonorbornene product.

The hydrogenations also proceeded well under batch conditions and required very little Pd catalyst to convert smoothly. Two fringe benefits were observed in the preparation of 7-oxabenzonorbornene diesters (dimethyl 2,3-dihydro-1,4-epoxynaphthalene-1,4-dicarboxylate and 1,4-dimethyl-2,3-dihydro-1,4-epoxynaphthalene): (1) improved processability and (2) long term bench stability.

5.6.3.2. General Procedure for Batch Hydrogenation (Follow-up to Scheme 5.18)

Since the strained olefin did not require aggressive hydrogenation conditions, a batch hydrogenation was prepared which used minimal quantities of catalyst. A round bottom flask was charged with substrate (between 5 and 50 mmol, 1 eq.), THF (1 M), 10% palladium on carbon (0.23 mol%) and the flask was sealed with a rubber septum. A hydrogen line was used to flush the headspace of the flask through a modified syringe/disposable needle combination. Another

modified syringe/needle combination topped with a balloon was installed through the septum and kept charged with hydrogen as the reaction was stirred at room temperature for 30–40 h).

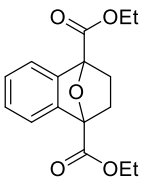
The hydrogenation mixture was separated by filtering through Celite 545 and concentrated by rotary evaporation. The product crystallized in the freezer in the case of dimethyl 2,3-dihydro-1,4-epoxynaphthalene-1,4-dicarboxylate and dimethyl 3,3'-2,3-dihydro-1,4-epoxynaphthalene-1,4-diyl)dipropionate while yields were comparable to the flow methodology. Unfortunately, crude benzyne Diels-Alder reaction mixtures could not be subjected to direct hydrogenation. Contaminants always killed the catalyst.

5.6.3.3. General Procedure (Table 5.10)

A 250 mL single neck round bottom flask was charged with 7-oxabenzonorbornadiene substrate. The flask was flushed with argon and charged with 10% palladium on carbon (less than1 mol%). The flask was sealed with a white rubber serum septum, evacuated with a H_2O aspirator. The needle connecting the system with the aspirator was removed and the evacuated flask was charged with HPLC grade MeOH (to form a 0.1 M solution), then flushed with hydrogen. The mixture was stirred at room temperature for 24 h.

The headspace of the flask was flushed with argon and the mixture was suction filtered through Celite, rinsed through with MeOH, concentrated by rotary evaporation under reduced pressure. The residue was vacuum dried to constant mass and analyzed by ^{1}H NMR, ^{13}C NMR and FTIR. The results have been tabulated in Table 5.10 of this document.

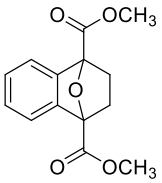
5.6.3.4. Diethyl 7-oxabenzonorbornene-1,4-dicarboxylate



Light yellow crystalline solid melting point range: 50–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J*=3.1, 5.5 Hz, 1H), 7.27 (dd, *J*=3.1, 5.5 Hz, 1H), 3.95 (s, 3H), 2.48–2.37 (m, 1H), 1.94–1.83 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 142.5,

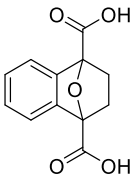
127.8, 119.2, 86.3, 52.7, 32.2; FTIR (ATR, neat) cm^{-1} 2956, 1755, 1451, 1430, 1351, 1321, 1268, 1225, 1169, 1117, 1069, 1044, 927, 897, 794, 763, 743, 658, 605.

5.6.3.5. Dimethyl 7-oxabenzonorbornene-1,4-dicarboxylate[3]



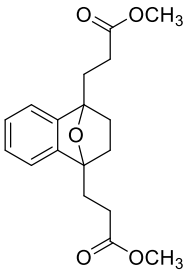
Off-white solid; 18 months old stored on the bench: melting point range: 97–99 °C, freshly prepared sample: melting point range: 97–99 °C; HRMS $[C_{14}H_{14}O_5Na]^+$ Calcd.: 285.0739, found: 285.0767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J*=3.1, 5.5 Hz, 1H), 7.27 (dd, *J*=3.1, 5.5 Hz, 1H), 3.95 (s, 3H), 2.48–2.37 (m, 1H), 1.94–1.83 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 142.5, 127.8, 119.2, 86.3, 52.7, 32.2; FTIR (ATR, neat) cm^{-1} 2956, 1755, 1451, 1430, 1351, 1321, 1268, 1225, 1169, 1117, 1069, 1044, 927, 897, 794, 763, 743, 658, 605; MP: 98–104 °C.

5.6.3.6. 7-Oxabenzonorbornene-1,4-dicarboxylic Acid[3]



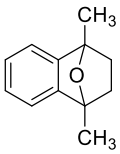
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (dd, *J*=3.0, 5.4 Hz, 1H), 7.29 (dd, *J*=3.1, 5.4 Hz, 1H), 2.34–2.19 (m, 1H), 1.75–1.59 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.8, 143.3, 127.5, 118.9, 85.5, 31.7; FTIR (ATR, neat) cm^{-1} 3486, 3078, 2215, 1925, 1733, 1681, 1481, 1460, 1410, 1365, 1329, 1281, 1215, 1181, 1121, 1064, 1030, 1013, 951, 889, 838, 761, 737, 698, 600, 574, 515, 449, 429.

5.6.3.7. Dimethyl 3,3'-(7-Oxabenzonorbornene-1,4-dipropionate)[3]



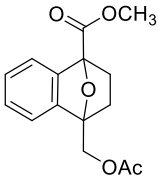
HRMS $[C_{18}H_{22}O_5Na]^+$ Calcd.: 341.1365, found: 341.1394; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 1H), 7.13 (m, 1H), 3.66 (s, 3H), 2.65-2.81 (m, 4H), 1.95–1.84 (m, 1H), 1.48–1.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 146.8, 126.7, 118.0, 86.8, 51.7, 33.8, 29.9, 26.7; FTIR (Neat) cm^{-1} 2980, 2951, 1742, 1432, 1360, 1308, 1193, 1169, 1078, 1010, 975, 895, 863, 758, 720, 657, 618, 534, 447; MP: 67 °C.

5.6.3.8. 1,4-Dimethyl-7-Oxabenzonorbornene[3]



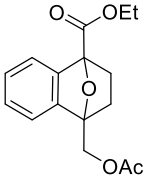
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.13 (m, 2H), 1.99–1.89 (m, 1H), 1.83 (s, 3H), 1.58–1.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 126.5, 117.5, 84.8, 35.7, 17.8; FTIR (ATR, neat) cm^{-1} 3047, 2972, 2933, 2864, 1454, 1380, 1348, 1303, 1229, 1204, 1141, 1097, 1009, 901, 853, 750, 613.

5.6.3.9. Methyl 4-(Acetoxymethyl)-7-oxabenzonorbornenyl-1-carboxylate



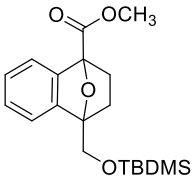
Brown viscous oil. HRMS $[C_{15}H_{16}O_5Na]^+$ Calcd.: 299.0895, found: 299.0896; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.46 (m, 1H), 7.24–7.22 (m, 2H), 7.18–7.17 (m, 1H), 4.90 (d, *J*=13.0 Hz, 1H), 4.75 (d, *J*=12.7 Hz, 1H), 3.93 (s, 3H), 2.40–2.29 (m, 1H), 2.19–2.12 (m, 1H), 2.09 (s, 3H), 1.89–1.79 (m, 1H), 1.53–1.43 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 169.8, 143.8, 143.7, 127.8, 127.5, 119.5, 118.5, 87.2, 86.5, 62.5, 52.9, 33.2, 29.8, 21.1; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2954, 1737, 1458, 1438, 1370, 1328, 1227, 1198, 1109, 1077, 1042, 907, 863, 800, 758, 634, 610.

5.6.3.10. Ethyl 4-(Acetoxymethyl)-7-oxabenzonorbornenyl-1-carboxylate



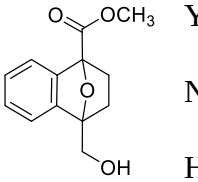
Brown viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.41 (m, 1H), 7.29–7.20 (m, 2H), 7.20–7.12 (m, 1H), 4.90 (d, *J*=12.6 Hz, 1H), 4.75 (d, *J*=12.7 Hz, 1H), 4.51–4.32 (m, 2H), 2.42–2.32 (m, 1H), 2.18–2.11 (m, 1H), 2.09 (s, 3H), 1.88–1.76 (m, 1H), 1.52–1.43 (m, 1H), 1.39 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 169.4, 144.0, 143.8, 127.7, 127.5, 119.5, 118.5, 87.0, 86.4, 62.5, 61.9, 33.1, 29.9, 21.0, 14.5; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2985, 2954, 1739, 1459, 1369, 1326, 1230, 1193, 1174, 1106, 1072, 1044, 856, 759, 611.

5.6.3.11. Methyl 4-(((tert-Butyldimethylsilyl)oxy)methyl)-7-oxabenzonorbornenyl-1-carboxylate



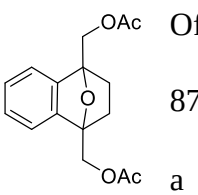
Cream colored solid, melting point range: 60–61 °C; HRMS $[C_{19}H_{28}O_4SiNa]^+$ Calcd.: 371.01655, found: 371.1665; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 1H), 7.37–7.31 (m, 1H), 7.23–7.15 (m, 2H), 4.40 (d, *J*=10.7 Hz, 1H), 4.23 (d, *J*=10.7 Hz, 1H), 3.91 (s, 3H), 2.29 (ddd, J_1=3.96, J_2=J_3=6.8 Hz, 1H), 2.11 (ddd J_1=4.06, J_2=J_3=7.1 Hz, 1H), 1.87–1.77 (m, 1H), 1.62–1.52 (m, 1H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 145.6, 144.2, 127.5, 127.0, 119.2, 119.0, 88.6, 86.3, 63.7, 52.7, 33.2, 30.2, 26.1, 18.5, -5.18, -5.23; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2955, 2930, 2855, 1755, 1459, 1439, 1354, 1324, 1244, 1221, 1191, 1163, 1106, 1079, 1052, 1024, 937, 837, 798, 777, 752, 661, 608, 583.

5.6.3.12. Methyl 4-(Hydroxymethyl)-3,4-dihydro-7-oxabenzonorbornenyl-1-carboxylate



Yellow viscous oil; HRMS $[C_{13}H_{14}O_4Na]^+$ Calcd.: 257.0790, found: 257.0790; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.35 (m, 1H), 7.23–7.11 (m, 3H), 4.32 (d, *J*=12.8 Hz, 1H), 4.24 (d, *J*=12.7 Hz, 1H), 3.88 (s, 3H), 2.73 (br s, 1H), 2.26 (ddd, J_1=4.0 Hz, J_2=J_3=6.9 Hz, 1H), 2.10 (ddd, J_1=3.9 Hz, J_2=J_3=7.0 Hz, 1H), 1.87–1.73 (m, 1H), 1.43–1.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 144.0, 144.0, 127.5, 127.0, 119.1, 118.7, 89.6, 86.1, 61.4, 52.6, 33.2, 28.8; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 3455, 2953, 1738, 1458, 1439, 1356, 1327, 1270, 1194, 1161, 1109, 1072, 1048, 849, 800, 755, 610.

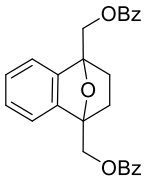
5.6.3.13. 1,4-Bis(acetoxymethyl)-7-oxabenzonorbornene



Off-white sample purified by flash chromatographic purification melting point range: 87–89 °C; sample concentrated from the reaction hydrogenation mixture appeared as a yellow solid: melting point range: 83–85 °C; HRMS $[C_{16}H_{18}O_5Na]^+$ Calcd.:

313.1052, found: 313.1047; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.10 (m, 4H), 4.83 (d, *J*=12.6 Hz, 1H), 4.70 (d, *J*=12.6 Hz, 1H), 2.10–1.90 (m, 2H), 2.04 (s, 6H), 1.5–1.3 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 144.7, 127.0, 118.2, 86.5, 62.4, 30.1, 20.7; FTIR (ATR, diamond, neat) cm^{-1} 2970, 2951, 2878, 1733, 1460, 1431, 1365, 1274, 1228, 1032, 979, 954, 854, 768, 637, 606.

5.6.3.14. 1,4-Bis(benzoyloxymethyl)-7-oxabenzonorbornene



Off-white crystalline solid crystallized from Et_2O melting point range 109–112 °C; HRMS $[C_{26}H_{22}O_5Na]^+$ Calcd.: 437.1365, found: 437.1415; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J*=1.3 Hz, J_2=8.3 Hz, 2H), 7.54 (tt, J_1=1.2 Hz, J_2=7.5 Hz, 1H), 7.41 (t, *J*=8.0 Hz, 2H), 7.24 (dd, J_1=3.0 Hz, J_2=5.2 Hz, 1H), 7.22 (dd, J_1=3.0 Hz, J_2=5.2 Hz, 1H), 5.08 (d, *J*=12.5 Hz, 1H), 5.04 (d, *J*=12.5 Hz, 1H), 2.29–2.15 (m, 1H), 1.67–1.55 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 145.1, 133.2, 129.84, 129.80, 128.42, 127.2, 118.4, 86.8, 63.3, 30.5; FTIR (ATR, diamond, neat) cm^{-1} 3047, 2977, 2943, 2866, 1714, 1600, 1582, 1449, 1402, 1311, 1266, 1176, 1156, 1116, 1069, 1027, 972, 872, 764, 713.

5.6.4. Cellulose Derived Naphthalenes

5.6.4.1. General Procedure (Table 5.11)

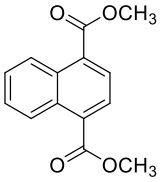
A 50 mL single neck round bottom flask was charged with 1,4-disubstituted-7-oxabenzonorbornene (2.012 mmol, 1 eq.), concentrated hydrochloric acid (12 mL) and the mixture was heated in a 100 °C oil bath beneath a West condenser and an empty balloon (to contain the evolved HCl). The mixture was stirred for 2.2 h then pulled from the oil bath and allowed to cool. In the cases of carboxylic acid products, the mixture was chilled on ice, then isolated by suction filtration, rinsed with ice cold H_2O, pressed, chopped and spread on paper to air dry. In all other cases, the condenser was washed with DCM and the reaction was observed to partition between DCM solution (bottom) and a cloudy acidic aqueous solution. The mixture was further diluted

with DCM which was isolated from the acid with a separatory funnel. The DCM solution was washed with H_2O three times and then once with saturated sodium chloride before drying (Na_2SO_4).

5.6.4.2. General Procedure for Catalytic Dehydration: (Schemes 5.21–5.23)

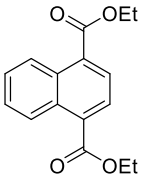
A 5 mL single neck round bottom flask was charged with 7-oxabenzonorbornene (1 mmol, 1 eq.) which was taken up in solvent (3 mL, 0.3 M or 10 mL to make a 0.1 M solution). The solution was charged with Amberlyst 15 (34 mg, 15 mol% when taking the wt equivalent to be 4.4 eq./kg resin and thereby making 0.227 g Amberlyst /eq.) and refluxed for 90 min. The mixture was separated by suction filtration, concentrated, adsorbed onto silica gel and purified by flash chromatography using EtOAc and Hex. No hydrolysis products were observed in these reaction mixtures.

5.6.4.3. Dimethyl Naphthalene-1,4-dicarboxylate[3]



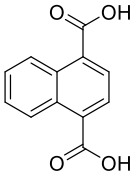
^{1}H NMR (400 MHz, CDCl3) δ 8.82 (dd, J_1=3.4 Hz, J_2=6.7 Hz, 1H), 8.09 (s, 1H), 7.63 (dd, J_1=3.4 Hz, J_2=6.7 Hz, 1 H), 4.03 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 167.7, 131.8, 131.5, 128.1, 127.9, 126.1, 52.6; FTIR (ATR, neat) cm^{-1} 2992, 2944, 2841, 1712, 1580, 1516, 1459, 1432, 1281, 1243, 1198, 1126, 1035, 1013, 900, 816, 784, 741.

5.6.4.4. Dimethyl Naphthalene-1,4-dicarboxylate



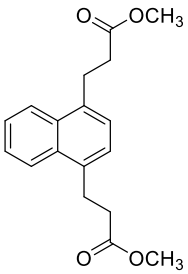
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, J_1=3.4 Hz, J_2=6.6 Hz, 1H), 8.05 (s,1H), 7.61 (dd, J_1=3.4 Hz, J_2=6.6 Hz, 1H),4.47 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 167.5, 132.2, 131.6, 128.0, 129.9, 126.2, 61.7, 14.5; FTIR (ATR, neat) cm^{-1} 2983, 2904, 1908, 1705, 1670, 1583, 1514, 1472, 1443, 1361, 1283, 1248, 1172, 1129, 1041, 969, 840, 774.

5.6.4.5. 1,4-Naphthalenedicarboxylic Acid[3]



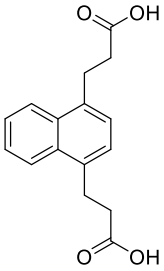
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (br s, 1H), 8.79 (dd, *J*=3.4, 6.7 Hz, 1H), 8.10 (s, 1H), 7.70 (dd, *J*=3.5, 6.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.4, 132.2, 130.7, 127.8, 127.5, 125.9; FTIR (ATR, neat) cm^{-1} 2960, 2808, 2629, 2558, 1679, 1582, 1518, 1463, 1415, 1282, 1258, 1199, 1125, 1024, 883, 769, 718, 613, 454.

5.6.4.6. Dimethyl 3,3'-(Naphthalene-1,4-dipropionate)[3]



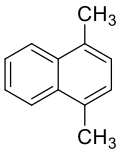
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J*=3.3, 6.5 Hz, 1H), 7.54 (dd, *J*=3.3, 6.5 Hz, 1H), 7.27 (s, 1H), 3.70 (s, 3H), 3.40 (t, *J*=8.0 Hz, 2 H), 2.76 (t, *J*=8.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 135.4, 132.0, 125.8, 125.7, 124.2, 51.7, 35.0, 28.1; FTIR (ATR, neat) cm^{-1} 3075, 3000, 2956, 2916, 1729, 1601, 1516, 1439, 1354, 1294, 1234, 1197, 1148, 1040, 980, 920, 826, 749, 687, 583.

5.6.4.7. 3.3'-(Naphthalene-1,4-dipropionic Acid)



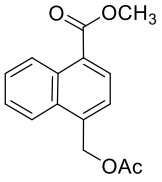
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (br s,1H), 8.08 (dd, *J*=3.3, 6.5 Hz, 1H), 7.57 (dd, *J*=3.3, 6.5 Hz, 1H), 7.29 (s, 1 H), 3.27 (t, *J*=7.9 Hz, 2H), 2.62 (t, *J*=7.7 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.8, 135.3, 131.5, 125.8, 125.4, 124. 2, 34.6, 27.4; FTIR (ATR, neat) cm^{-1} 3080, 2918, 2630, 2559, 1871, 1697, 1604, 1518, 1428, 1408, 1365, 1301, 1205, 967, 840, 741, 673, 543.

5.6.4.8. 1,4-Dimethylnaphthalene[3]



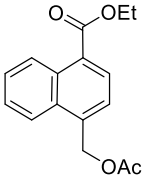
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J*=3.3, 6.4 Hz, 1H), 7.55 (dd, *J*=3.3, 6.4 Hz, 1H), 7.23 (s, 1H), 2.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8, 132.5, 126.4, 125.5, 124.8, 19.5; FTIR (ATR, neat) cm^{-1} 3071, 2940, 2863, 1597, 1510, 1462, 1393, 1273, 1158, 1023, 820, 749, 694, 566.

5.6.4.9. Methyl 4-(Acetoxymethyl)-1-naphthoate



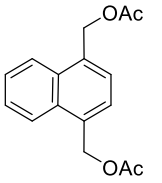
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04–8.89 (m, 1H), 8.15 (d, *J*=7.4 Hz, 1H), 8.09–8.00 (m, 1H), 7.73–7.52 (m, 3H), 5.62 (s, 2H), 4.02 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 167.9, 136.7, 131.8, 131.6, 129.6, 128.2, 127.7, 127.0, 126.7, 125.5, 123.8, 64.2, 52.4, 21.1; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2952, 1739, 1713, 1595, 1516, 1435, 1368, 1282, 1220, 1196, 1124, 1066, 1021, 914, 847, 767, 603.

5.6.4.10. Ethyl 4-(Acetoxymethyl)-1-naphthoate



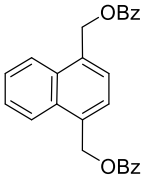
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97–8.87 (m, 1H), 8.10 (d, *J*=7.4 Hz, 1H), 8.05–7.98 (m, 1H), 7.67–7.51 (m, 3H), 5.58 (s, 2H), 4.46 (q, *J*=7.1 Hz, 2H), 2.11 (s, 3H), 1.44 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 167.6, 136.5, 131.8, 131.6, 129.4, 128.7, 127.7, 126.9, 126.7, 125.6, 123.8, 64.3, 61.4, 21.1, 14.5; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2981, 2928, 1739, 1710, 1595, 1517, 1465, 1367, 1281, 1220, 1190, 1123, 1066, 1024, 964, 919, 847, 768, 603.

5.6.4.11. 1,4-Di(acetoxymethyl)naphthalene



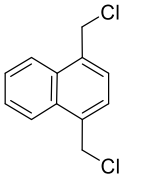
White solid; melting point range: 79–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J_1=3.3 Hz, J_2=6.4 Hz, 1H), 7.57 (dd, J_1=3.3 Hz, J_2=6.5 Hz 1H), 7.50 (s, 1H), 5.54 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 132.7, 131.8, 126.8, 126.6, 124.3, 64.4, 21.0; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 2934, 1728, 1595, 1517, 1432, 1336, 1236, 1065, 1024, 970, 916, 831, 748, 603.

5.6.4.12. 1,4-Di(benzoyloxymethyl)naphthalene



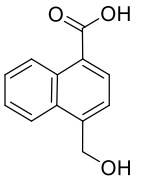
White crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J_1=3.3 Hz, J_2=6.3 Hz, 1H),8.05 (d, J=1.4 Hz, J_2=8.4 Hz, 2H), 7.64 (s, 1H), 7.61 (dd, J_1=3.3 Hz, J_2=6.3 Hz, 1H), 7.53 (tt, J_1=1.3 Hz, J_2=7.5 Hz, 1H), 7.40 (t, J=8.0 Hz, 2H), 5.82 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 133.3, 133.0, 132.2, 130.2, 130.0, 128.6, 127.1, 126.9, 124.5, 65.2; FTIR (ATR, diamond, neat) cm^{-1} 3072, 2940, 1712, 1601, 1450, 1315, 1278, 1262, 1178, 1114, 1068, 1044, 1026, 827, 704.

5.6.4.13. 1,4-Di(chloromethyl)naphthalene



White crystalline solid melting point range: 155–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, J_1=3.3 Hz, J_2=6.4 Hz, 1H), 7.68 (dd, J_1=3.3 Hz, J_2=6.4 Hz, 1H), 7.51(s, 1H), 5.06 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 131.8, 127.3, 127.1, 124.7, 44.5; FTIR (ATR, diamond, neat) cm^{-1} 3080, 2974, 2872, 1964, 1896, 1705, 1595, 1515, 1449, 1281, 1256, 1142, 1054, 854, 772, 754, 686, 582

5.6.4.14. 4-(Hydroxymethyl)-1-naphthoic Acid[215]



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J=8.4 Hz, 1H), 8.19–8.07 (m, 2H), 7.73–7.56 (m, 3H) 7.13–2.80 (br s, 2H), 5.03 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 143.1, 130.74,130.69, 129.5, 127.1, 126.8, 126.1, 126.0, 123.9, 122.6, 60.9; FTIR (ATR, diamond, thin film from $CDCl_3$) cm^{-1} 3275, 3054, 2858, 2614, 1692, 1591, 1519, 1464, 1431, 1411, 1283, 1250, 1204, 1136, 1079, 748, 761.

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