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Platform approach to diversification: bio-based methyl coumalate to functionalized aromatics via a Diels-Alder strategy

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Platform approach to diversification: Bio-based methyl coumalate to functionalized aromatics *via* a Diels–Alder strategy

by

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TABLE OF CONTENTS

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LIST OF ABBREVIATIONS

Å	angstrom
Ac	acetyl
APCI	atmospheric-pressure chemical ionization
Bu	butyl
^{o}C	degrees centigrade
calcd	calculated
δ	NMR chemical shift in ppm downfield from tetramethylsilane
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
DMT	dimethyl terephthalate
dr	diastereomeric ratio
EI	electron ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
FDCA	2,5-furandicarboxylic acid

g	gram
GC/MS	gas chromatography/mass spectrometry
h	hour
HMF	5-hydroxymethylfurfural
HRMS	high-resolution mass spectrometry
IEDDA	inverse electron-demand Diels–Alder
J	coupling constant
L	liter
M	molarity
m	meta
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol %	mole percent
m.p.	melting point
Ms	methanesulfonyl
NMR	nuclear magnetic resonance

p	para
Pd/C	palladium on carbon
PET	poly(ethylene terephthalate)
Ph	phenyl
ppm	parts per million
p-TSA	*para*-toluenesulfonic acid
q	quartet
quant.	quantitative
R_f	retention factor
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethlsilyl
t-BuOH	*tert*-butanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time of flight
TPA	terephthalic acid
UV	ultraviolet
wt.	weight

ABSTRACT

The chemical industry relies on crude oil to manufacture the vast majority of chemicals. However, the increasing demand cannot be supported with the simultaneous decrease in natural crude oil reserves and increasing prices. Green chemistry solutions may resolve the issue utilizing biorenewable feedstocks, especially for the functionalized aromatic compounds that are ubiquitous in a wide variety of consumer materials. The atom economical Diels–Alder reaction installs two carbon-carbon bonds with high levels of regio-, chemo-, and stereocontrol, which was effectively utilized in a platform approach.

Through metabolic engineering, glucose can be converted to malic acid. Afterwards, dimerization and esterification provided the 2-pyrone methyl coumalate as a platform molecule for the methodology. Although unactivated alkenes resulted in aromatic compounds, palladium was required, and with electron-deficient alkene dienophiles, mixtures of regioisomers were observed. In contrast, we developed an inverse electron-demand Diels–Alder/retro-Diels–Alder/elimination domino methodology from methyl coumalate with electron-rich olefins to regioselectively furnish diverse aromatic compounds.

Vinyl ether dienophiles provided a broad range of aromatic compounds, which were equipped with an alkoxy leaving group to facilitate aromatization without a catalyst. The scope was expanded with readily prepared acetal and orthoester dienophile equivalents that could be utilized in crude form. As practical bench-stable compounds, elimination occurred under the thermal conditions to reveal the dienophile. The metal-free, one-pot

domino sequence efficiently provided high yields and regioselectivities for the desired aromatic compounds. The expansive range of accessible aromatic compounds through the methodology included carbazoles, tricyclic, fused, anisole, and biphenyl systems. Notably, captodative dienophile derivatives from methyl pyruvate provided a 100% biorenewable formal synthesis to terephthalic acid with dimethyl terephthalate as the intermediate. As commodity co-monomers for poly(ethylene terephthalate), the green methodology was further optimized to remove the reaction solvent and recrystallize the product in up to 95% yield. In summary, methyl coumalate represents a convenient bio-based platform for diverse aromatics which fulfills many green chemistry principles in the progress toward a sustainable future.

CHAPTER 1.

INCORPORATING GREEN PRINCIPLES TO ACHIEVE AROMATICS FROM 2-PYRONES

1.1. Introduction: Green Chemistry

Organic compounds are prevalent across many sectors of industry as constituents of everyday consumer materials from therapeutic agents to plastics to fragrances. Since the vast majority of organic compounds are ultimately derived from crude oil, society faces the critical predicament of a constantly increasing demand of petrochemicals with their simultaneously depleting supply. The U.S. Energy Information Administration projects that world petroleum and liquid fuel usage will increase from 87 million barrels per day in 2010 to 115 million in 2040.[1] The chemical sector is the largest industrial energy consumer, which claims 19% of the world's industrial usage, of which 60% is devoted to petrochemical feedstocks for further modification.[1] Within the chemical industry, the demand has noticeably increased from a global chemical output of $171 billion in 1970 to $4.12 trillion in 2010, which the Organization for Economic Cooperation and Development predicts will grow at a rate of 3% per year until 2050.[2] Unfortunately, econometric modelling estimates that demand could potentially exceed the capacity of natural oil reserves as early as 2046.[3] Furthermore, volatile oil prices are steadily increasing and are anticipated to reach $163 per barrel in 2040.[1] The compounding pressures of supply and demand modulated by price discourages positive

forecasts for a sustainable future should the chemical industry continue with a sole reliance on fossil fuels.

Apart from the depleting supply of crude oil, additional drivers prompt the development of alternative feedstocks. First, public perception of the chemical industry on the whole would improve, decreasing the aversion for manufactured chemicals. Governmental policies and programs encourage research to decrease the barriers for adoption of greener technologies. Industries generating bio-sourced chemicals could benefit from the legislative mandates and additionally wield competitive advantages in the marketplace as an economic incentive.[4] Finally, chemists are equipped with the technological capability to reduce the effects of pollution and toxicity detrimental to the environment and human health through the logical design of methods and processes.[5] The combination of these collective factors motivates the transition to alternative and renewable sources like biomass through developments in green chemistry.

As conceptualized by Paul Anastas and John Warner in their seminal text,[5] green chemistry is defined as "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products." They progressively codified twelve principles of green chemistry (Figure 1) which continue to guide industrial considerations today. The principles address a broad expanse of topics with an emphasis on reaction and process design to decrease toxicity and auxiliary substances while increasing the use of catalytic reagents and improving biodegradability. Atom economy is featured in the second principle

which was also promoted by Trost[6,7] to transfer as many atoms as possible from the starting material

The Twelve Principles of Green Chemistry

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Figure 1. Anastas and Warner's Twelve Principles of Green Chemistry.[5]

into the product to prevent unnecessary waste, as epitomized by the Diels–Alder reaction. The seventh principle asserts that feedstocks should be renewable if technically feasible,[2] which resonates with our goals and those of many research groups around the world[8] to remove the technical barriers, especially with the impending prospect of limited petroleum-based sources.

Biomass, consisting of biological matter derived from plant material,[9,10] is a promising alternative resource since it can be regenerated over a much shorter time frame compared to fossil fuels. Biorenewable feedstocks with their oxygenated functionality have inherent advantages over petroleum-based hydrocarbons as the limited functionality on the latter often requires challenging oxidation steps before achieving high-value compounds. In general, bio-based feedstocks are broadly categorized into three general classes for the production of biorenewable fuels and chemicals: starch, triglycerides, and lignocellulose (Figure 2).[11] Starch from corn and sugar cane is composed of glucose subunits that can easily be hydrolyzed to their monomeric form, whereas triglycerides, consisting of fatty acids and glycerol, are present in soybeans and algae. Lignocellulose is primarily composed of cellulose, which in addition to lignin and hemicellulose, provide the rigid structural elements within most agricultural residues and energy crops.[12] Of the three classes, carbohydrate-based resources are produced in the highest quantity and are predicted to be an important renewable feedstock in the future, particularly for transformations of sugars like glucose.[8]

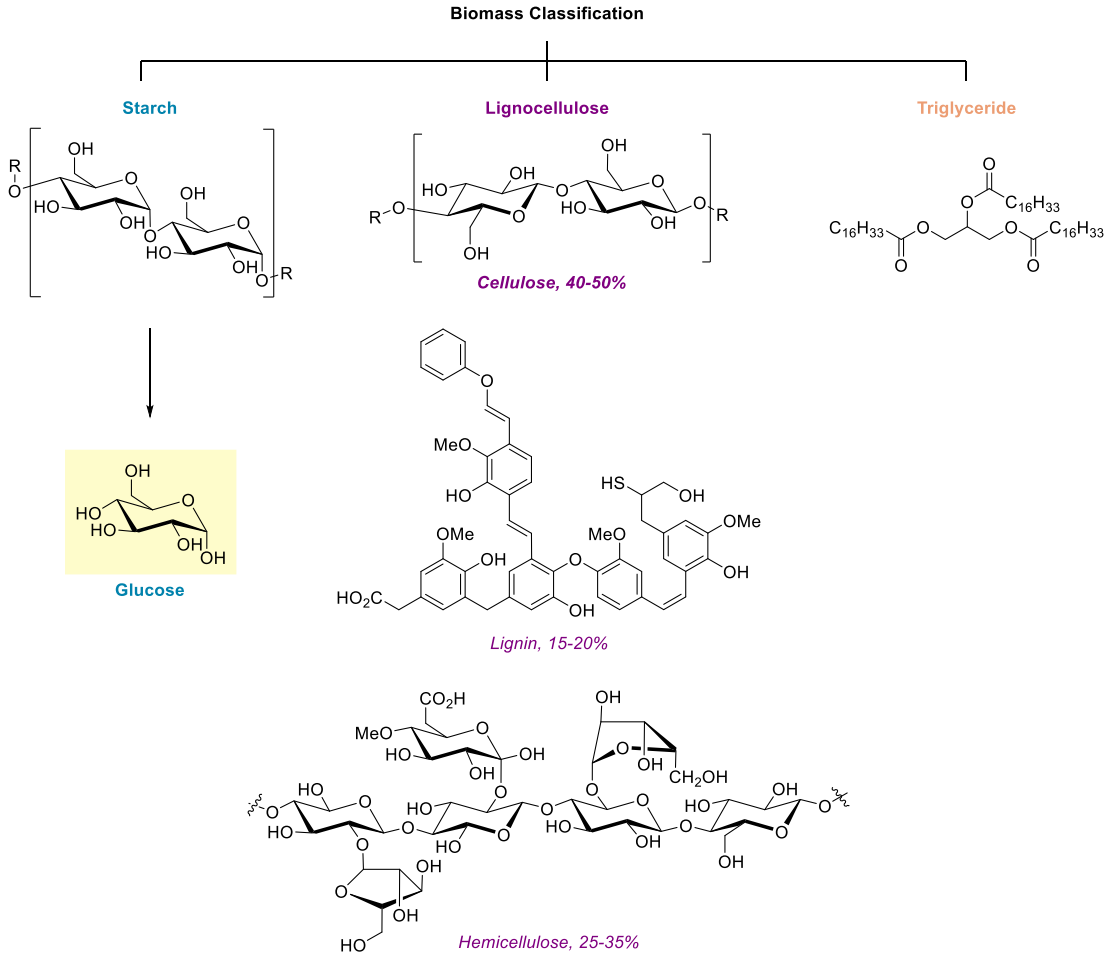


Figure 2. Major categories of biomass feedstocks.[5]

Feedstock choice is crucial for biorefineries as they optimize the variables to process raw biomass into usable form for conversion into higher value products. Since biorefineries integrate equipment to maintain the efficiency of conversions on an industrial scale, their role is vital to achieving the chemical industry goal where 30% of raw materials will be produced from biomass by 2025.[13] The overall pathway from biomass to chemicals as implemented in biorefineries could be described as a two-step process after the pretreatment phase to first transform sugars to building blocks, usually

through biotechnological routes. Afterwards, chemical transformations generally predominate to upgrade building blocks into secondary chemicals for further diversification.

Taking advantage of the metabolic machinery in microorganisms is one main biotechnological route to transform sugars into building blocks. Compounds are classified as natural-inherent chemicals if they already exist in nature and are formed along a microorganism's preexisting pathway.[14] Advances in metabolic engineering have allowed researchers to improve fluxes in a host strain's native pathways to increase the yield, titer, and productivity of the targeted chemical.[15] The yields are measured relative to the amount of the desired chemical produced per mole of the substrate, with titer reflecting the product concentration in the medium, and the productivity metric indicating the efficient performance of reactors for extrapolation to an industrial scale.[16] With natural-inherent chemicals, metabolic engineering primarily relies on an understanding of protein structure and function to rationally modify specific biochemical reactions through the enzymes that catalyze the reactions.[17] Recombinant DNA techniques alter specific amino acids of the biocatalysts that affect the reaction outputs along the overall pathway. Particularly in the microbial fermentation of sugars, competitive pathways are inactivated or interrupted while desired pathways are overexpressed. Systems biology assures the microorganisms with optimized native pathways have the capability to efficiently produce industrial quantities of chemicals outside their natural environment for integration into biorefineries.

1.2. Platform Molecules

One of the most efficient and divergent approaches for upgrading feedstocks to valuable products in biorefineries is through the convenience of platform molecules. Generally endowed with functionality to serve as flexible starting points for producing additional derivatives, they are also referred to as derivative molecules.[11] The U.S. Department of Energy has recognized the power of platform molecules and included the capability of molecules to function as platforms as an evaluative benchmark to determine the potential opportunities from biomass.[18,19] An original list of twelve building blocks was assembled in 2004[19] but was revised and reduced to ten compound classes by Bozell in 2010[18] to reflect the technological advances made in the interim (Figure 3). The list of potential chemical opportunities was created to stimulate research toward the creation of high-value, low-volume chemicals from biomass which would ultimately improve the techno-economic analysis for integration into industry.

Many of the compounds were selected based on the amount of active research associated with the molecule, but having potential as a platform was an important factor as only biohydrocarbons and lactic acid did not meet the platform requirement. To highlight the variability that can arise from platform molecules, the U.S. Department of

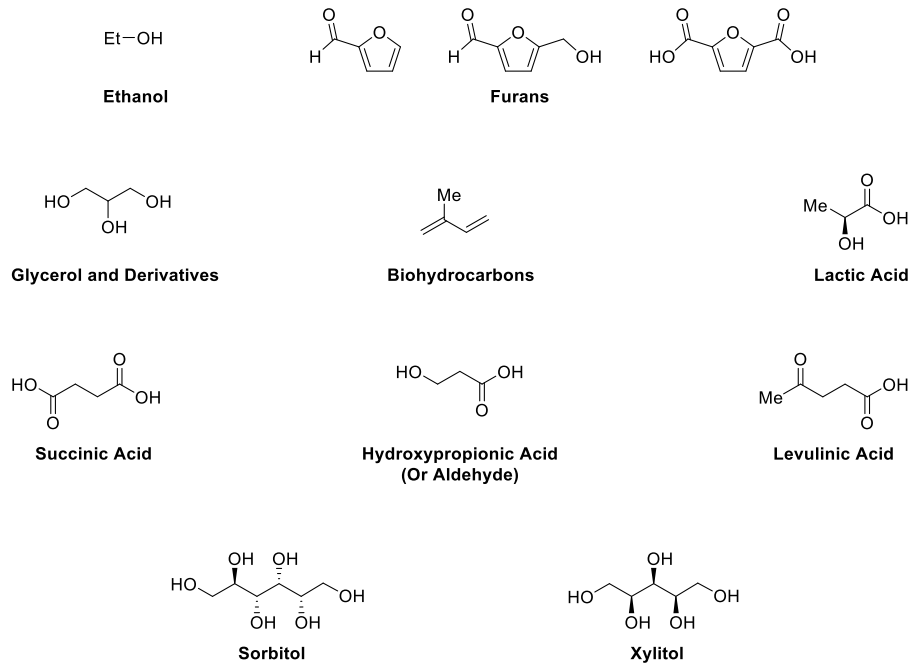


Figure 3. Potential chemical building block opportunities from carbohydrates.[18]

Energy devised star diagram representations from which the end products or secondary chemicals could be more easily visualized. The power of platform molecules lies in their ability to generate structural diversity in addition to their applicability across a variety of industrial sectors. One platform that has been a major area of active research and development both in academia and industry includes 5-hydroxymethylfurfural (HMF). The bifunctional furan can be obtained from glucose if an initial isomerization is performed beforehand or fructose using acid catalysis or ionic liquids (Figure 4).[20,21] The arrows in the diagram lead to the eventual product after one or more chemical manipulations that range from oxidation or reduction reactions to aldol condensations. As a platform molecule, HMF has been a starting point with multiple applications in

polymers, agrochemicals, flavors and fragrances, and natural products with an increasing number of applications continually under development.

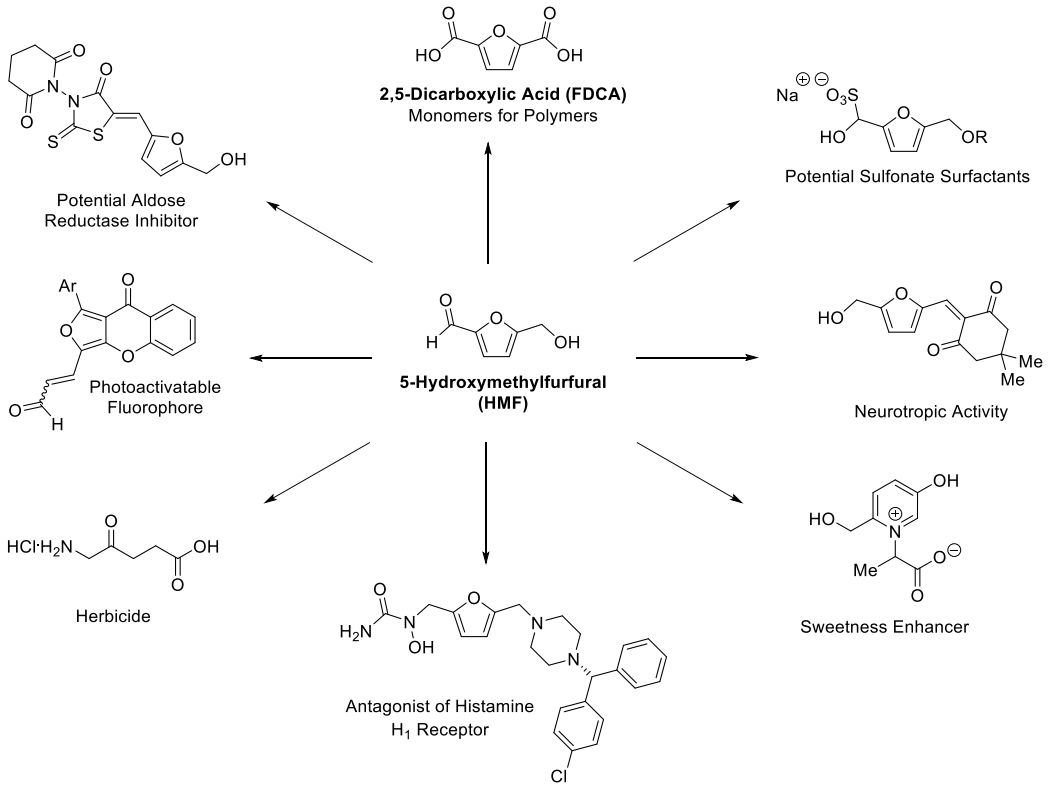


Figure 4. Star diagram with selected compounds from 5-hydroxymethylfurfural.[21,22]

Platform molecules have been frequently incorporated into value chains from biomass to either commodity or specialty chemicals. The bulk presence of chemicals in the former classification has high potential to drive the market and impact the chemical industry compared to the smaller volumes associated with targeting fine or specialty chemicals. Regardless of market demand, either the drop-in strategy or the emerging strategy is utilized, depending on whether the target already exists in the market. The

drop-in strategy upgrades biomass into a replacement compound that is currently produced from petroleum-based starting materials. On the contrary, emerging strategies introduce new bio-based chemicals that are not available in the market.[23] The drop-in strategy takes advantage of the well-established industrial infrastructure and benefits from the market data based on the existing demand. Either approach contributes to the valorization of biomass and its assimilation into industry toward a bio-economy.

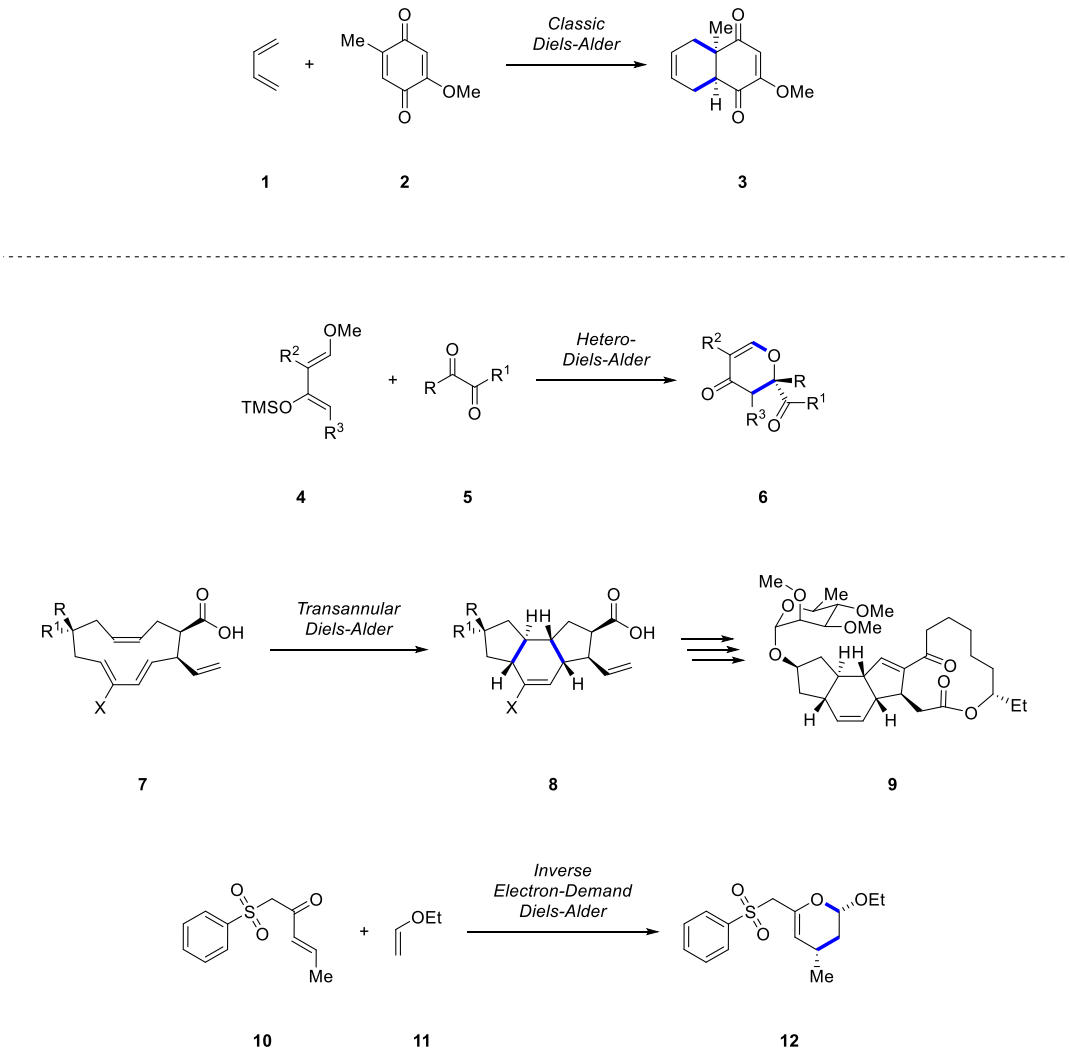
1.3. 2-Pyrones as Dienes to form Diels–Alder Cycloadducts

The underlying premise throughout Anastas and Warner's book[5] asserted that reducing problems associated with chemical production and processes at the source is more effective than attempting to retroactively control the consequences afterwards. By improving the synthetic design for petrochemicals, we investigated two main reaction components: alternative starting materials and reaction condition optimization to address both the feedstock and process. Our research aimed to integrate synthetic organic methodologies with green chemistry principles to generate functionalized aromatic systems through a bio-based platform technology. The key transformation to aromatize the platform was an inverse electron-demand Diels–Alder-initiated cascade reaction.

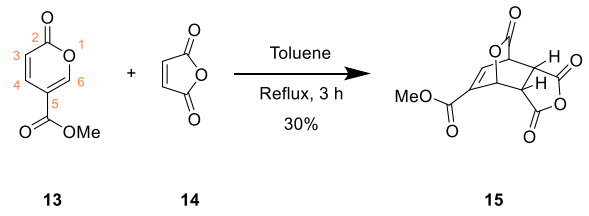
The Diels–Alder cycloaddition is a foundational pillar of organic synthesis to generate complexity from simpler substrates through concomitant carbon-carbon bond formation and high levels of regio-, chemo-, and stereocontrol. Since its discovery in 1928,[24] the reaction has been regularly incorporated into numerous syntheses to construct

sophisticated frameworks in academia[25,26] and industry.[27] Further advances have yielded variations from hetero-Diels–Alder[28] to transannular Diels–Alder[29] to inverse electron-demand Diels–Alder (IEDDA)[30,31] reactions as depicted in Scheme 1 which are a testament to its scope and utility. A critical aspect in controlling the regiochemistry of the reaction involves effectively matching an electron-deficient diene with an electron-rich dienophile for optimal orbital overlap in the IEDDA reaction which is governed by the electronics of the Diels–Alder partners.

With geometrically constrained *s*-cis conjugated alkenes, 2-pyrones are pre-organized dienes for the Diels–Alder reaction.[32–34] However, since 2-pyrones are partially aromatic compounds, thermal conditions or activation are generally needed, which is further supplemented by appropriate substitution to tune the electronics for more optimal reactivity. Diels and Alder reported the first reaction of the 2-pyrone methyl coumalate (**13**) with maleic anhydride (**14**) in 1931[35] to obtain the corresponding adduct **15**, but in only 30% yield (Scheme 2). They were unclear about the stereochemistry of the adduct, but the *endo* product was verified by Effenberger and co-workers.[36] After the initial proof-of-concept experiment, researchers realized the ability of 2-pyrones to install additional functionality at the cycloadduct stage with high regio- and stereoselectivity through the use of alternative alkenes. To understand the scope of the Diels–Alder reaction and the effects of substituents on the 2-pyrone system, reactions from the literature will be described beginning with the parent 2-pyrone, followed by electron-rich and electron-deficient 2-pyrones to generate bicycloadducts.

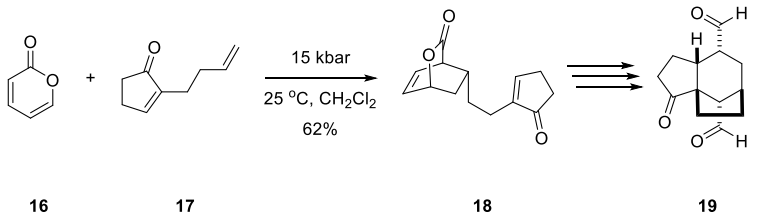


Scheme 1. Selected variations on the Diels–Alder reaction.[25,28–30]



Scheme 2. First-reported Diels–Alder reaction between the 2-pyrone methyl coumalate (**13**) and maleic anhydride (**14**).[35]

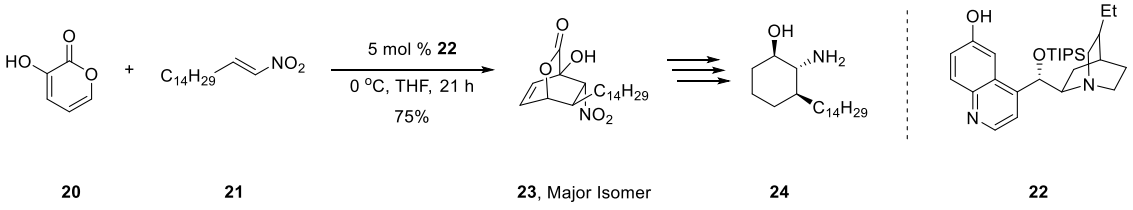
Lacking additional substitution, the parent 2-pyrone (**16**) undergoes a Diels–Alder reaction with alkene **17**, to provide bicycloadduct **18** (Scheme 3).[34] Elevated pressure was required to effect the transformation to slow the carbon dioxide decarboxylation and favor adduct formation. Proton NMR and x-ray diffraction analysis with methyl acrylate as the model system[37] confirmed the *syn-endo* adduct as the major isomer. Further Lewis-acid catalysis and functional group manipulation furnished the skeleton for gibberellin natural products **19** (Scheme 3).[34] Although the model system demonstrates that 2-pyrone can undergo a normal electron-demand Diels–Alder reaction with enones, it preferentially reacted with the alkyl-substituted alkene when both were present in the high-pressure system.



Scheme 3. High-pressure conditions of 2-pyrone to gibberellin backbone by Markó.[34]

Although increasing the pressure will induce Diels–Alder reactions in the pyrone system, another option is to functionalize the substrate which changes the electronics for the reaction. When a hydroxy group was introduced on the 3-position of the 2-pyrone **20**, it could participate in normal electron-demand Diels–Alder reactions with nitroalkenes **21** in the presence of cinchona alkaloid catalysts (Scheme 4).[38] The catalyst **22** that provided the highest enantio- and diastereoselectivity for the Diels–Alder adduct **23**

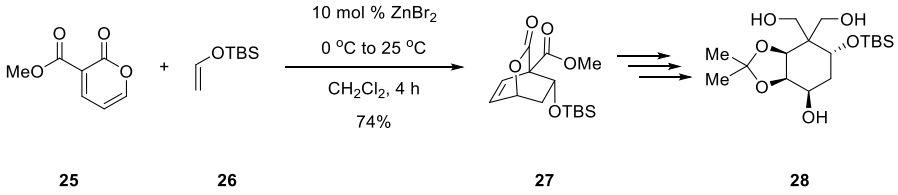
contained a hydrogen bond donor moiety and a bulky silyl group. While the *endo*-adduct **23** was the primary diastereomer, some of the *exo*-adduct also formed in addition to small and inseparable amounts of the *endo*-epimer at the carbon bearing the nitro group. The controlled Diels–Alder reaction was the key to the first enantioselective synthesis of a sphingosine natural product **24** with antiparasitic activity. Similarly, the Lewis acid-catalyzed normal electron-demand Diels–Alder of substituted 5-hydroxy-2-pyrones with methyl acrylate was essential in generating primarily *endo*-adducts.[39] While interesting systems were accessible through the route, some instances necessitated long reaction times, which indicate that 2-pyrones may not be inherently suited for normal electron-demand Diels–Alder reactions.



Scheme 4. Synthesis of sphingosine analogue *via* normal electron-demand Diels–Alder of 3-hydroxy-2-pyrone.[38]

Accordingly, IEDDA reactions with pyrones were investigated with sulfonyl electron-withdrawing groups[40] and brominated pyrones[41] with a more ambident character to promote the rate of the Diels–Alder reaction. Much research has arisen from ester-substituted 2-pyrones, especially at the 3- and 5-positions, which are particularly facile locations to install an electron-poor substituent. Posner and co-workers introduced multiple consecutive stereogenic centers to synthesize polyoxygenated cyclohexanes

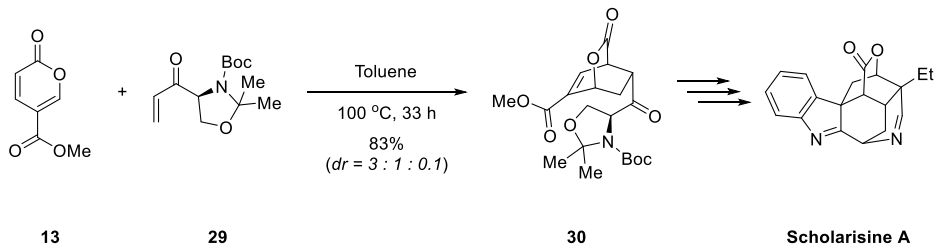
starting with commercially available methyl-2-oxo-2*H*-pyran-3-carboxylate (**25**).[42] The zinc bromide-assisted IEDDA reaction with *tert*-butyldimethylsilyl vinyl ether (**26**) regiospecifically provided the corresponding [2.2.2]oxabicyclic lactone **27** with nearly complete stereocontrol (Scheme 5). The selectivity resulting from the IEDDA conversion allowed them to synthesize cyclitol **28** with potential biological activity, characteristic of the class of compounds. They similarly demonstrated that the analogous pentafluorophenyl ester pyrone resulted in 88% yield of the *endo*-adduct under microwave conditions.[42] Their results suggest that creating a more electron-deficient system facilitates the IEDDA since a Lewis acid was no longer necessary.



Scheme 5. Cyclitol derivative synthesis through 3-substituted pyrone IEDDA reaction.[42]

The methyl ester at the 3-position of the 2-pyrone smoothly participated in the IEDDA reaction and demonstrated some parameters of the IEDDA based on the degree of the electronics. Similarly, the literature also demonstrates reactions with 5-substituted pyrones, especially methyl coumalate (**13**) in a comparison between the normal electron-demand Diels–Alder and IEDDA. Methyl coumalate was utilized as the partner in a normal electron-demand Diels–Alder reaction as elucidated by Snyder and his group in the first step of their elegant total synthesis of (+)-scholarisine A [43] as shown in Scheme

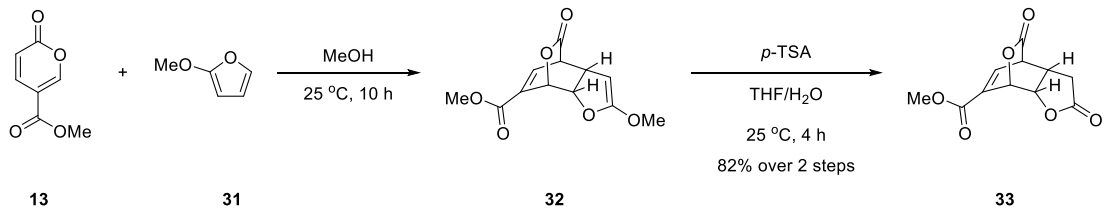
6. Although the reaction provided the requisite stereochemistry for convenient elaboration to the natural product, both diastereomeric adducts and an unidentified by-product were formed after an extended reaction time, which was challenging for purification.



Scheme 6. Route to (+)-scholarisine A involving normal electron-demand Diels–Alder reaction of methyl coumalate.[43]

In contrast, methyl coumalate in the IEDDA reaction provided better yields under milder conditions to synthesize tricyclic γ-butyrolactone natural products. In addition to matching the electronics for their substrates, Chen and Liao[44] decreased the reaction temperature to prevent carbon dioxide extrusion. Methyl coumalate (**13**) with 2-methoxyfuran (**31**) and methanol chemoselectively provided the Diels–Alder adduct **32** which simultaneously exhibited high regio- and stereoselectivities (Scheme 7). The effectively matched electronics with the IEDDA mechanism was substantiated by computational and experimental studies when the parent 2-pyrone did not result in any product formation after three days. Not all the cycloadducts were isolated since the crude mixture could be subjected to acidic conditions for conversion to the desired tricyclic lactone **33**. They observed that ester substituted 3- and 5-pyrones reacted faster than 4-

and 6-substituted pyrones, where electronic stabilization in the transition state and steric effects played important roles. The milder reaction conditions and higher chemo-, regio-, and stereoselectivities highlight the electronic preference for methyl coumalate in the IEDDA reaction over normal electron-demand Diels–Alder reactions.



Scheme 7. Tricyclic butyrolactone structures from the IEDDA reaction with methyl coumalate.[44]

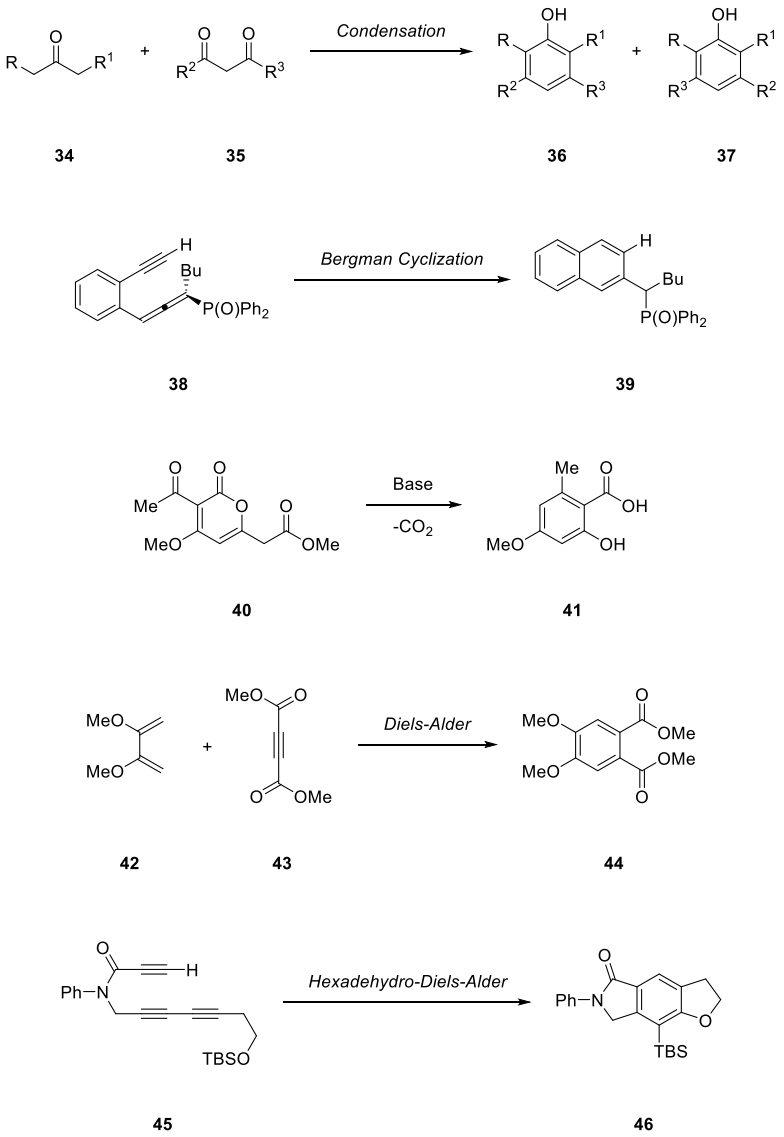
In a parallel comparison, 3-carbomethyoxy-2-pyrone (**25**) and methyl coumalate (**13**) were paired with the same set of dienophiles in IEDDA reactions.[45] The data show that 3-substituted 2-pyrones are generally more *endo*-selective, which might be related to their relatively faster reaction times. Steric considerations likely influenced the overall yields which are higher for methyl coumalate since it lacks substituents adjacent to the sites of carbon-carbon bond formation. Despite minor differences in stereoselectivity, all reactions with the electron-deficient 2-pyrones were highly regioselective as predicted for the electron-matched IEDDA reactions.

1.4. Electron-Deficient 2-Pyrones as Dienes to form Aromatics

The adducts resulting from the Diels–Alder reaction have been effective to introduce consecutive stereogenic centers for ultimate incorporation into diverse natural products, particularly with electron-matched pyrones. Not only are pyrones important for producing cycloadduct intermediates, but they also are instrumental in generating aromatic compounds. Functionalized aromatic systems are indispensable from commodity or value-added building blocks in the chemical industry[46] to structural components in natural products and pharmaceutical agents.[47] Aromatic systems have been functionalized in a controlled manner through electrophilic substitution of less-substituted aromatic precursors, especially through directed *ortho* metalation.[48] Additionally, functionalized aromatic systems have been constructed from condensation of acyclic species,[49] cycloaromatization of radical species,[50] base-mediated ring-opening then aromatization of 2-pyrones,[51] and most popularly from pericyclic reactions (Scheme 8).[52–54] Some aromatization methods have encountered challenges; regioselectivity is an issue for the condensation-type reactions, resulting in **36** and **37** from non-symmetric starting materials. However, researchers have utilized varying functionality including a combination of esters and ketones as the dicarbonyl unit **35** to favor deprotonation at the α-position. The Bergman cyclization as a subset of cycloaromatization reactions, effectively generates aromatic systems including **39** but substituents must be carefully selected on the allenyl unit in **38** to favor benzene formation over cyclopentadienyl formation. While base can be used to first open the 2-pyrone lactone **40** then cyclize to

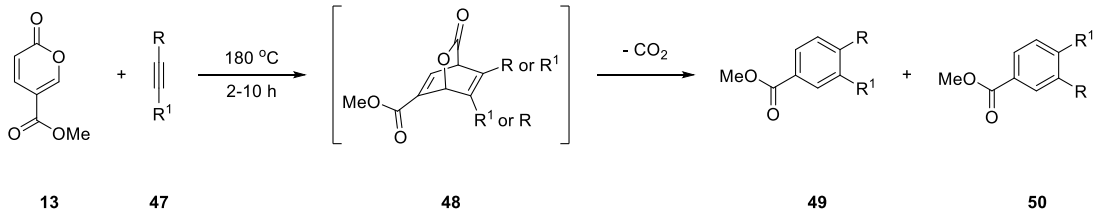
the more stable aromatic system **41**, it can be challenging to functionalize the initial pyrone for the substituents to transfer to the newly formed aromatic system. In addition to the Diels–Alder reaction with alkyne dienophiles **43**, the hexadehydro-Diels–Alder variant occurs through the pericyclic reaction of triyne **45** followed by *in situ* formation of a benzyne intermediate for subsequent trapping. However, pyrones have been fruitful to build aromatic systems through varying approaches, with a broad scope especially in the Diels–Alder reaction.

As dienes in the Diels–Alder reaction, 2-pyrones have been combined with either alkynes or alkenes to generate aromatic systems. The oxabicyclo intermediate **48** has not been isolated since it is too highly strained, but carbon dioxide extrusion through a retro-Diels–Alder reaction reveals the aromatic system. Both electron-deficient and electron-rich alkynes were investigated with methyl coumalate (Scheme 9) to efficiently generate a known aromatic intermediate in the synthesis of retinal-based molecular probes.[55] Ethyl propiolate (**47a**) as the dienophile afforded mixtures of regioisomers when both electron-poor species were combined. The regioselectivity and yield improved significantly with the more electron-rich ethyl 2-butynoate (**47b**) as the dienophile. Finally, a Lewis acid was again used to aid the Diels–Alder reaction with propargyl acetate (**47c**), where only one regioisomer resulted.



Scheme 8. Selected strategies to generate functionalized aromatic systems.[49–54]

As the dienophiles became more electron-rich, the regioselectivity and yields improved accordingly based on the effective match between the partners for the IEDDA reaction.



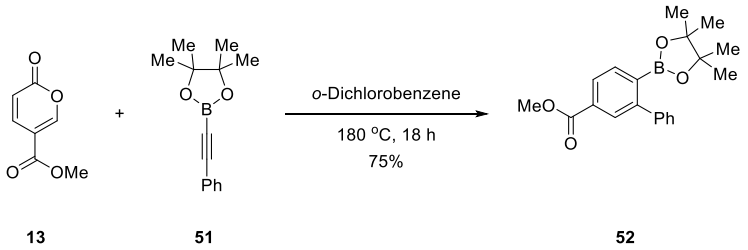
13 47 48 49 50

Dienophile	R	R^1	Yield (%)	Ratio **49** : **50**
47a	H	CO_2Et	47	1.15 : 1
47b	Me	CO_2Et	Quant.[a]	9 : 1
47c	CH_2OAc	H	78[a]	1 : 0

[a]0.5 equiv. citric acid added to the reaction

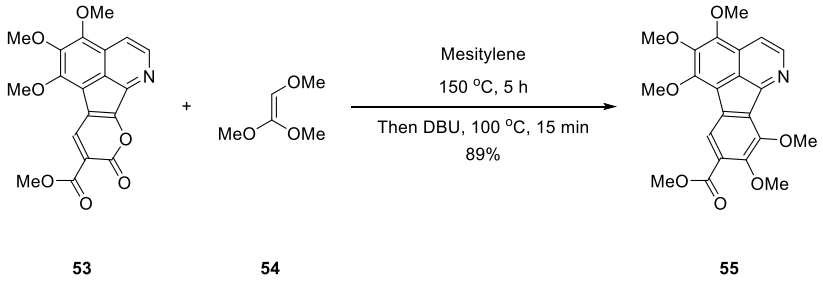
Scheme 9. Alkynyl dienophiles with methyl coumalate to aromatic systems.[55]

Harrity and co-workers investigated the more electron-rich class of alkynylboronates as the resulting aromatic compounds could participate in cross-coupling reactions for additional functionalization. Methyl coumalate conveniently provided aromatic boronate ester **52** in 75% yield with a 14:1 ratio for the predicted regioisomer upon reaction with alkynyl boronate **51** (Scheme 10).[56] Although higher overall yields could be achieved with TMS- and alkyl-substituted alkynyl boronates, neither were regioselective and both isomers formed in a nearly 1:1 ratio. Along with methyl coumalate, they investigated methyl esters substituted on the 3-, 4-, and 6-positions of the 2-pyrone which were less efficacious dienes compared to methyl coumalate. As previously observed, the 3- and 6-substituted 2-pyrones reacted more slowly due to sterics and the proposed zwitterion transition state[57] disfavored effective reaction with the 4-substituted 2-pyrone through electronic delocalization. The electronic character of the alkynyl dienophiles influences the efficiency of the match with methyl coumalate in the IEDDA reaction in a similar fashion to alkenes to alter both yield and regioselectivity.



Scheme 10. Aromatic boronates from the IEDDA reaction with methyl coumalate.[56]

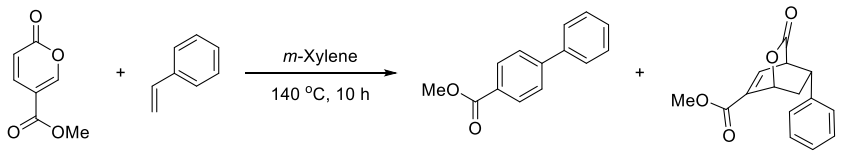
Alkyne dienophiles were convenient partners with methyl coumalate as they provided a metal-free route to aromatic systems after a thermal Diels–Alder reaction. However, alkenes could potentially introduce a broader range of functionality since they can tolerate greater functionality than alkynes if they could be converted into aromatic systems. Two general approaches to effect aromatization after formation of the bicycloadduct included base-mediated elimination or transition metal-catalyzed oxidation. Boger extensively examined the IEDDA reaction with 2-pyrones and reported that a substituted 3-carbomethoxy-2-pyrone **53** could be paired with 1,1,2-trimethoxyethylene (**54**) to provide the adduct.[58] After the crude reaction mixture containing the adduct was treated with DBU and heated again, the aromatic product **55** was generated after elimination of an equivalent of methanol (Scheme 11). The resultant aromatic system was a single step from the azafluoranthene alkaloid imeluteine that possesses cytotoxicity against certain cancer cell lines.[59] The functionalized benzoate proceeded in good yield with an electron-rich dienophile to install additional functionality compared to the alkyne Diels–Alder reaction, although additional base expedited the reaction.



53 54 55

Scheme 11. Functionalized aromatic from 3-substituted-2-pyrone and electron-rich dienophile.[56]

In the second general approach to aromatics from alkenes, catalytic palladium on carbon could perform the oxidative aromatization from the bicyclo[2.2.2]octene intermediate. In line with green chemistry principles, the heterogeneous nature of the palladium catalyst could potentially allow catalyst recovery for re-use in additional reaction cycles. Matsushita et al. studied reactions with methyl coumalate as the diene with various aromatic olefins under thermal conditions.[60] They first conducted the reaction in the absence of palladium on carbon which provided the Diels–Alder adduct **58** as the major product with some formation of the desired aromatic compound **57** (Scheme 12). The inclusion of palladium on carbon dramatically improved yields with complete conversion of methyl coumalate and the [2.2.2]oxabicyclic lactone **58** to methyl 4-biphenylcarboxylate (**57**) when styrene (**56**) was the dienophile. They extended the reaction to heteroaromatic olefins and achieved up to 93% yield with 2,4-dichloro-1-vinylbenzene. Exploring the scope of the reaction led to the observation that increasing the temperature could improve yields for less reactive substrates.



13 56 57 58

Catalyst	Yield (%)	Ratio **57** : **58**
-	58	1 : 9
10% Pd/C	81[a]	1 : 0

[a]2.5 wt. equiv. Pd/C added to the reaction

Scheme 12. The role of palladium on carbon in the DA reaction with methyl coumalate and styrene to aromatic systems.[60]

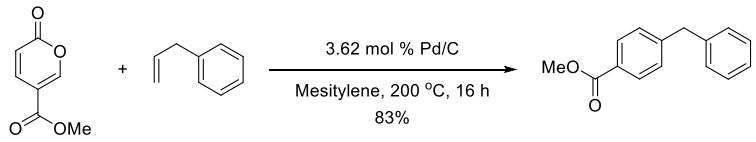
A similar route was utilized in the normal electron-demand Diels–Alder reaction of methyl coumalate with electron-deficient alkenes **59**. Palladium on carbon productively generated aromatic systems **60** and **61** in an attempt to introduce more electron-withdrawing groups onto the aromatic ring. However, regioselectivity was problematic as previously mentioned in the isolation of the oxabicyclo species from the normal electron-demand Diels–Alder reaction. Acrolein (**59a**) provided the best regioselectivity but did not exceed a ratio of 4.3 : 1 for the *para*-substituted over the *meta*-substituted product (Scheme 13).[61] Methyl acrylate (**59b**) had a diminished yield and regioselectivity, while acrylonitrile (**59c**) provided the best yield but the lowest regioselectivity since it was the most electron-deficient dienophile and not ideally suited for a Diels–Alder reaction with methyl coumalate.

13 **59** **60** **61**

Dienophile	EWG	Yield (%)	Ratio **60** : **61**
59a	CHO	47	4.3 : 1
59b	CO_2Me	25	2.9 : 1
59c	CN	60	1.7 : 1

Scheme 13. Methyl coumalate in the normal electron-demand Diels–Alder reaction with electron-deficient alkenes toward aromatic systems.[61]

In contrast, methyl coumalate in conjunction with unactivated alkenes regioselectively provided aromatic products after dehydrogenation with palladium on carbon. Although alkene substituents ranged from alkyl chains and allyl ethers, they are mildly electron-donating groups which only generated *para*-substituted aromatic compounds in 51-83% yield.[62] The olefin that resulted in the highest yield was allyl benzene (**62**) to provide the corresponding *para*-substituted aromatic compound **63** (Scheme 14). The reactivity pattern supports the IEDDA mechanism particularly when both electron-rich and unactivated alkenes were combined as dienophiles with the methyl coumalate diene in the Diels–Alder reaction.



13 **62** **63**

Scheme 14. Formation of aromatic compounds from methyl coumalate and unactivated alkenes.[56]

1.5. Conclusion

Petrochemicals are prevalent in many consumer materials across nearly all market sectors, particularly in the form of aromatic compounds. However, the increasing demand and price for the traditional crude oil feedstock, coupled with the decreasing supply could lead to an ambiguous prospect for future sustainability. To ameliorate the problem, twelve principles of green chemistry were formalized by Anastas and Warner, where they promote researching atom economical methods and alternative feedstocks. Biomass is an important alternative feedstock as it is renewable over a much shorter time period, from which the glucose monomer of starch is a useful starting material. The generation of platform molecules from biomass feedstocks is an attractive approach, as recognized by biorefineries and the U.S. Department of Energy as efficient modes to diversify biomass.

Diversification may potentially arise from the atom economical Diels–Alder reaction which transfers most of the carbon atoms from the starting materials into the products. With its high levels of regio-, chemo-, and stereocontrol, it is a promising methodology for application to bio-based feedstocks and industrially relevant compounds. Aromatic compounds have been identified by the U.S. Department of Energy as among the highest priority valuable product classes for further investigation from biomass.[19] The Diels–Alder reaction has popularly been utilized toward obtaining aromatics, and with 2-pyrones as the diene, the approach has generated either bicyclic cycloadducts for further derivitization or aromatic systems directly. Many of the routes

that provided aromatic systems have utilized alkyne dienophiles or the normal Diels–Alder approach with unactivated or electron-deficient alkenes. The reactions with alkenes required an additional palladium catalyst to facilitate aromatization and utilizing electron-deficient alkenes resulted in mixtures of regioisomers. However, the 2-pyrone methyl coumalate has shown promise in the literature as regioselective dienes in inverse electron-demand Diels–Alder strategies that could be leveraged to generate a variety of substituted aromatic compounds.

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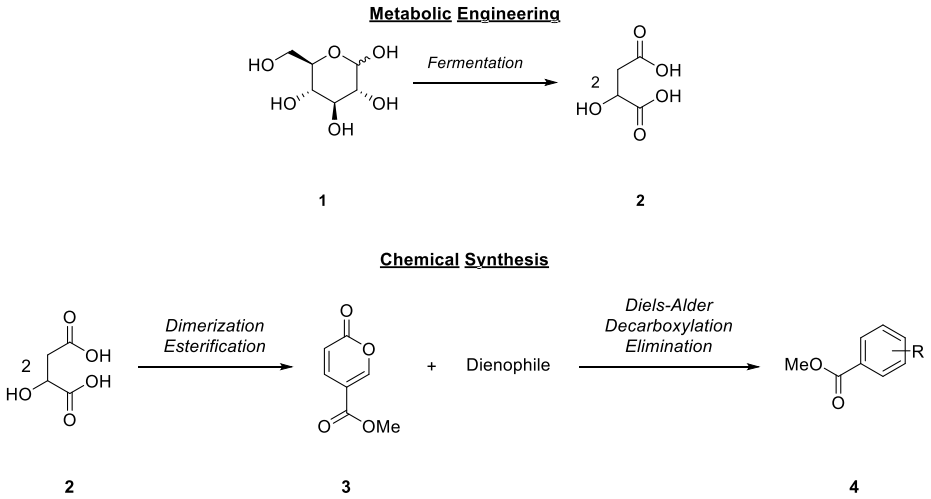
CHAPTER 2.

METHYL COUMALATE PLATFORM APPROACH TO SUBSTITUTED AROMATICS[†]

2.1. Upgrading Glucose to the Methyl Coumalate *via* Malic Acid

While aromatics have been demonstrated as important targets, substituted benzoates in particular have been useful in many industrial applications from plasticizers[1] and pharmaceutical agents[2] to novel materials.[3] With the importance of designing synthetic methods in the context of green chemistry principles, we aimed to create a platform approach that would furnish secondary chemicals in the form of substituted benzoates toward creating a sustainable bio-economy. Cognizant of the literature precedent, we capitalized on methyl coumalate as a bio-based platform for diversification to a broad range of biorenewable benzoates. Overall, we envisioned that the general process would involve metabolic engineering from glucose to malic acid as described in the literature, followed by chemical transformations. The chemical synthesis could again be divided into two major stages: the dimerization of malic acid to generate the coumalate platform and the Diels–Alder methodology to functionalized aromatics (Scheme 1).

[†] Adapted from Lee, J. J.; Kraus, G. A., *Tetrahedron Lett.* **2013**, *54*, 2366–2368, with permission from Elsevier; adapted from Lee, J. J.; Kraus, G. A. *Green Chem.* **2014**, *16*, 2111–2116 with permission from The Royal Society of Chemistry; adapted from Lee, J. J.; Pollock, G. R.; Mitchell, D.; Kasuga, L.; Kraus, G. A. *R. Soc. Chem. Adv.* **2014**, *4*, 45657–45664 with permission from The Royal Society of Chemistry.



Scheme 1. Technology overview from glucose to functionalized aromatics.

Metabolic engineering has become a reliable method to enhance the pathways of microorganisms to produce natural-inherent chemicals. Discovered in 1924 from yeast fermentation,[4] malic acid is a naturally-inherent C4 dicarboxylic acid, as defined by Lee and co-workers.[5] It can be generated during the native glucose fermentation pathway in a variety of prokaryotic and eukaryotic microorganisms.[6] Its corresponding petroleum-based route is through the hydration of maleic anhydride which ultimately arises from benzene.[7] Malic acid's application in the food and beverage industry as a flavor modifier resulted in its annual production of 40,000 tons in 2006.[7] Its potential as a platform molecule alongside other C4 diacids and its sizeable production volume stimulates research into bio-based alternatives, especially as they stereoselectively generate *L*-malic acid instead of racemic mixtures.

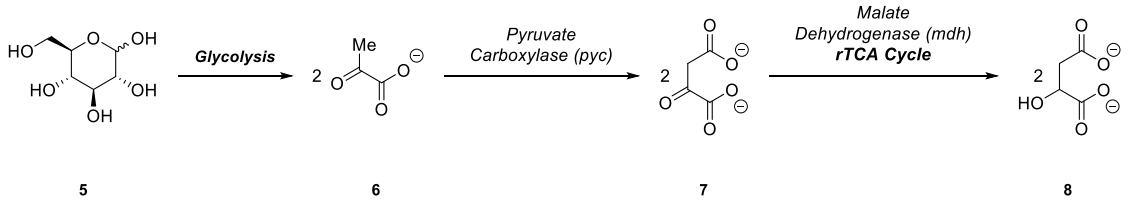


Figure 1. Native metabolic pathway of glucose fermentation to malate.

Malic acid in its ionized form, malate, can be generated through four possible pathways from glucose, but the most efficient route is *via* the reductive tricarboxylic acid TCA (rTCA) cycle as delineated in Figure 1. The pathway first requires glycolysis of glucose (**5**) to pyruvate (**6**) after which oxaloacetate (**7**) is reduced to malate (**8**) through enzymatic action. Modifications of the rTCA pathway in yeast, bacteria, and fungal cells have resulted in promising opportunities for industry. The yeast species *Saccharomyces cerevisiae* was metabolically engineered to add a malate transporter from another species and increase the expression of the key proteins pyruvate carboxylase (pyc) and malate dehydrogenase (mdh) along the native pathway.[4] After optimization trials, Zelle and co-workers obtained malate in the highest yields from *S. cerevisiae* to date of 0.42 moles of malate per mole of glucose with a titer of 59 g liter^{-1} and productivity of 0.29 g liter^{-1} h^{-1} (Table 1).

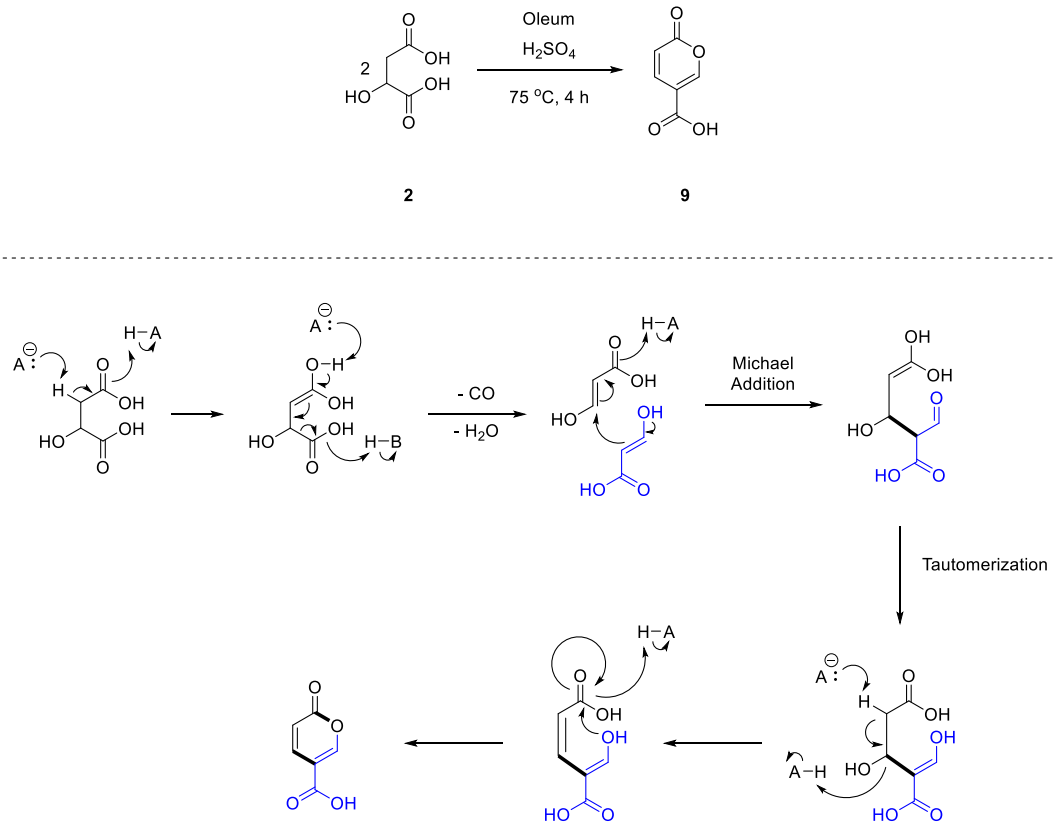
Table 1. Comparison of malate production through glucose fermentation

Microorganism	Yield (mol mol^{-1})	Titer (g liter^{-1})	Productivity (g liter^{-1} h^{-1})
S. cerevisiae	0.42	59	0.29[4]
E. coli	1.42	34	0.47[8]
A. oryzae	1.38	154	0.94[7]

Alternatively, the *Aspergillus oryzae* similarly involved overexpression of pyc and mdh in addition to another transporter, although many *Aspergillus* species tend to intrinsically produce more malate.[7] The *A. oryzae* system has potential for industrial malate production especially with its high productivity levels and titers; however, there are some concerns that toxins may be generated as side products and there are challenges with the lack of replicating extrachromosomal vectors. The resulting yield was an improvement from *S. cerevisiae* with 1.38 moles of malate per mole of glucose along with the productivity (Table 1). The highest reported yield of 1.42 moles of malate from 1 mole of glucose resulted from the modification of glucose fermentation in the bacterium *Escherichia coli* which took advantage of modifications for the related C4 succinate with additional gene deletions for fumarate production to increase malate formation.[8] While there are advantages and disadvantages to each system, *L*-malic acid can readily be generated in a variety of microbial hosts through metabolically engineering native pathways to enhance malate production from glucose.

Since malic acid can be directly obtained from glucose through metabolic engineering, it was a convenient starting material for subsequent chemical modification. Malic acid dimerization was initially investigated by von Pechmann in 1891 to obtain coumalic acid where the proposed mechanism involves acid-catalyzed dehydration and decarbonylation to the enol form of 3-oxopropanoic acid.[9] Condensation with another molecule through a Michael addition followed by elimination then leads to coumalic acid (Scheme 2). However, stringent and corrosive reaction conditions were utilized in the process with oleum, a combination of fuming sulfuric acid with sulfuric acid as the

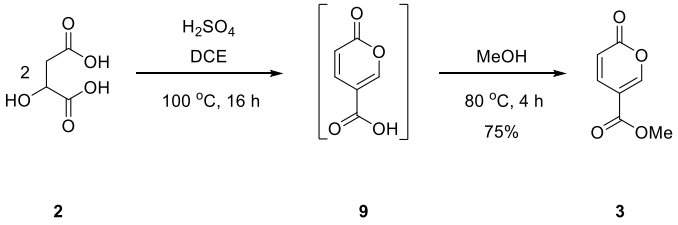
solvent.[10] Despite the harsh reaction conditions, few investigations have been devoted to optimizing the process; rather, these reaction conditions have generated coumalic acid in 65-70% yield starting from 200-gram batches of malic acid.[9,11,12]



Scheme 2. Proposed dimerization mechanism of malic acid (**2**) to coumalic acid (**9**).[9]

Many literature accounts describe the procurement of methyl coumalate as a stepwise protocol involving the isolation of coumalic acid, followed by a separate esterification step. The methyl ester can be obtained either with sulfuric acid and methanol[13,14] or diisopropylethylamine and dimethylsulfate.[9] However, we took

advantage of precedent where coumalate esters were generated in one step from malic acid to reduce an intermediary purification step. The dimerization first occurred under fuming sulfuric acid conditions after which an alcohol was added to the crude mixture to afford the desired coumalate.[15–17] The conversion was modified to avoid fuming sulfuric acid and utilize a solvent other than sulfuric acid to reduce tar formation and make the reaction more amenable for industrial scale (Scheme 3).



Scheme 3. One-pot reaction conditions from malic acid (**2**) to methyl coumalate (**3**).

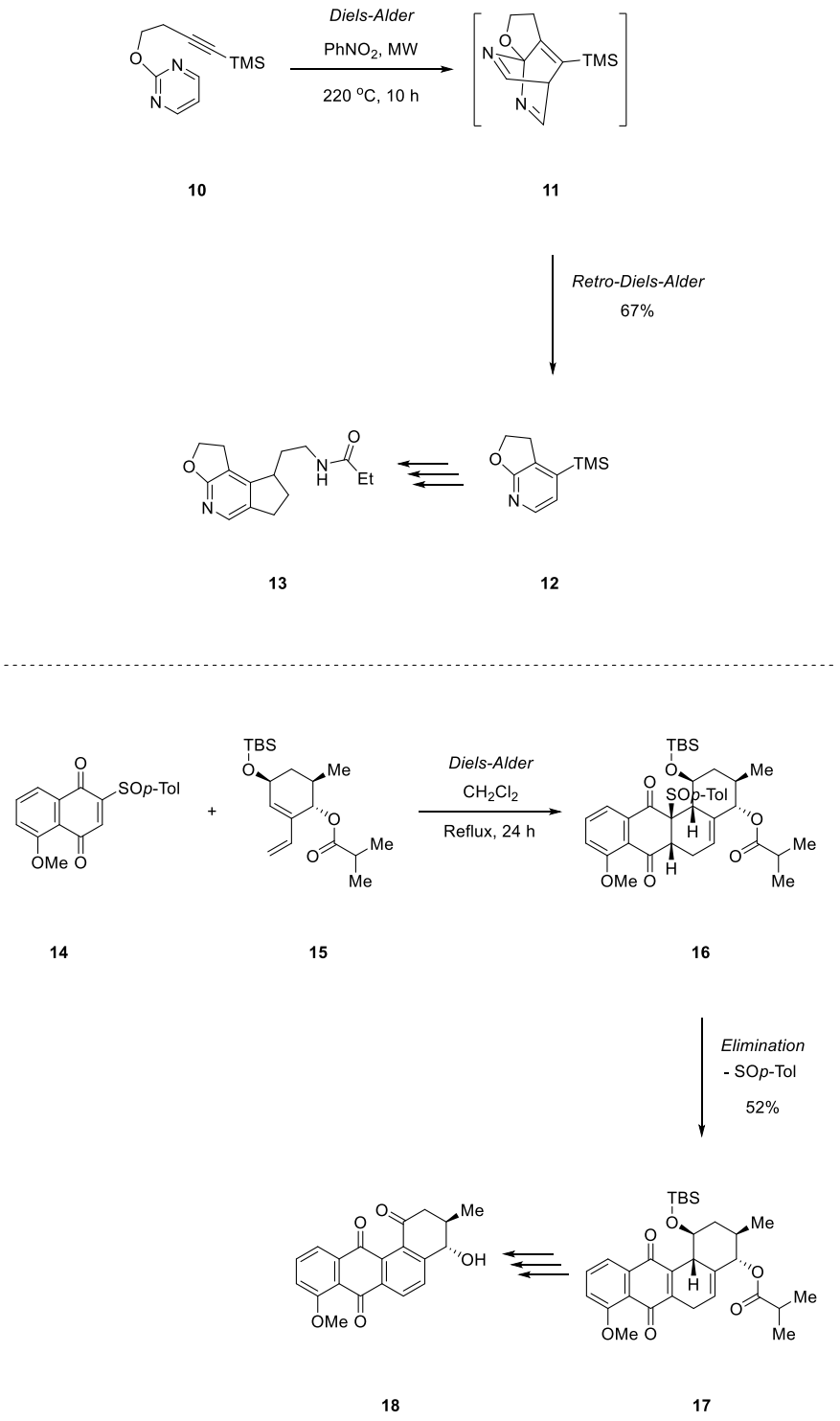
With a route for bio-based methyl coumalate, we set out to explore its potential in the IEDDA reaction since the literature precedent with methyl coumalate as a diene primarily focused on unactivated and electron-poor alkenes. To achieve aromatization with the previous dienophiles, palladium on carbon was required; however, we aimed to design a methodology to feature the Diels–Alder reaction that would simultaneously avoid the need for an additional transition metal catalyst. A domino reaction was attractive as carefully functionalizing the dienophile could establish methyl coumalate as a platform for biorenewable chemicals.

2.2. Diels–Alder-Initiated Domino Strategy with Methyl Coumalate and Vinyl Ether Dienophiles

Domino reactions are a subset of sequential reactions, which are even more broadly classified as one-pot reactions. Similar to the game from which the name is derived, domino sequences describe two or more reactions that occur in succession where the resultant compound of the initial reaction serves as the reactant for the next reaction. True domino reactions result in product formation under the same reaction conditions without adding or changing reagents over the course of the reaction.[18] Domino reactions have been identified by mostly interchangeable names in the literature, including tandem or cascade, although the former could be a more inclusive category[19] and the latter has been narrowly distinguished to refer to sequences which have been more clearly initiated and terminated.[20] The second category of sequential reactions, termed consecutive reactions, differ since the reaction conditions are changed after completion of an initial conversion through addition of a reagent or temperature changes. Based on the definitions, the preparation of methyl coumalate from malic acid as previously described is a consecutive process. In the one-pot process, malic acid dimerization occurs first to generate coumalic acid which is not isolated before the reaction continues with the addition of methanol and a decrease in temperature to furnish methyl coumalate.

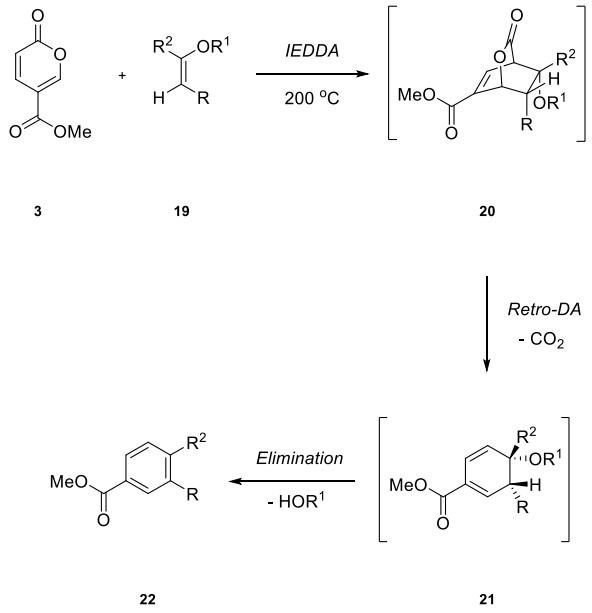
Domino reactions efficiently lead to the formation of several bonds at once and readily adhere to green chemistry principles over stepwise syntheses since fewer purification steps are required and less waste is generated. Efficiency arises across many

parameters including time, energy, and production costs, which make domino reactions amenable for industrial production. Domino reactions comprise a range of different types according to the mechanisms of the steps; accordingly, homo-domino reactions involve reactions with the same mechanism unlike hetero-domino reactions.[21] The multistep Diels–Alder reaction is frequently invoked as a key transformation in many pericyclic domino sequences with its concomitant bond-forming ability and high levels of stereocontrol.[22] Within organic synthesis, pericyclic domino reactions have led to the creation of polycyclic systems through an intramolecular Diels–Alder/retro-Diels–Alder sequence of azine **10** to the pyridine analogue of the ramelteon sleep agent **13** after extrusion through the retro-Diels–Alder reaction[23] (Scheme 4). Additionally, asymmetric pericyclic-elimination domino reactions with a normal Diels–Alder/elimination sequence resulted in the synthesis of members from the biologically active rubiginone family **18**[19,24] (Scheme 4). In each instance, additional complexity was generated by the combination of steps in the domino reaction sequence, especially with the participation of both the normal and inverse electron-demand Diels–Alder reactions. Recognizing the ability to form multiple bonds while simultaneously upholding green chemistry principles, we endeavored to utilize a two-component IEDDA/retro-Diels–Alder/elimination domino sequence between methyl coumalate and electron-rich dienophiles to flexibly generate aromatic systems with increasing structural diversity.



Scheme 4. Pericyclic domino reactions as key steps in the synthesis of polycyclic compounds.[19,23,24]

Literature precedent with 2-pyrones as dienes in the Diels–Alder reaction revealed that designing electronically-compatible dienophiles was crucial to control regioselectivity. Modest regioselectivity was observed with methyl coumalate and electron-poor olefinic dienophiles which was attributed to the mismatched electronics.[25] In contrast, alkyl and remote ether substituents on the dienophile provided *para*-substituted compounds,[26] but both routes required oxidation by palladium on carbon to obtain the final aromatic compound. To maintain the high regioselective capability of the Diels–Alder reaction with methyl coumalate while increasing the functionality of the resulting aromatics, oxygen-containing moieties were introduced directly onto the alkene to increase the electron density and avoid the need for a transition metal catalyst. We envisioned that the mechanism involved formation of the intermediary bicyclo[2.2.2]octadiene adduct **20** through the IEDDA reaction. Subsequently, a retro-Diels–Alder reaction would expel carbon dioxide then alcohol elimination would complete the domino reaction with each conversion contingent on the previously formed *in situ* intermediate to furnish a targeted aromatic compound **22** (Scheme 5). Carbon dioxide extrusion likely occurred immediately after cycloadduct formation as loss of gaseous compounds is thermodynamically and entropically favorable and has been strategically used in natural product synthesis.[27] After removal of carbon dioxide, the resulting diene **21** is primed for elimination to an aromatic system in the same pot, expedited by the alkoxide leaving group to avoid supplementary reagents.

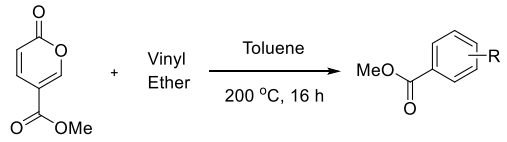


Scheme 5. Putative mechanism for domino reaction sequence to functionalized aromatics.

The investigation of electron-rich dienophiles commenced with vinyl ethers as the partner for methyl coumalate (Table 2). The simplest vinyl ether for comparison with a compatible boiling point for the reaction conditions was butyl vinyl ether (**23a**). After combining the substrates and solvent into a sealable reaction vessel, no additional reagents were added until after the reaction was completed to determine whether the domino reaction sequence would occur. As predicted, palladium on carbon was not required for the aromatization as an equivalent of butanol was eliminated over the course of the reaction to smoothly provide methyl benzoate (**24a**) in 89% yield. Methyl benzoate can easily be hydrolyzed to benzoic acid, a widespread preservative in food and cosmetics,[28] normally produced through the oxidation of petroleum-derived toluene.[1]

While methyl benzoate is naturally present in certain plant species that leads to its application in fragrant oils,[29] utilizing a synthetic route would increase availability while avoiding harsh oxidation conditions.

Table 2. Scope of vinyl ether dienophiles to generate aromatic compounds[a]



3 **23** **24**

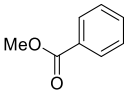
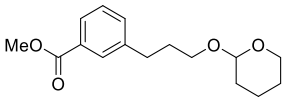
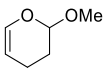
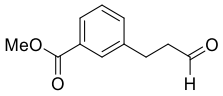
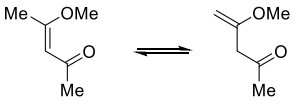
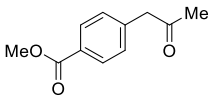
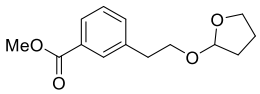
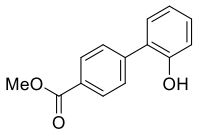
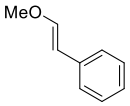
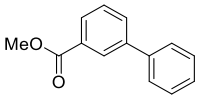
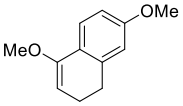
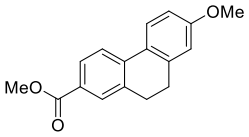
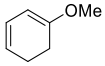
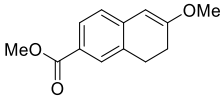
Entry	Vinyl Ether	Aromatic Product	Yield (%)[b]
1	 **23a**	 **24a**	89
2	 **23b**	 **24b**	77
3	 **23c**	 **24c**	77
4	 **23da** **23db**	 **24d**	79

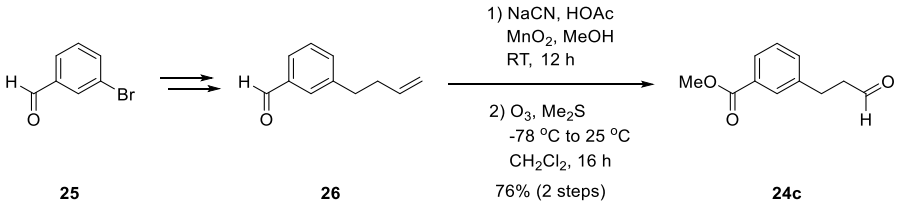
Table 2 (Continued)

5	 **23e**	 **24e**	61
6	 **23f**	 **24f**	77
7	 **23g**	 **24g**	51
8	 **23h**	 **24h**	34
9	 **23i**	 **24i**	72

[a]Reaction conditions: **3** (1 mmol) and **23** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube, with the exception of entries 2 and 5 which utilized 5 mmol of **23b** and **23e**, respectively. [b]Isolated yield.

Although butyl vinyl ether (**23a**) proved that the methodology efficiently provided an aromatic compound, it was unclear whether the reaction proceeded with high regioselectivity since each atom from the starting material was not specifically tracked in the final aromatic compound. We then sought to generate disubstituted aromatic systems

with cyclic vinyl ethers, from which the regioselectivity of the initial IEDDA reaction could be inductively determined. By using an excess of commercially available 3,4-dihydro-2*H*-pyran (**23b**), the IEDDA/retro-Diels–Alder/elimination sequence occurred, followed by additional alcohol protection to provide **24b** in 77% yield. The simultaneous alcohol protection is particularly applicable where the presence of a primary alcohol could potentially interfere with other desired synthetic manipulations. Aromatic compound **24b** has already proven beneficial as one of the primary starting materials for a cholesterol inhibitor **33** (Figure 2).[30] In general, preparations of **24b** entail protecting the corresponding alcohol which is only commercially available from very few suppliers and is a simple functional group manipulation which does not construct the aromatic portion of the molecule. The success of the reaction not only demonstrates the extension of the domino reaction to include an additional transformation, but also affirms the exclusive regioselectivity predicted for the IEDDA reaction since the *para*-substituted isomer was not observed. As a further extension, the more highly substituted 2-methoxy-3,4-dihydro-2*H*-pyran (**23c**) allows the introduction of an additional carbonyl moiety to the aromatic system *via* the hemiacetal. The resultant methyl 3-(3-oxopropyl)benzoate (**24c**) demonstrates the methodology's efficiency as a previous approach required multiple steps involving a palladium-catalyzed homologation then oxidation of 3-bromobenzaldehyde,[31] as delineated in Scheme 6.

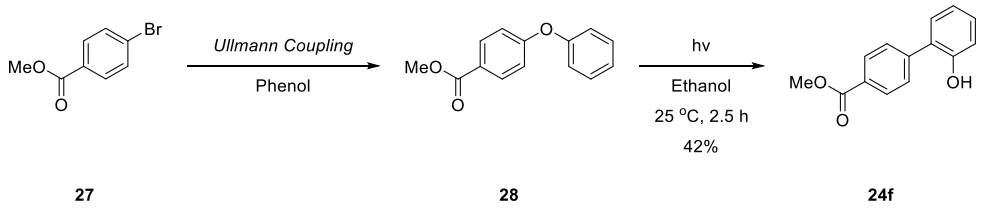


Scheme 6. Previous literature synthesis of **24c** from 3-bromobenzaldehyde (**25**).[31]

The second carbonyl functionality could also be achieved by converting 2,4-pentanedione to 4-methoxypent-3-en-2-one **23da** by an acid-catalyzed procedure.[32] Surprisingly, exclusive formation of **24d** was observed when **23da** was subjected to the established Diels–Alder conditions, which was confirmed by ^{1}H NMR data with a singlet at 3.77 ppm for the methylene protons adjacent to the aromatic ring. Presumably, the thermal environment facilitates isomerization of **23da** to the less sterically hindered **23db** dienophile which more readily participates in the ensuing reaction sequence.

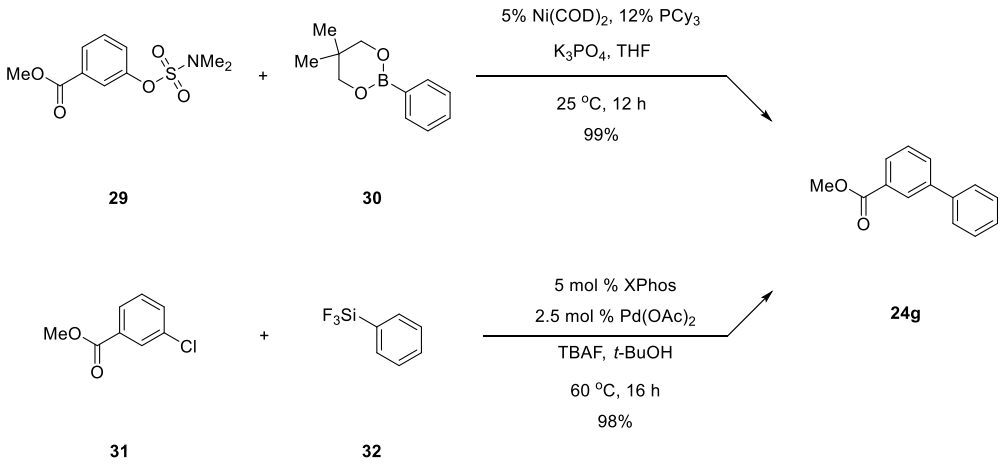
In similar fashion to the six-membered pyran **23c**, the corresponding 2,3-dihydrofuran (**23e**) follows the same reaction progression, but with a shorter methylene linker for the protected alcohol **24e**. With the confirmation of 2,3-dihydrofuran (**23e**) as a viable dienophile, 2,3-benzofuran (**23f**) was a logical substrate toward more intricate aromatic systems. Unexpectedly, **23f** regioselectively furnished *para*-substituted biphenyl alcohol **24f** in 77% yield, as evidenced by the two sets of coupled doublets at 8.13 and 7.59 ppm in the ^{1}H NMR spectrum. Based on the experimental evidence, it appears that the Diels–Alder adduct exhibits the opposite regiochemistry relative to the preceding vinyl ethers. The regioselectivity likely arises from the preferred benzofuran reactivity at the 2-position adjacent to the oxygen, as observed with Friedel-Crafts

acylation studies of 2,3-benzofuran (**23f**).[33] The previous synthesis of **24f** resulted in mixtures of compounds in lower yields from advanced precursors[34] that focused on forming the C-C bond between the aromatic rings (Scheme 7). However, **24f** is a precursor for G-protein agonists **35** to treat diabetes and other related disorders[35] in addition to dibenzofurans **36**[36] (Figure 2).



Scheme 7. Previous route to biphenyl compound **24f**.[34]

The methodology conveniently grants entry to the *meta*-substituted biaryl system including methyl [1,1'-biphenyl]-3-carboxylate (**24g**) when methyl coumalate is combined with (*E*)-(2-methoxyvinyl)benzene (**23g**). Previous cyclic vinyl ethers had utilized *Z*-substituted alkenes, but *E*-olefins were also effective substrates in the domino sequence to provide aromatic compounds. Further derivitization of the biphenyl system exposes treatments for psychotic disorders[37] and potential organic materials[38] (Figure 2). By comparison, literature syntheses necessitate the use of transition metal catalysts and aromatic starting materials with halogen[39] or sulfamate[40] substituents (Scheme 8).



Scheme 8. Transition metal-catalyzed routes to biphenyl system **24g**.[39,40]

To supplement the scope of aromatic compounds through vinyl ethers to cyclic systems fused to the aromatic ring, the vinyl ether **23h** of 6-methoxy-1-tetralone was prepared.[41] When **23h** was subjected to the thermal conditions, the fused tricyclic molecule **24h** was furnished with complete regioselectivity. The resulting 34% yield reflects the tendency of vinyl ether **23h** to revert to the initial tetralone which was present in the crude ^{1}H NMR, and also observed to a larger extent with the corresponding dimethyl ketal as the dienophile. Notwithstanding, the cascade reaction quickly established the more complex **24h** backbone, which could potentially lead to anthracene derivatives following oxidation. Vinyl ether systems with extended conjugation was explored with 1-methoxy-1,3-cyclohexadiene (**23i**) which solely afforded **24i**. The chemoselectivity for the more distant alkene was verified in a similar system by Corey[42] to broaden the range of attainable benzoates through the methodology. Vinyl ethers as

electron-rich dienophiles already resulted in a range of aromatic compounds that could be elaborated to a variety of more complex architectures as depicted in Figure 2.

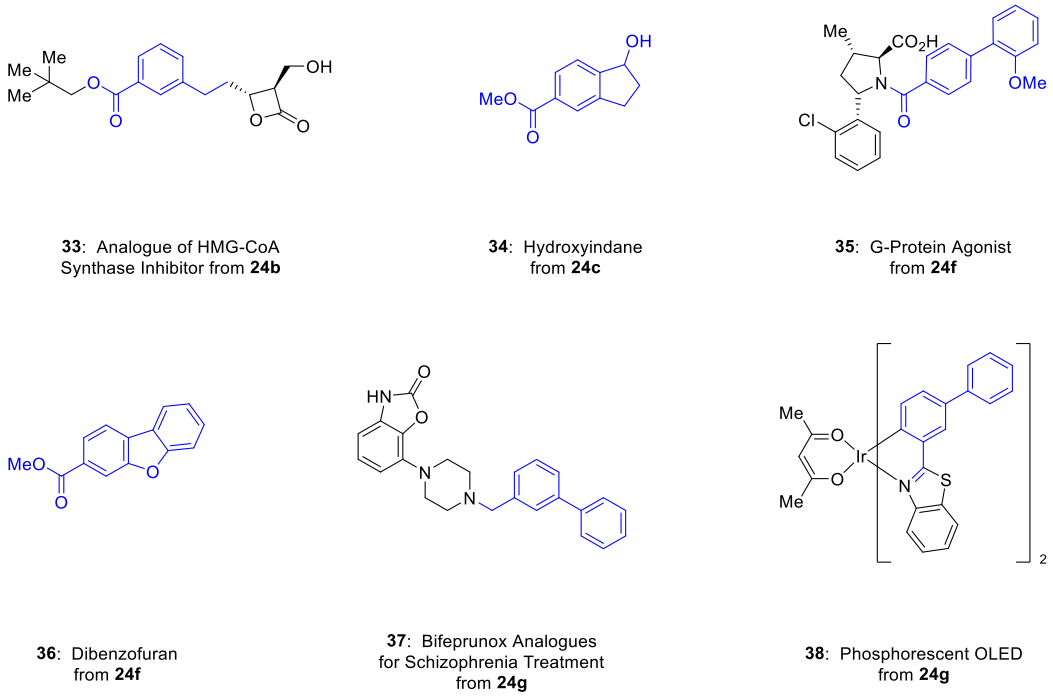


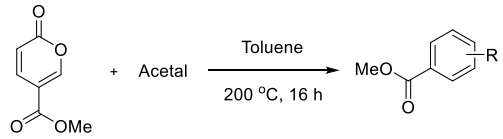
Figure 2. Elaboration of aromatic compounds from vinyl ether dienophiles.[30,31,35–38]

2.3. Methodology Expansion to Acetal and Orthoester Dienophile Equivalents

The successful initial trials with vinyl ethers stimulated the extension to ketals to determine if they could function as equivalents of vinyl ether dienophiles (Table 3). Commercially available symmetrical 2,2-dimethoxypropane (**39a**) smoothly produces methyl 4-methylbenzoate (**40a**) under our established reaction conditions in 89% yield. Presumably, the methoxy group in the dienophile is situated for elimination to first

generate 2-methoxypropene *in situ*. The resulting vinyl ether then reacts with methyl coumalate as previously detailed to furnish substituted aromatic system **40a**, whose spectral data match those of the commercially available compound, and can be carried on to biologically active anti-hepatitis B virus agents[43] and anti-HIV-1 drugs[44] (Figure 3).

Table 3. Scope of acetal dienophile equivalents to generate aromatic compounds[a]



3 **39** **40**

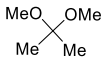
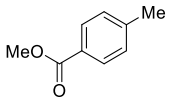
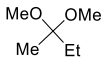
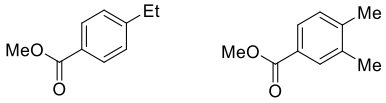
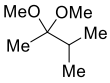
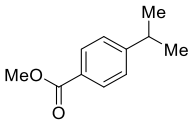
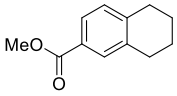
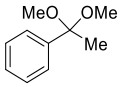
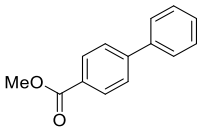
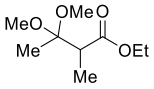
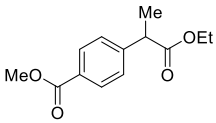
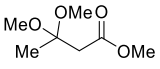
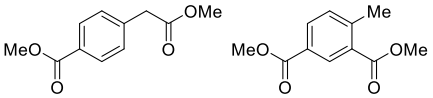
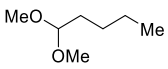
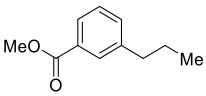
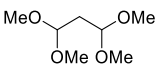
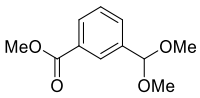
Entry	Acetal	Aromatic Product(s)	Yield[b] (%)
1	 **39a**	 **40a**	89
2	 **39b**	 **40ba** and **40bb**	73 2 : 3[c]
3	 **39c**	–	0
4	 **39d**	 **40d**	40

Table 3 (Continued)

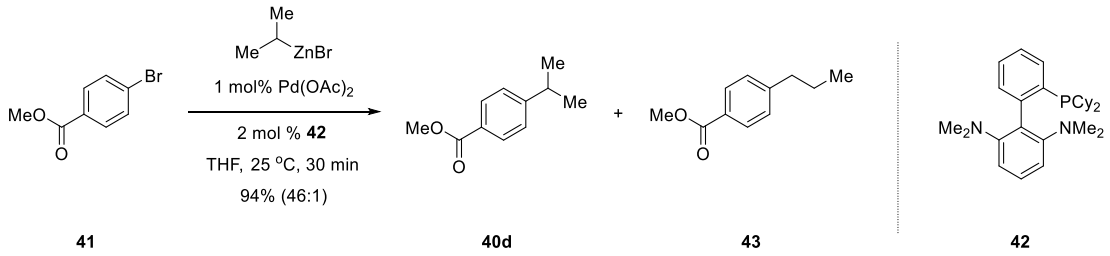
5	 **39e**	 **40e**	81
6	 **39f**	 **40f**	85
7	 **39g**	 **40g**	76
8	 **39h**	 **40ha** and **40hb**	76 2 : 1[d]
9	 **39i**	 **40i**	43
10	 **39j**	 **40j**	0

[a]Reaction conditions: **3** (1 mmol) and **39** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube. [b]Isolated yield, with the exception of entry 1. [c]An inseparable mixture of regioisomers resulted in a 2 : 3 ratio of **40ba** : **40bb**, as determined by integration of the crude ^{1}H NMR. [d]A mixture of regioisomers resulted in a 2 : 1 ratio of **40ha** : **40hb**, as determined by integration of the crude ^{1}H NMR.

An analysis of the overall transformation renders **39a** a regioselective replacement for propyne, with practical implications since **39a** is a liquid at room temperature, unlike propyne which is in the gas phase at ambient temperature.

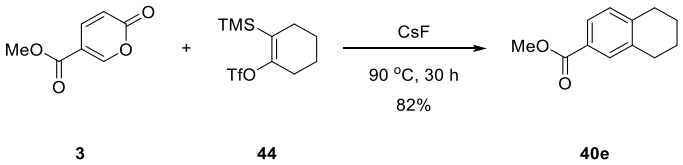
Ketals could be prepared from their corresponding ketones, which proceeded in nearly quantitative yields and could be used in crude form without additional purification. The scope and limitations were more thoroughly probed with the ketal **39b** from 2-butanone,[45] to determine whether selectivity would arise. We did not predict strong selectivity since the adjacent secondary carbons seemed nearly identical but wanted to confirm our prediction. A slight preference for the tri-substituted product **40bb** was detected from *in situ* formation of the more thermodynamically stable dienophile; however, it was part of an inseparable mixture which would not be feasible for incorporation into an efficient synthetic strategy. The analogous cyclic ketal **39c** was similarly utilized as the dienophile, but only starting material was recovered. The non-reactivity was ascribed to the higher likelihood of **39c** to maintain the stable dioxolane rather than elimination to form an *in situ* dienophile. The exclusive regioselectivity we had observed with vinyl ethers returned once the ketal was adjacent to an isopropyl group in **39d**, which would only form one productive dienophile to provide aromatic product **40d** in 40% yield. In contrast, earlier preparations resorted to a palladium-catalyzed Negishi cross-coupling[46] with methyl 4-bromobenzoate (**27**) or the corresponding methyl 4-chlorobenzoate (Scheme 9). Alternatively, oxidation and esterification of (4-isopropylphenyl)methanol could also furnish **40d**.[47] Regardless of the pathway to **40d**,

the aromatic compound has been an important intermediate for the synthesis of a potential treatment for Alzheimer's and related diseases (Figure 3).[48]



Scheme 9. Negishi coupling to form methyl 4-isopropylbenzoate (**40d**).[46]

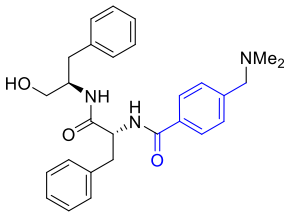
While the examples thus far concentrate on altering the substituents on the aromatic ring, the methodology was directed toward an annulation strategy to assemble fused bicyclic compounds. The cyclic ketal **39e** from cyclohexanone undergoes the same *in situ* elimination to afford tetrahydronaphthalene **40e** in 81% yield. Multiple routes have employed **40e** as a target through a three-step synthesis,[49] a dienamine Diels–Alder reaction,[50] and cycloaromatization with sulfide intermediates.[51]



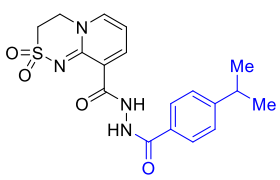
Scheme 10. Alternate route to **40e** *via* cyclohexyne dienophile formed *in situ*.[52]

An additional route included a Diels–Alder reaction with methyl coumalate[52] (Scheme 10); however, the reaction involved a cyclohexyne equivalent that was prepared over a few steps and the aromatic system was obtained after a longer time frame. We then turned to ketals adjacent to existing aromatic systems to expand the scope. Analogous to 2,2-dimethoxypropane (**39a**), ketal **39f** derived from acetophenone functions as an equivalent of the phenylacetylene dienophile. Either **39f** or phenylacetylene[53] resulted in the same exclusive regioselectivity in addition to excellent yields of the desired methyl [1,1'-biphenyl]-4-carboxylate (**40f**).[16] In effect, **39f** provides an alternative entry to substituted biphenyl systems with several applications for pharmaceuticals[54,55] and materials[56] (Figure 3) as a metal-free supplement to the transition metal-catalyzed Suzuki cross-coupling.[57,58]

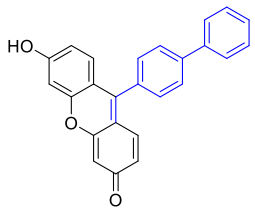
Additional functionality was introduced by situating the acetal in the β-position of a carbonyl. In accordance with previous findings, the ketal of ethyl 2-methylacetoacetate **39g** as a dienophile equivalent regioselectively constructed **40g** in 76% yield without transesterification during the reaction. Literature precedent for the preparation of **40g** depended on a palladium coupling of the methyl 4-iodobenzoate with a ketene silyl acetal.[59] The 2-methyl substituent imparted regioselectivity to the transformation as the ketal **39h** of methyl acetoacetate afforded a 76% overall yield of isomers. Although **40ha** was the major product from the analogously less-substituted dienophile, a fraction of the more substituted *in situ* alkene reacted under the thermal conditions to provide **40hb** in a 2 : 1 ratio.



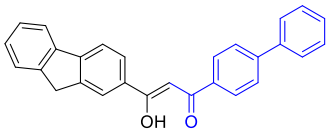
45: Intermediate toward anti-Hepatitus B Virus Agent from **40a**



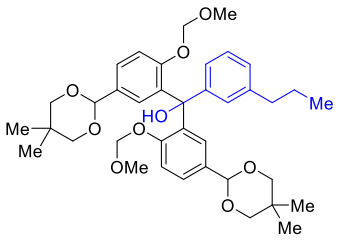
46: Isoxazolopyridone Derivative from **40d**



47: Xanthene Dyes from **40f**



48: Ligand for Luminescent Applications from **40f**



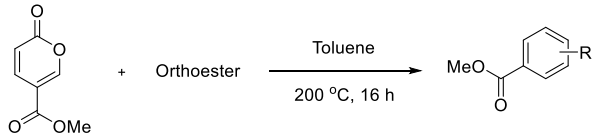
49: Intermediate toward Pneumovirus Infection Treatment from **40i**

Figure 3. Elaboration of aromatic compounds from acetal dienophile equivalents.[44,48,54,56,60]

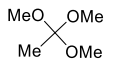
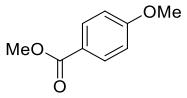
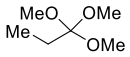
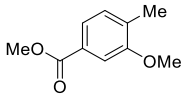
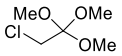
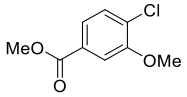
The methodology could also be extended to acetals of aldehydes including 1,1-dimethoxypentane (**39i**) in 43% yield. In general, the total yield is lower relative to most of the parallel ketal systems as by-products appeared under the reaction conditions from decomposition of the acetal and regeneration of the starting pentanal. However, the resultant methyl 3-propylbenzoate (**40i**) demonstrated that acetals of aldehydes are suitable substrates and can alternatively be used to generate aromatic compounds instead of incrementally functionalizing benzene derivatives. Furthermore, **40i** is the core structure for inhibitors to treat disease progress including pneumovirus infection[60] (Figure 3). The double acetal of malonaldehyde **39j** seemed to be an interesting substrate that might lead to methyl 3-(dimethoxymethyl)benzoate (**40j**); unfortunately, the predicted

vinyl ether from the elimination of one equivalent of methanol conceivably isomerized *in situ*. The supposition was mirrored by the crude ^{1}H NMR which contained a complex mixture of aromatic peaks, suggesting the formation of multiple aromatic products.

Table 4. Scope of orthoester dienophile equivalents to generate aromatic compounds[a]



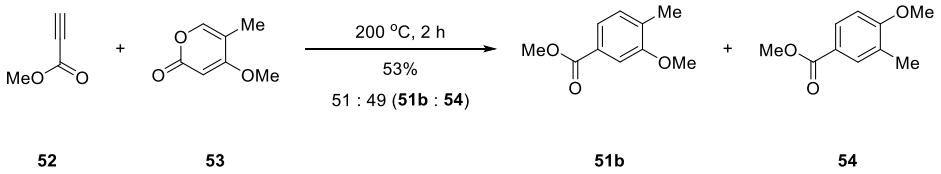
3 **50** **51**

Entry	Orthoester	Aromatic Product	Yield[b] (%)
1	 **50a**	 **51a**	73
2	 **50b**	 **51b**	94
3	 **50c**	 **51c**	72

[a]Reaction conditions: **3** (1 mmol) and **50** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube.
[b]Isolated yield.

The aforementioned aromatic compounds installed functionality with a carbon atom directly attached to the aromatic ring. However, the use of orthoesters allows the introduction of an oxygen bond onto the aromatic ring to generate anisole derivatives that

would broaden the utility of the substituted aromatic compounds. Commercially available trimethyl orthoacetate (**50a**) was evaluated as a dienophile to lead to anisole methyl 4-methoxybenzoate (**51a**), with incorporation into disease inhibitors[61,62] (Figure 4) and potential for demethylation to unmask its phenolic character. More importantly, **50a** can be equated to the dienophiles methoxy ethyne or the corresponding ketene acetal. The former is not commercially available, and the latter has literature precedent with 2-pyrones,[63,64] but is labile. Trimethyl orthopropionate (**50b**) reacted with **3** to afford a quantitative yield of **51b**, cleanly establishing the tri-substituted aromatic ring. On the contrary, an earlier normal electron-demand Diels–Alder reaction with 4-methoxy-5-methyl pyrone (**53**) and methyl propiolate (**52**) resulted in a non-selective 51 : 49 mixture of regioisomers (Scheme 11).[53] However, creating a regioselective pathway to methyl 3-methoxy-4-methylbenzoate (**51b**) provides opportunities for further elaboration to kinase inhibitors[65] or immunosuppressants[66] (Figure 4).



Scheme 11. Previous route to **51b** through a normal electron-demand Diels–Alder reaction.[53]

Halogen substituents were tolerated as demonstrated by 2-chloro-1,1,1-trimethoxyethane (**50c**) which provided methyl 4-chloro-3-methoxybenzoate (**51c**) which has been experimentally purified from a mixture of isomers[67] by multi-step routes.[68] The chloride

would rapidly enable the modification to advanced systems, as it has the essential functionality for organometallic coupling. Consequently, the relevance of our Diels–Alder approach with orthoesters is validated with the ability to expeditiously generate tri-substituted aromatic products with substantial therapeutic applicability[68,69] (Figure 4).

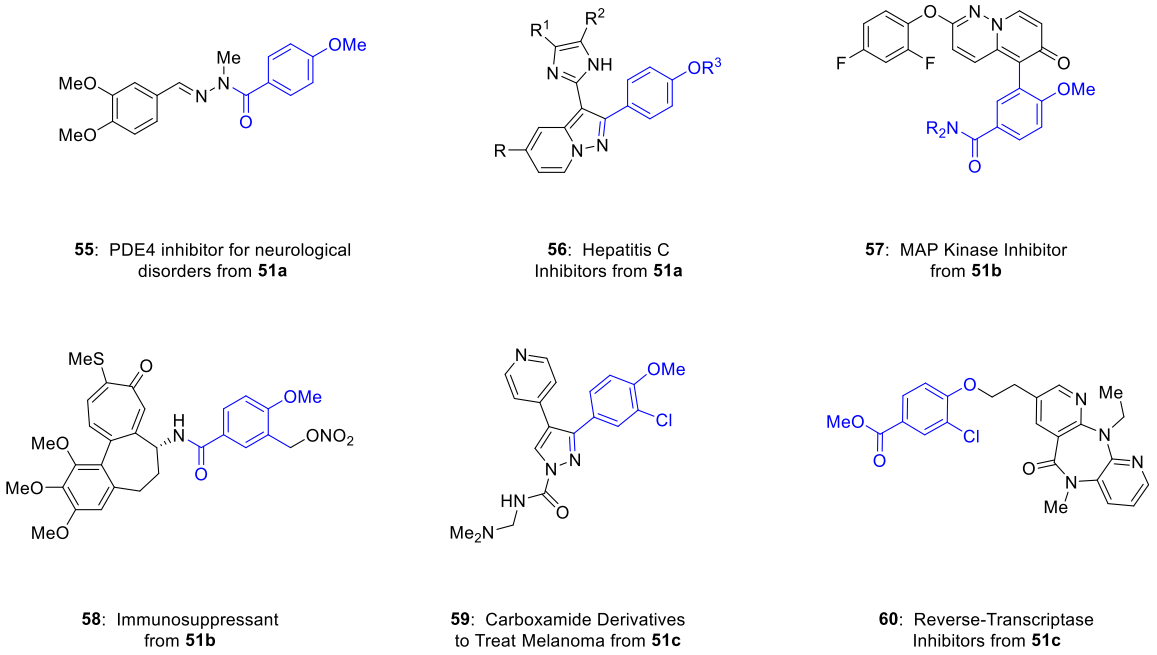


Figure 4. Elaboration of aromatic compounds from orthoester dienophile equivalents.[61,62,65,66,68,69]

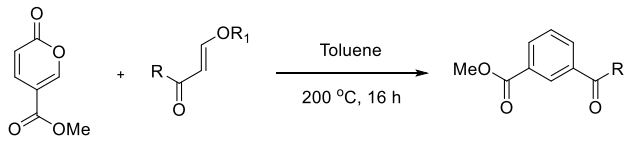
2.4. Methodology Expansion to Electron-Rich and Electron-Poor Substituted Dienophiles

While the literature and our examples thus far describe the scope of electron-rich, unactivated, and electron-poor dienophiles with methyl coumalate, dienophiles with both an electron-rich and an electron-poor moiety have remained largely uninvestigated. We

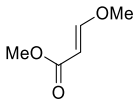
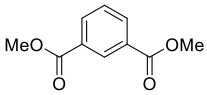
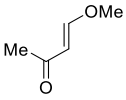
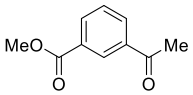
initially began pairing substituted dienophiles with methyl coumalate (Table 5) to determine whether the additional electron-withdrawing group would mitigate the regioselectivity previously observed with electron-rich vinyl ethers. When methyl *trans*-3-methoxyacrylate (**61a**) is incorporated as the dienophile, only the *meta*-substituted dimethyl isophthalate (**62a**) is produced in 83% yield. The singly obtained regioisomer is attributed to the accompanying selectivity for the bicyclo[2.2.2]octene adduct formed *in situ*. Earlier Diels–Alder approaches with methyl coumalate and electron-deficient alkynes like methyl propiolate have attempted to target **62a** selectively; however, only mixtures of regioisomers resulted in a 42 : 58 ratio favoring the *para*-substituted product.[53] The newly introduced synthetic strategy provides facile access to **62a** for integration into polymers.[70,71]

Consonantly, ketones can function as the electron-withdrawing component in the dienophile, which undergoes similar reactivity (Table 5, entry 2). The resultant 3-acetylbenzoic acid methyl ester (**62b**) is not readily available through commercial suppliers, although it is a building block for anti-obesity[72,73] or cardiovascular drugs.[74] Most approaches to **62b** begin with a disubstituted aromatic system which can undergo further functionalization.[75,76]

Table 5. *meta*-Selective aromatics from 1,2-substituted dienophiles[a]

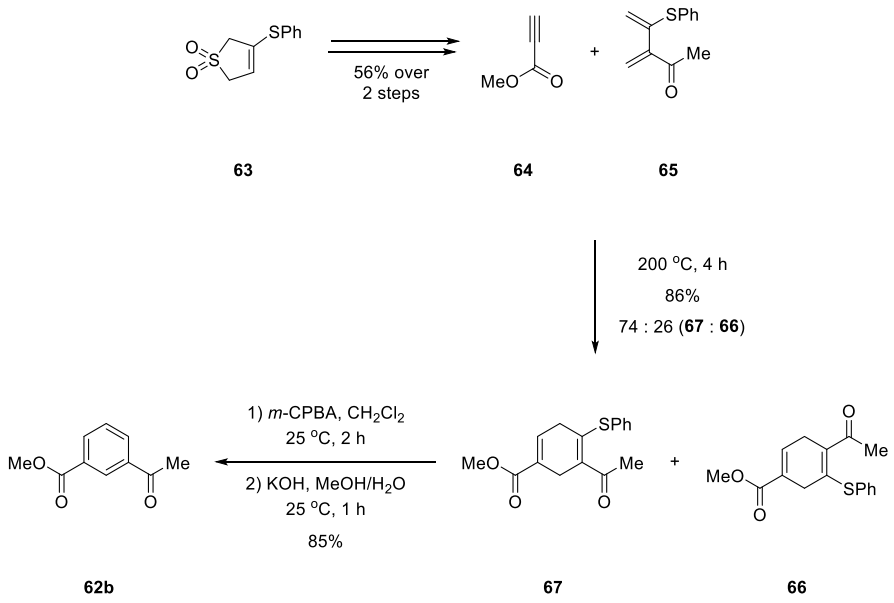


3 **61** **62**

Entry	Dienophile	Aromatic Product	Yield[b] (%)
1	 **61a**	 **62a**	83
2	 **61b**	 **62b**	92

[a]Reaction conditions: **3** (1 mmol) and **61** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube.
[b]Isolated yield.

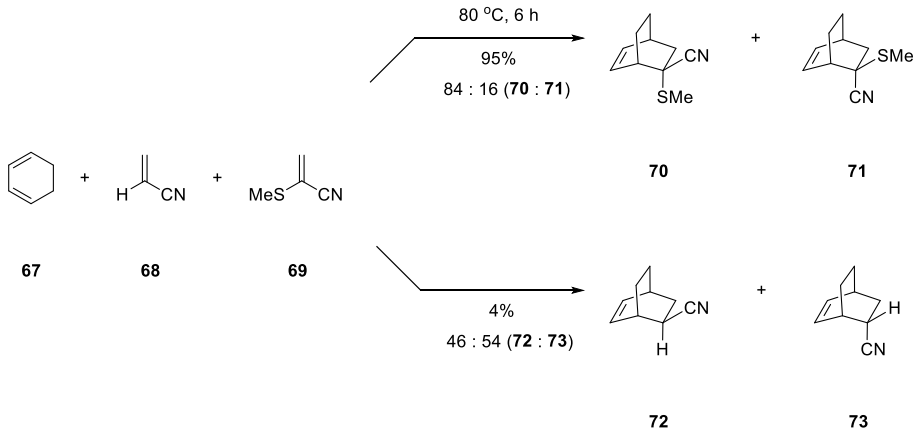
Although a Diels–Alder sequence has been developed from a butadiene equivalent (**63**) and an electron-deficient alkyne (**64**), multiple discrete steps are necessary to generate the diene. Additionally, the ensuing Diels–Alder reaction is not completely regioselective so an additional purification and oxidation/elimination are required before aromatization to the desired compound[77] (Scheme 12). Dienophiles **61a** and **61b** are synthetically practical synthons since both substituents provide synergistic electronic stabilization, analogous to the cooperativity of enamine dienophiles.[78] The promising regiochemical results from two electronically contrasting substituents on the same dienophile led to investigations of captodative olefins.



Scheme 12. Earlier approach to **62b** *via* a Diels–Alder reaction and diene equivalent.[77]

The captodative effect was originally conceived by Viehe to describe radical stabilization when a geminally substituted electron-withdrawing group (captor) and an electron-donating group (donor) cooperatively improved the stabilization of a radical.[79,80] Captodative centers can also be referred to as radicophilic to describe the thermodynamic stabilization of radicals and their tendency to efficiently trap radicals. They have been successfully and broadly incorporated in radical polymerizations,[80] Friedel-Crafts reactions,[81] 2,3-cycloadditions,[82] and Diels–Alder transformations.[83–85] It was postulated that captodative dienophiles are primed for the Diels–Alder reaction since the mechanism may involve a biradical transition state.[83] In the Diels–Alder reaction, the captodative effect is particularly applicable to improve dienophilic character, resulting in complete regioselectivity and stereochemical advantages over non-captodative dienophiles (Scheme 13).[83] In a competition experiment, both the captodative dienophile 2-

(methylthio)acrylonitrile (**69**) and acrylonitrile (**68**) were placed in a flask with excess 1,3-cyclohexadiene (**67**) to determine the relative reactivity of the normal electron-demand Diels–Alder reaction. No rate increase was observed with captodative dienophiles, presumably due to the more sterically hindered center of **69** compared to the analogous alkene **68**. Despite the increased substitution of captodative dienophiles, electronic considerations outweigh the steric influence for the reaction. The captodative olefin resulted in the overwhelming 95% majority of product formation, presumably due to the enhanced stabilization of the transition state.

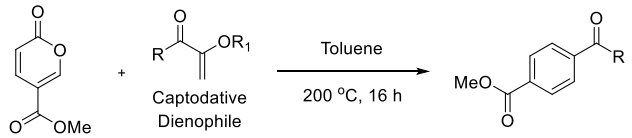


Scheme 13. Competition experiment to determine effect of captodative dienophiles.[83]

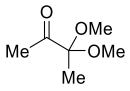
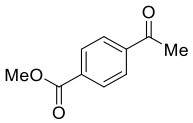
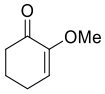
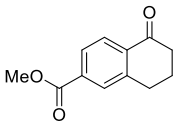
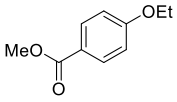
The successful generation of *meta*-substituted aromatics stimulated expansion of the captodative dienophiles to favor *para*-substituted aromatic compounds (Table 6). The exploration commenced with 3,3-dimethoxy-2-butanone[86] (**74a**) as a captodative dienophile equivalent since ketals are primed to eliminate methanol under the thermal conditions to reveal the dienophile. As predicted, the Diels–Alder reaction sequence

forms only *para*-substituted methyl 4-acetylbenzoate (**75a**). This compound has been utilized as an advanced intermediate to synthesize alkaloids[87] and enzyme modulators.[88] Literature precedent majorly focuses on manipulating commercially available aromatic compounds;[89] however, the posited methodology allows functionalized aromatics to be constructed from two non-aromatic substrates.

Table 6. *para*-Selective aromatics from captodative dienophiles[a]

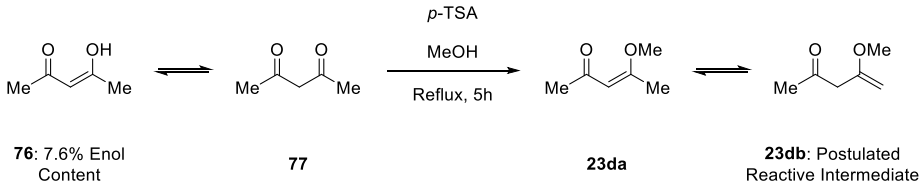


3 **74** **75**

Entry	Dienophile	Aromatic Product	Yield[b] (%)
1	 **74a**	 **75a**	94
2	 **74b**	 **75b**	75
3	 **74c**	 **75c**	48

[a]Reaction conditions: **3** (1 mmol) and **74** (3 mmol) in 2.0 mL toluene at 200 °C for 16 h in a sealable tube.
[b]Isolated yield.

While ketals are obtained in one step from the corresponding ketones, we envisioned that the thermal conditions might induce a shift in the keto-enol equilibrium to allow the enol to react as a captodative dienophile. By employing 2,3-butanedione, the same regioselective aromatic isomer **75a** resulted, albeit in 18% unoptimized yield. The yield likely was limited by the experimentally determined 1.1% enol content at equilibrium based on the entropically disfavored restricted rotation in the enol over the keto form, characteristic of acyclic systems.[90] However, the yield is significantly greater than the 3% observed by crude ^{1}H NMR with acetophenone as the substrate, which lacks captodative stabilization. Among the dicarbonyl systems, α-diones are the most amenable for generating aromatics through the reaction sequence. Although the 1,3-dione acetylacetone (**77**) was calculated to have a higher 7.6% enol content at equilibrium,[90] it was unreactive to the same reaction conditions (Scheme 14). The non-reactivity may imply a predilection for reaction at the less-substituted olefin **23db** through isomerization, which was observed when dienophile **23da** was isolated and subjected to the standard reaction conditions.



Scheme 14. Enol content and reactivity of acetylacetone (**77**).

Cyclic methoxy enone **74b** cleanly furnishes substituted tetralone **75b** which is not readily available through commercial suppliers. The complementary 1,2-cyclohexanedione was subjected to similar reaction conditions and provided **75b** in a reasonable 36% unoptimized yield likely through an increased thermal enolization from the ambient 4.0% enol content.[90] Captodative dienophiles in the IEDDA with methyl coumalate maintained complete regioselectivity despite their electron-poor constituent, which suggests that the electron-donor is the major contributor to predict regiochemistry. Lastly, commercially available 2,2-diethoxypropanenitrile (**74c**) smoothly supplied methyl 4-ethoxybenzoate (**75c**) in 48% yield. The slightly depressed yield presumably originates from the mitigating effect of the strongly withdrawing cyano group on the captodative dienophile created in the reaction medium. While pyrones have been exploited in the literature to synthesize **75c**, the reaction of methyl coumalate and ethoxyethyne only furnished 9% of the desired compound.[91] In a normal electron-demand Diels–Alder reaction, 4-ethoxy-2-pyrone was combined with methyl propiolate but mixtures of regioisomers resulted, and **75c** was the minor product relative to the *meta*-substituted compound in a 23:77 ratio of *para*- to *meta*- isomers.[53] Furthermore, pharmaceutically-active agents against tuberculosis[92] and cancer[93] have been elucidated after derivitizing the **75c** aromatic system. In addition to conserving regioselectivity, captodative olefins have proven their merit as entities that introduce electron-deficient functionality adjoined to the resulting aromatic system.

2.5. Formal Synthesis of Biorenewable Terephthalic Acid from Methyl Coumalate

We then turned to terephthalic acid (TPA) with its *para*-substituted carboxylic acids, which was ultimately the high-value target for our promising technology capitalizing on captodative dienophiles. TPA as a commodity chemical commands a dominant presence since it has been ranked within the six highest domestically produced organic commodity chemicals in 2001 by the U.S. International Trade Commission.[94] On a global scale, production reached 50.7 million tons which translates to a $58 billion market within the last year.[95] The industrial significance of TPA and its ester dimethyl terephthalate (DMT) lies in their ability to act as condensation co-monomers for poly(ethylene terephthalate) (PET).[96] Various companies specifically favor DMT as the co-monomer with ethylene glycol due to its preferential properties.[96–99] PET's societal significance is reflected by its annual production of nearly 60 million tons and its incorporation in numerous consumer applications, with the highest volumes in polyester fibers then in bottles and packaging.[96] While TPA has formidably impacted society and is projected to continue its ascent into the future,[100] its industrial synthesis relies on a harsh oxidation of petroleum-based *p*-xylene,[101] itself isolated from a complex mixture of isomers.

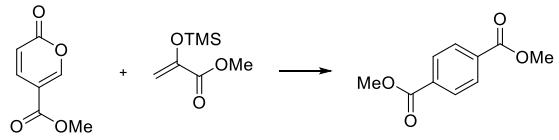
The most commonly used industrial method is termed the AMOCO process which accounts for the production of 70% of the world's TPA.[102] The AMOCO process begins with *p*-xylene, obtained from catalytic reforming of pyrolysis gasoline, followed by

isomerization.[103] The oxidation process occurs stepwise and is catalyzed by a cobalt – manganese – bromine system in an aerobic atmosphere in acetic acid from 175 – 225 ^{o}C.[102] Although the reaction proceeds nearly quantitatively, it is associated with many disadvantages since the presence of a metal catalyst system and corrosive reagents require additional titanium reinforcement on reactors.[102] The stepwise oxidation from *p*-xylene to *p*-toluic acid to 4-formyl-benzoic acid to TPA poses a problem since 4-formylbenzoic acid closely resembles TPA, creating additional effort in purification, yet must be removed since it interferes with successful polymerization to PET. Unreacted 4-formylbenzoic acid co-crystallizes with TPA but must be effectively exposed to the catalytic system to drive the reaction to completion.[101] One of the substantial drawbacks to the AMOCO process is the petrochemical-based *p*-xylene prerequisite. In contrast, bio-based captodative dienophiles in conjunction with methyl coumalate may create a sustainable shift toward biorenewable feedstocks.

With potential to profoundly impact the process for a high-volume commodity chemical, the reaction conditions were specifically optimized for DMT using the enol silyl ether of methyl pyruvate (**78a**) as delineated in Table 7. Methyl pyruvate was identified as an exemplary dienophile since its preparation involves an esterification of pyruvic acid, the major natural product from the glycolysis cycle.[104] In general, the effectiveness of the systematic changes in reaction conditions was analyzed by comparing the ratio of the characteristic DMT methyl ester peak at 3.95 ppm to the methyl ester peak of the limiting reagent methyl coumalate at 3.88 ppm in the crude ^{1}H NMR spectra. The reaction sequence is concentration-dependent (Table 3, entries 2 and

11) and allowing the Diels–Alder/aromatization sequence to proceed without solvent allows the reaction to occur with fewer equivalents of the dienophile but with similar completion. Along the parameter of the dienophile : diene ratio (Table 3, entries 3-5 and 10-11), an excess of 3.0 equivalents of the dienophile **78a** was necessary for complete consumption of methyl coumalate (**3**) at 0.5M, but an excess of 1.5 equivalents was sufficient under neat conditions. The effect of temperature was investigated (Table 3, entries 2-6 and 11), and decreasing the temperature to 150 ^{o}C was effectual in the absence of solvent. Finally, the optimal reaction conditions are collated in Table 3, entries 11-12. Both conditions completely consume the limiting reagent, depending whether the reaction was run at a lower temperature or with more dienophile equivalents.

Table 7. Reaction optimization trials

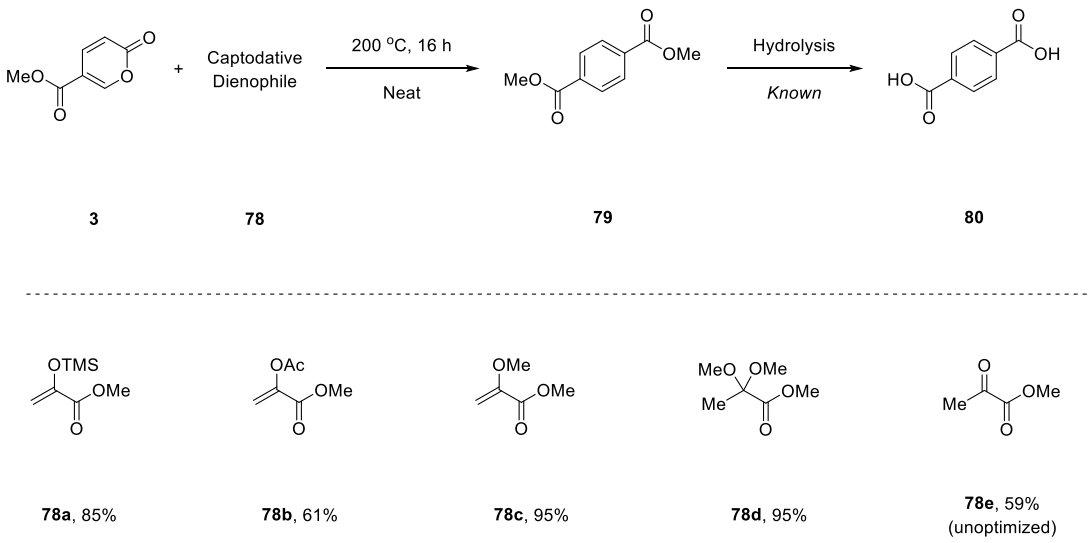


3 **78a** **79**

Entry	Conc. (M)[a]	Temp. (^{o}C)	Time (h)	Equiv. of **78a**	Ratio of **79** : **3**[b]
1	0.5	200	16	3.0	1 : 0
2	0.5	150	18	3.0	1 : 0.48
3	0.5	100	17	3.0	1 : 4.00
4	0.5	200	17	1.5	1 : 0.53
5	Neat	150	16	1.5	1 : 0.12
6	Neat	125	18	1.5	1 : 0.72
7	Neat	150	6	1.5	1 : 0.50
8	Neat	150	3	3.0	1 : 0.49
9	Neat	150	1	1.5	1 : 1.31
10	Neat	150	17	1.0	1 : 1.12
11	**Neat**	**150**	**16**	**3.0**	**1 : 0**
12	**Neat**	**200**	**16**	**1.5**	**1 : 0**

[a]Entries 1-4 were run with toluene as the solvent. [b]Ratios determined by integration of crude ^{1}H NMR.

With the optimal reaction conditions in hand, five captodative dienophiles were explored to flexibly generate DMT (Scheme 15), which can undergo a facile hydrolysis to TPA.[105,106] At the outset, the enol silyl ether of methyl pyruvate[107] (**78a**) was isolated through recrystallization after subjection to the reaction conditions in Table 3, entry 12, which resulted in 85% yield. Although recrystallization is a convenient purification method conducive for industrial scale, pure DMT spontaneously sublimes on the walls of the sealed flask during the reaction as captured in Figure 5. Recognizing that the enol silane would not be feasible for industrial-scale reactions, 2-acetoxyacrylate[108] (**78b**) became the next dienophilic partner, with a straightforward acid-catalyzed preparation from acetic anhydride and methyl pyruvate. The desired *para*-substituted DMT was the major product, along with 3% dimethyl isophthalate (DMI), presumably due to the heightened electron-withdrawing nature of the dienophile as a whole. Conversely, 2-methoxyacrylate[86] (**78c**) generated DMT regioselectively in 95% yield without formation of DMI. While advantageous, generating **78c** from methyl pyruvate involved isolating the ketal then eliminating one equivalent of methanol under acidic conditions. We were interested in assembling DMT as rapidly as possible with the fewest modifications of bio-



Scheme 15. Captodative dienophiles to generate dimethyl terephthalate.

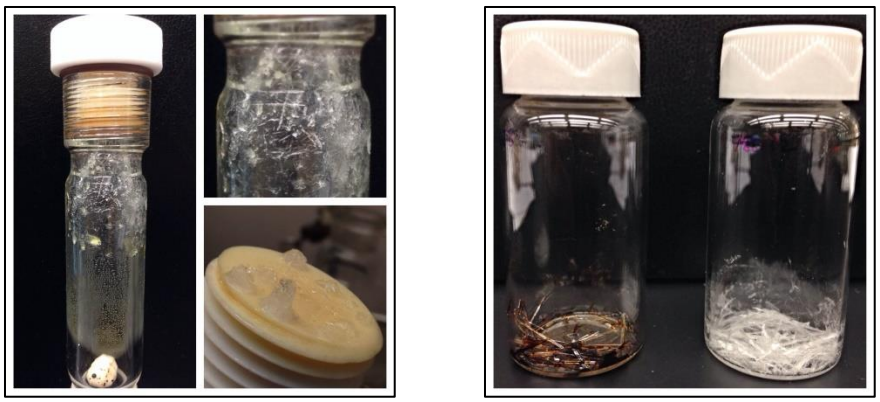


Figure 5. Left: DMT sublimation during reaction. Right: Crude and recrystallized DMT.

based methyl pyruvate, which successively led to using the crude ketal directly. Strikingly, methyl 2,2-dimethoxypropanoate[86] (**78d**), which is only a single step from methyl pyruvate, equally affords high yields of DMT. We postulated that the <10% enol content of pyruvic acid in CCl_4, stabilized by intramolecular hydrogen bonding,[109] would allow even more direct access to DMT with methyl pyruvate (**78e**). The hypothesis was

corroborated by the 59% yield which may be elevated if left for a longer period of time since methyl coumalate was not completely consumed during the standard 16 hours. Utilizing a ketone adjacent to the ester functions as a better captodative dienophile assumedly due to the placating electron-withdrawing effect of the ester compared to a ketone as observed in previous cases with an adjacent ketone. Since unaltered methyl pyruvate presents itself as a captodative dienophile equivalent to successfully achieve DMT, it adds another dimension of flexibility and convenience to the biorenewable methodology.

2.6. Conclusion

The cascade reaction sequence of methyl coumalate and dienophiles in an IEDDA/retro-Diels–Alder/elimination methodology has created a metal-free entryway to a broad spectrum of functionalized aromatics utilizing green chemistry design principles (Figure 6). Naturally-occurring malic acid could be derived through microbial metabolic engineering of glucose pathways before dimerization that led to the emergence of the versatile methyl coumalate platform. The main determinant for the successful one-pot cascade was designing electronically coordinated dienophiles to complement the electron-deficient methyl coumalate diene to regioselectively assemble targeted aromatic systems. A systematic analysis into the scope and limitations of the methodology revealed that classical vinyl ether dienophiles were effective partners for methyl coumalate. However, more bench-stable dienophile equivalents including acetals and

orthoesters could be activated under the thermal conditions to conveniently provide aromatic systems with increased functionality. Cyclic acetals presented some challenges for the system in addition to acetals adjacent to both primary and secondary carbons. Advantageously, all dienophiles are either commercially available or prepared in one step and can be used without purification.

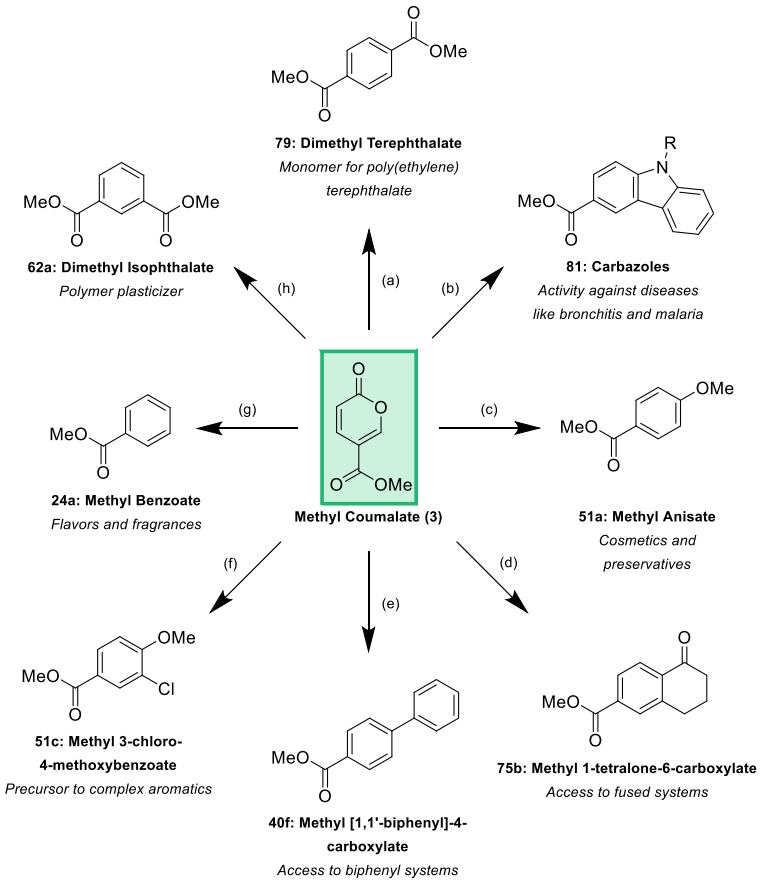


Figure 6. The coumalate platform and valuable applications of resultant benzoates.[110–114] Dienophiles: (a) methyl pyruvate (b) 1-alkyl-3-chloroindole (c) trimethyl orthoacetate (d) 2-methoxycyclohex-2-en-1-one (e) (1,1-dimethoxyethyl)benzene (f) 2-chloro-1,1,1-trimethoxyethane (g) butyl vinyl ether (h) methyl *trans*-3-methoxyacrylate.

The resultant aromatics from the methodology included both synthetic and biologically-active carbazoles **81** which were achieved with the first report of 1-alkyl-3-

chloroindole dienophiles in an IEDDA domino reaction with methyl coumalate.[112] Furthermore, the examination unearthed successful access to tricyclic, fused, anisole, and biphenyl frameworks to characterize the expanse of the methodology emanating from methyl coumalate. In particular, dienophiles containing both an electron-rich and an electron-poor moiety allowed access to electron-withdrawing substituents directly on the resultant aromatic structure. Implementing the strategy in the case of methyl coumalate and methyl pyruvate leads to a 100% biorenewable formal synthesis to the mass market commodity chemical terephthalic acid, although dimethyl terephthalate (DMT) itself is sometimes preferred as a co-monomer in industry. The regioselective, high-yielding, and single-pot experimental procedure expediently delivers substituted aromatic systems compared to previous routes that were either not selective for a single target, involved multi-step syntheses, or required the use of palladium catalysts. Advantageously, an additional petroleum-based solvent is avoided for DMT and a versatile approach to accommodate varying dienophiles provides high yields and rapid assembly of DMT. From an industrial perspective, the methodology features a facile purification by recrystallization, and introduces a potentially scalable drop-in replacement for DMT or TPA that bypasses the harsh oxidation of *p*-xylene. The use of alternative biorenewable feedstocks in addition to the elimination of solvent and catalysts, while featuring the key one-pot Diels–Alder reaction conformed to many of the Twelve Principles of Green Chemistry. The methodology addresses the immediate global issue of rapidly depleting petrochemicals and highlights biorenewable alternative feedstocks as a green innovation toward the chemical building blocks of a sustainable future.

2.7. Experimental

General Procedures

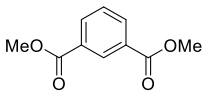
All starting materials and solvents were purchased from Sigma-Aldrich and used without further purification. All reactions were carried out in flame-dried glassware under argon with dry solvents under anhydrous conditions. All yields refer to isolated products either by column chromatography or by recrystallization. Thin-layer chromatography (TLC) data was obtained with 0.20 mm silica gel plates using UV light as a visualizing agent and potassium permanganate with heat as the developing agent. Silica gel 60Å, particle size 0.032 – 0.063 mm, was used for flash column chromatography. ^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ on a Varian MR-400 or Bruker Avance III 600 MHz spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual protonated chloroform peak ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm) as an internal reference. High-resolution mass spectra (HRMS) were recorded on an Agilent 6540 QTOF (quadrupole time of flight) mass spectrometer using ESI (electrospray ionization) or APCI (atmospheric-pressure chemical ionization) or EI (electron ionization) on an Agilent 6890 GC/MS. Melting points are uncorrected and were analyzed on a Mel-Temp II capillary melting point apparatus.

All vinyl ethers, acetals, and enol silyl ethers were prepared according to literature precedent and utilized in crude form since nearly quantitative conversion was observed. The dinophiles were used as the excess reagent in the subsequent Diels–Alder reaction and the ^{1}H NMR data matched those previously reported. Vinyl ether 4-methoxypent-3-

en-2-one (**23da**) was prepared according to the procedure of Kraus and Krolski.[32] Ketals **39e**, **39f**-**h**, **74a**, and **78d** and vinyl ethers **23h**, **74b**, and **78c** were prepared according to the procedure of Cooper.[86] Ketals **39b** and **39d** were prepared by the method of Harris,[45] while acetal **39i** was prepared according to the protocol by Ritter.[114] Enol silyl ether **78a** was prepared according to the procedure by Bäckvall[107] and 2-acetoxyacrylate (**78b**) was prepared according to the protocol developed by Monnin.[108]

Selected Experimental, Physical, and Spectral Data

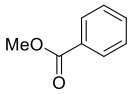
General Procedure: Diels–Alder Reaction of Methyl Coumalate with the Exception of Dienophiles **78a–e**



62a

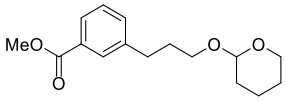
Dimethyl Isophthalate (**62a**): The synthesis of **62a** is representative with the exception of vinyl ethers **23b** and **23e** where 5.0 equivalents are required to solely obtain the protected alcohols **24b** and **24e**, respectively. To a sealable 15-mL pressure vessel was successively added methyl coumalate (0.154 g, 1.0 mmol), methyl *trans*-3-methoxyacrylate (0.3 mL, 3.0 mmol), and toluene (2 mL) under argon. The solution was heated to 200 ^{o}C and stirred for 16 h. Upon completion of the reaction, the sealable pressure vessel was cooled to room temperature. The solution was transferred to another flask, while rinsing with ethyl acetate, after which the solution was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:20) to afford **62a** (0.16 g, 83% yield) as a white solid. **62a**: m.p. 63-65 ^{o}C; R_f = 0.62 (silica gel,

EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.69 (s, 1H), 8.23 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 3.95 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.4, 133.9, 130.9, 130.7, 128.8, 52.5 ppm; HRMS (APCI-TOF) calcd for $C_{10}H_{11}O_4$ [*M* + H]$^+$ 195.0652, found 195.0655.



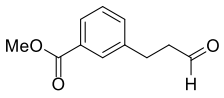
24a

Methyl Benzoate (**24a**): Yellow liquid (0.121 g, 89% yield); R_f = 0.92 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.04 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 3.91 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.2, 133.0, 130.2 (2C), 129.6 (2C), 128.4, 52.2 ppm; HRMS (APCI-TOF) calcd for $C_8H_9O_2$ [*M* + H]$^+$ 137.0597, found 137.0594.



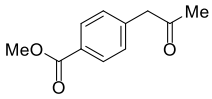
24b

Methyl 3-(3-((tetrahydro-2H-pyran-2-yl)oxy)propyl)benzoate (**24b**): Pale yellow liquid (0.214 g, 77% yield); R_f = 0.77 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.89 (s, 1H), 7.86 (d, *J* = 7.5, 1H), 7.40 (d, *J* = 1.6 Hz, 1H), 7.35 (dd, *J* = 7.5, 1.6 Hz, 1H), 4.57 (dd, *J* = 4.4, 2.8 Hz, 1H), 3.91 (s, 3H), 3.89 – 3.84 (m, 1H), 3.80 – 3.74 (m, 1H), 3.53 – 3.46 (m, 1H), 3.42 – 3.37 (m, 1H), 2.77 (t, *J* = 7.5 Hz, 2H), 1.98 – 1.91 (m, 2H), 1.89 – 1.80 (m, 1H), 1.76 – 1.69 (m, 1H), 1.63 – 1.51 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 142.4, 133.2 (2C), 129.7, 128.4, 127.2, 99.0, 66.7, 62.4, 52.1, 32.4, 31.3, 30.8, 25. 6, 19.7 ppm; HRMS (ESI-TOF) calcd for $C_{16}H_{22}NaO_4$ [*M* + Na]$^+$ 301.1410, found 301.1414.



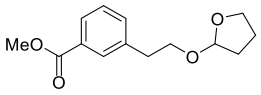
24c

Methyl 3-(3-oxopropyl)benzoate (**24c**): Pale yellow liquid (0.148 g, 77% yield); R_f = 0.65 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.82 (s, 1H), 7.88 (s, 2H), 7.44 – 7.31 (m, 2H), 3.91 (s, 3H), 3.00 (t, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 201.1, 167.2, 140.8, 133.1, 130.6, 129.5, 128.8, 127.7, 52.3, 45.2, 27.9 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{13}O_3$ $[M + H]^+$ 193.0859, found 193.0857.



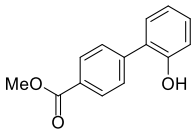
24d

Methyl 4-(2-oxopropyl)benzoate (**24d**): Yellow oil (0.152 g, 79% yield); R_f = 0.74 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.01 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 3.91 (s, 3H), 3.77 (s, 2H), 2.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.4, 167.0, 139.4, 130.2, 129.7, 129.2, 52.3, 50.9, 29.7 ppm; HRMS (APCI-TOF) calcd for $C_{11}H_{12}O_3$ $[M + H]^+$ 193.0859, found 193.0854.



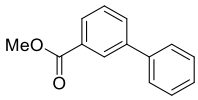
24e

Methyl 3-(2-((tetrahydrofuran-2-yl)oxy)ethyl)benzoate (**24e**): Pale yellow liquid (0.153 g, 61% yield); R_f = 0.67 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.92 (s, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.42 (q, *J* = 8.1 Hz, 1H), 7.36 (q, *J* = 7.8 Hz, 1H), 5.11 (dd, *J* = 3.8, 2.1 Hz, 1H), 3.91 (s, 3H), 3.86 – 3.77 (m, 2H), 3.65 – 3.59 (m, 2H), 2.97 – 2.88 (m, 2H), 1.99 – 1.79 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.4, 139.8, 133.7, 130.3, 130.2, 128.4, 127.6, 104.0, 67.6, 67.1, 52.2, 36.2, 32.5, 23.6 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{18}NaO_4$ $[M + Na]^+$ 273.1205, found 273.1099.



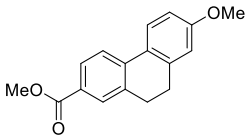
24f

Methyl 2'-hydroxy-[1,1'-biphenyl]-4-carboxylate (**24f**): Pale yellow needles (0.18 g, 77% yield); R_f = 0.58 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 8.13 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.1 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 5.39 (s, 1H), 3.94 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.1, 152.6, 142.4, 130.5, 130.4, 129.8, 129.3 (2C), 127.4, 121.2, 116.4, 52.4 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{13}O_3$ $[M + H]^+$ 229.0859, found 229.0857.



24g

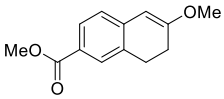
Methyl [1,1'-biphenyl]-3-carboxylate (**24g**): Pale yellow liquid (0.108 g, 51% yield); R_f = 0.74 (silica gel, EtOAc:hexanes 1:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.29 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 3.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 141.6, 140.3, 131.7, 130.8, 129.0 (3C), 128.5, 128.4, 127.9, 127.3 (2C), 52.4 ppm; HRMS (ESI-TOF) calcd for $C_{14}H_{13}O_2$ $[M + H]^+$ 213.0910, found 213.0908.



24h

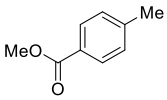
Methyl 7-methoxy-9,10-dihydrophenanthrene-2-carboxylate (24h): Pale yellow liquid (0.09 g, 34% yield); R_f = 0.74 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.93 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.88 (d, *J* = 1.4 Hz, 1H), 7.71 (dd, *J* = 8.4, 2.9 Hz, 2H), 6.86 (dd, J = 8.6, 2.7 Hz, 1H), 6.79 (d, *J* = 2.6 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 2.88 (t, *J* = 8.5 Hz,

4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 160.0, 139.9, 139.2, 136.5, 129.4, 128.5, 127.9, 126.6, 125.9, 123.0, 113.7, 112.8, 55.5, 52.2, 29.4, 29.0 ppm; HRMS (ESI-TOF) calcd for $C_{17}H_{17}O_3$ [*M* + H]$^+$ 269.1172, found 269.1180.



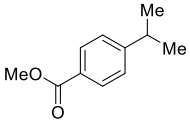
24i

Methyl 6-methoxy-7,8-dihydronaphthalene-2-carboxylate (**24i**): Yellow solid (0.156 g, 72% yield); R_f = 0.80 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.78 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.74 (s, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 5.59 (s, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 2.92 (t, *J* = 8.2 Hz, 2H), 2.43 (t, *J* = 8.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 163.1, 140.8, 131.9, 128.4, 128.2, 125.9, 124.6, 96.3, 55.2, 52.0, 28.4, 27.5 ppm; HRMS (ESI-TOF) calcd for $C_{13}H_{15}O_3$ [*M* + H]$^+$ 219.0943, found 219.1016.



40a

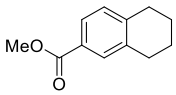
Methyl 4-methylbenzoate (**40a**): Pale yellow liquid (0.134 g, 89% yield); R_f = 0.94 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.93 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.90 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.3, 143.7, 129.7, 129.2, 127.5, 52.0, 21.8 ppm; HRMS (APCI-TOF) calcd for $C_9H_{11}O_2$ [*M* + H]$^+$ 151.0754, found 151.0753.



40d

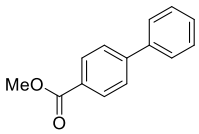
Methyl 4-isopropylbenzoate (**40d**): Yellow oil (0.072 g, 40% yield); R_f = 0.86 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.96 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.90 (s, 3H), 3.00 –

2.92 (m, 1H), 1.27 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 154.4, 129.8, 127.9, 126.6, 52.1, 34.4, 23.8 ppm; HRMS (ESI-TOF) calcd for $C_{11}H_{15}O_2$ $[M + H]^+$ 179.1067, found 179.1062.



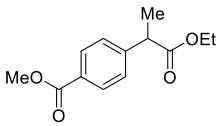
40e

Methyl 5,6,7,8-tetrahydronaphthalene-2-carboxylate (**40e**): Yellow-orange liquid (0.154 g, 81% yield); R_f = 0.93 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.75 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 7.9 Hz, 1H), 3.89 (s, 3H), 2.80 (ddd, J = 6.5, 4.0, 2.4 Hz, 4H), 1.81 (ddd, J = 6.6, 4.1, 2.8 Hz, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 167.5, 142.9, 137.4, 130.5, 129.3, 127.4, 126.6, 52.9, 29.7, 29.4, 23.1, 23.0 ppm; HRMS (APCI-TOF) calcd for $C_{12}H_{15}O_2$ $[M + H]^+$ 191.1067, found 191.1066.



40f

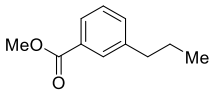
Methyl [1,1'-biphenyl]-4-carboxylate (**40f**): White solid (0.180 g, 85% yield); R_f = 0.88 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.11 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 7.47 (dd, J = 8.4, 7.2 Hz, 2H), 7.41 (d, J = 7.2 Hz, 1H), 3.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 145.9, 140.2, 130.3, 129.2, 129.1, 128.4, 127.5, 127.3, 52.4 ppm; HRMS (APCI-TOF) calcd for $C_{14}H_{13}O_2$ $[M + H]^+$ 213.0910, found 213.0912.



40g

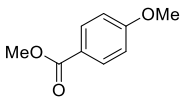
Methyl 4-(1-ethoxy-1-oxopropan-2-yl)benzoate (**40g**): White oil (0.179 g, 76% yield); R_f = 0.81 (silica gel, EtOAc:hexanes 1:1); ^{1}H

NMR ($CDCl_3$, 400 MHz) δ = 7.99 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.18 – 4.07 (m, 2H), 3.91 (s, 3H), 3.76 (q, *J* = 7.2 Hz, 1H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0, 167.0, 145.9, 130.1 (2C), 129.1, 127.7 (2C), 61.1, 52.2, 45.7, 18.6, 14.2 ppm; HRMS (ESI-TOF) calcd for $C_{13}H_{16}O_4$ $[M + H]^+$ 237.1121, found 237.1116.



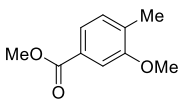
40i

Methyl 3-propylbenzoate (**40i**): Yellow liquid (0.077 g, 43% yield); R_f = 0.64 (silica gel, EtOAc:hexanes 1:3); ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.85 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 3.91 (s, 3H), 2.63 (t, *J* = 8.0 Hz, 2H), 1.66 (h, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 143.1, 133.3, 130.2, 129.7, 128.4, 127.1, 52.2, 37.9, 24.6, 13.9 ppm; HRMS (EI-GC/MS) calcd for $C_{11}H_{14}O_2$ $[M + H]^+$ 178.0994, found 178.0793.



51a

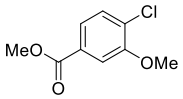
Methyl 4-methoxybenzoate (**51a**): Pale yellow solid (0.121 g, 73% yield); R_f = 0.80 (silica gel, EtOAc:hexanes 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ = 8.00 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0, 163.4, 131.7, 122.7, 113.7, 55.5, 52.0 ppm; HRMS (APCI-TOF) calcd for $C_9H_{11}O_3$ $[M + H]^+$ 167.0703, found 167.0702.



51b

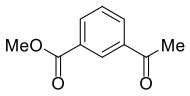
Methyl 3-methoxy-4-methylbenzoate (**51b**): Yellow-orange solid (0.169 g, 94% yield); R_f = 0.80 (silica gel, EtOAc:hexanes 1:1); ^1H NMR

($CDCl_3$, 400 MHz) δ = 7.88 (d, *J* = 8.6 Hz, 1H), 7.83 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 3.88 (s, 6H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.1, 161.5, 131.9, 129.3, 126.6, 121.9, 109.2, 55.4, 51.8, 16.2 ppm; HRMS (APCI-TOF) calcd for $C_{10}H_{13}O_3$ $[M + H]^+$ 181.0859, found 181.0859.



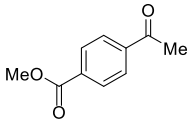
51c

Methyl 4-chloro-3-methoxybenzoate (**51c**): Yellow solid (0.1444 g, 72% yield). **5f**: R_f = 0.83 (silica gel, EtOAc:hexanes 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ = 8.04 (s, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0, 158.7, 131.7, 130.0, 123.4, 122.6, 111.3, 56.4, 52.3 ppm; HRMS (ESI-TOF) calcd for $C_9H_{10}ClO_3$ $[M + H]^+$ 201.0318, found 201.0324.



62b

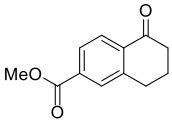
Methyl 3-acetylbenzoate (**62b**): Yellow oil (0.16 g, 92% yield); R_f = 0.69 (silica gel, EtOAc:hexanes 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ = 8.60 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 3.96 (s, 3H), 2.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.4, 166.4, 137.4, 134.1, 132.5, 130.8, 129.0, 52.6, 26.9 ppm; HRMS (APCI-TOF) calcd for $C_{10}H_{11}O_3$ $[M + H]^+$ 179.0703, found 179.0702.



75a

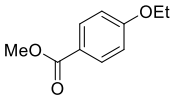
Methyl 4-acetylbenzoate (**75a**): Yellow solid (0.17 g, 94% yield); m.p. 85-87 °C; R_f = 0.73 (silica gel, EtOAc:hexanes 1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ = 8.12 (d, J = 8.2 Hz, 2H), 8.01 (d, *J* = 8.2 Hz, 2H), 3.95 (s,

3H), 2.64 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.7, 166.3, 140.3, 134.0, 130.0, 128.3, 52.6, 27.0 ppm; HRMS (EI-TOF) calcd for $C_{10}H_{10}O_3$ $[M + H]^+$ 178.0708, found 178.0706.



75b

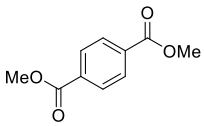
Methyl 5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (**75b**): Yellow solid (0.10 g, 75% yield); m.p. 60-61 ^{o}C; R_f = 0.70 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.08 (d, *J* = 7.9 Hz, 1H), 7.95 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 3.94 (s, 3H), 3.03 (t, *J* = 6.1 Hz, 2H), 2.70 (t, *J* = 6.1 Hz, 2H), 2.20 – 2.14 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.9, 166.5, 144.5, 135.6, 134.0, 130.3, 127.5, 127.4, 52.6, 39.3, 29.7, 23.2 ppm; HRMS (ESI-TOF) calcd for $C_{12}H_{13}O_3$ $[M + H]^+$ 205.0859, found 205.0857.



75c

Methyl 4-ethoxybenzoate (**75c**): Yellow oil (0.086 g, 48% yield); R_f = 0.82 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.98 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0, 162.9, 131.7 (2C), 122.5, 114.1 (2C), 63.8, 52.0, 14.8 ppm; HRMS (APCI-TOF) calcd for $C_{10}H_{13}O_3$ $[M + H]^+$ 181.0859, found 181.0854.

General Procedure: Diels–Alder Reaction of Methyl Coumalate with Dienophiles **78a–e**



79

Dimethyl Terephthalate (**79**): Methyl coumalate (0.154 g, 1.0 mmol) and **78a** (0.3 mL, 3.0 mmol) were combined in a sealable 15-mL pressure vessel. The solution was heated to 150 ^{o}C and stirred for 16 h. (Alternatively, 1.5 equivalents of **78a** can be combined with methyl coumalate at 200 ^{o}C for 16 h). Upon completion of the reaction, the sealable pressure vessel was cooled to room temperature. The solution was transferred to another flask, while rinsing with ethyl acetate, after which the solution was concentrated *in vacuo*. The crude product was purified by repeated trituration and recrystallization from ethyl acetate and hexanes to afford **79** (0.18 g, 95% yield) as a white solid. All the solvents during the purification process could be recovered and reused. **79**: m.p. 140-142 ^{o}C; R_f = 0.79 (silica gel, EtOAc:hexanes 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.10 (s, 4H), 3.95 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.4, 134.1, 129.7, 52.6 ppm; HRMS (ESI-TOF) calcd for $C_{10}H_{11}O_4$ $[M + H]^+$ 195.0652, found 195.0651.

2.8. References

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CHAPTER 3.

GENERAL CONCLUSIONS

The Duality of Complexity and Simplicity from Malic Acid to Functionalized Aromatics

Synthetic organic chemistry is an inarguably complex discipline. Especially in the total synthesis of natural products, readily available components are elaborated into sophisticated molecular architectures with soaring degrees of complexity. Subsequent biological testing has revealed potent and beneficial therapeutic activity with potential analogue development opportunities for the pharmaceutical industry. However, for a facile translation from a microscale academic environment to a viable and cost-effective industrial process, individual chemical transformations and the overall synthesis should strive toward simplification. Similarly, simple procedures and succinct syntheses are preferred in the manufacture of commodity chemicals. Complexity and simplicity are not necessarily diametrically opposed, as the interplay between building complex molecules or breaking down complex molecules with simple design features present equal challenges for innovation. Synthetic solutions that seem elegantly simple likely were proceeded by numerous experiments and iterative methodical design. Generally, designing toward simplicity inherently coincides with solutions aligned with green chemistry principles that would address the current situation of depleting feedstock supply.

The industrial chemical landscape is characterized by a predominant dependence on crude oil for the resultant petrochemical intermediates for integration into useful

consumer products. However, with the concerted effects of decreasing supply coincident with the increasing demand and price of crude oil, ensuring continued future access to petrochemicals is uncertain. With the capacity to synthesize molecules through systematic design, chemists have the potential to positively impact the field through innovations in green chemistry. Guided by the Twelve Principles of Green Chemistry as delineated by Anastas and Warner, we focused on utilizing alternative biorenewable feedstocks utilizing the atom economical Diels–Alder reaction which primarily conserves the atoms between the starting material and the final product. The reaction beneficially provides high levels of regio-, chemo-, and stereocontrol in addition to the concurrent formation of multiple carbon-carbon bonds. We targeted functionalized aromatic compounds since they are present in many consumer materials and have been identified by the U.S. Department of Energy as an important class of compounds to investigate from biomass. Capitalizing on platform molecules has become a popular approach to upgrade biomass into chemicals since one molecule efficiently leads to a diverse range of derivatives.

The 2-pyrone class of compounds has been demonstrated in the literature as a convenient diene in the Diels–Alder reaction with alkene dienophiles to generate bicycloadducts for further elaboration. Depending on the nature of the substituents on the 2-pyrone, either the normal electron-demand Diels–Alder reaction or the inverse electron-demand Diels–Alder reaction (IEDDA) can be favored. The 2-pyrone methyl coumalate with a carbomethoxy group on the 5-position is an electron-deficient diene which resulted in low regioselectivity for reactions with electron-deficient alkynes or alkenes. Instead, electronically matched electron-rich alkynes smoothly generated aromatic systems, but

additional functionality could potentially be introduced with substituted alkene dienophiles. Although mildly electron-rich unactivated alkenes regioselectively provided aromatic compounds, an additional palladium on carbon catalyst was required to facilitate aromatization, which we aimed to avoid to create a greener method to aromatic compounds.

Methyl coumalate could be obtained from glucose through metabolic engineering to generate naturally-occurring malic acid. Subsequently, chemical synthesis could effect the dimerization and esterification to methyl coumalate, which represents a bio-based platform for diversification. In a domino IEDDA/retro-Diels–Alder/elimination sequence with electron-rich vinyl ether dienophiles, the alkoxy leaving group promoted aromatization without the necessity for an additional catalyst. The star diagram for methyl coumalate was enhanced by acetal and orthoester dienophile equivalents that presumably created *in situ* dienophiles during the thermal reaction conditions. Numerous advantages arise from the one-pot domino sequence over earlier routes that were not highly selective, necessitated multi-step syntheses or conversions from pre-formed aromatic precursors, and required the use of palladium catalysts. A broad multitude of aromatic compounds originated from methyl coumalate including carbazoles, tricyclic, fused, anisole, and biphenyl systems that encompassed a variety of applications in diverse industrial sectors. In the context of potentially translating the technology to an industrial setting, captodative dienophile derivatives from methyl pyruvate resulted in a 100% biorenewable formal synthesis to terephthalic acid via dimethyl terephthalate (DMT). As high-volume co-monomers for the polymer industry, the transformation to DMT was optimized to offer additional benefits including the elimination of solvent and catalysts unlike the current

AMOCO process for the oxidation of petroleum-based *p*-xylene. Furthermore, DMT is facilely purified through recrystallization in up to 95% yield, with the potential to access biorenewable poly(ethylene terephthalate) for direct consumer products including beverage containers or carpet fibers.

The thermal IEDDA/retro-Diels–Alder/elimination domino sequence with the bio-sourced methyl coumalate platform and methyl pyruvate to achieve DMT could potentially supplant the traditional petroleum-based route. Petrochemicals from crude oil generally begin with hydrocarbon compounds that contain little functionality which must be added later to increase the complexity. In contrast, complex biomass feedstocks like glucose usually commence with a highly hydroxylated framework from which some of the functionality is replaced to generate the desired chemical building blocks. Complexity and simplicity conceptually intermingle with the methodology's design because multiple transformations occur during the domino progression while maintaining a simple procedure since all the reagents are in the same reaction vessel. Additional design features for DMT in particular augment the simplicity by removing the catalyst and solvent, utilizing stable dienophile equivalents that do not require rigorous purification, and purifying the product through recrystallization rather than flash chromatography. The intentional experimental simplicity juxtaposed with the power to upgrade methyl coumalate to aromatic precursors of more complex molecules has implications across the chemical industry. From industrially-relevant pharmaceuticals to plastics, a myriad of possibilities is achievable through the domino reaction of methyl coumalate as an

alternative route for biorenewable functionalized aromatics to advance the goals of green chemistry and approach the reality of a sustainable future.