SYNTHESIS OF TEREPHTHALIC, ISOPHTHALIC AND PHTHALIC ACIDS FROM METHANE AND CARBON DIOXIDE

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ABSTRACT

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Terephthalic, isophthalic and phthalic acids are commodity chemicals valuable in the syntheses of a variety of different polymers. Current production of these benzenedicarboxylic acids relies on petroleum-derived xylenes as chemical feedstocks via Amoco-MidCentury oxidation, a process that releases sizeable amount of carbon dioxide and methane and poses other environmental challenge. Rather than generating greenhouse gases, this investigation focuses on using the single carbon (C1) greenhouse gases methane (CH_4) and carbon dioxide (CO_2) as synthetic starting materials. Proof-of-concept syntheses of terephthalic, isophthalic and phthalic acids are elaborated from acetylenemonocarboxylic acid, which is obtained by reaction of carbon dioxide with methane-derived acetylene.

Acetylenemonocarboxylic acid was first employed as a dienophile in a cycloaddition reaction with isoprene to afford terephthalic and isophthalic acids. A more versatile synthetic approach employed metal-catalyzed or Bronsted acid-catalyzed hydration of acetylenemonocarboxylic acid to afford malonic acid semialdehyde and pyruvic acid. Proposed reaction of malonic acid semialdehyde with two equivalents of acetylenemonocarboxylic acid leads to terephthalic and isophthalic acids via intermediacy of coumalic acid. Proposed reaction of pyruvic acid with two equivalents of acetylenemonocarboxylic acid leads to phthalic and isophthalic acids via intermediacy of isocoumalic acid.

This dissertation is dedicated to my parents
For their love, understanding, and support
In memory of
Nguyen Mai Quan

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Words cannot describe how grateful I am to my advisor, Dr. John W. Frost. From the first meeting I had in his office with Dr. Karen Draths, for the last five years, between research and teaching, John has taught me how to tackle a problem by asking the right question and paying attention to details. John's patience with our "miscommunication" problem and his tolerance of my peculiarity have helped me complete the work described in this thesis.

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I would like to thank my mother and father who have been patient and understanding of my absence from home for the last five years. They inspired me to continue their paths as chemists, and their love and support help me get up in the morning to go to the lab and finish what I set out to do. I am grateful to my friends and family in Vietnam who are half the world away yet never stop reaching out to me and understand my absence in the milestones of their lives.

I wrote this dissertation in memory of my grandfather, who, for the first six years of my life and last of his, took care of me when parents were busy, walked me to school, picked me up every day, and taught me how to read before I could even form a proper sentence. Through his eyes I learned that there is no limit to curiosity when looking at the world full of wonders waiting to be discovered.

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KEY TO ABBREVIATIONS

AMCA	acetylenemonocarboxylic acid
$BOB(OAc)_4$	tetraborylacetate
CBA	4-carboxybenzaldehyde
DCE	1,2-dichloroethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEHP	di(2-ethylhexyl)phthalate
DINCH	diisononyl cyclohexane 1,2-dicarboxylate
Exp.	Experiment
HOAc	acetic acid
h	hour
HPLC	high pressure liquid chromatography
IPA	isophthalic acid
NADH	nicotinamide adenine dinucleotide, reduced
NMR	nuclear magnetic resonance
PA	phthalic acid
PET	poly(ethylene terephthalate)
PLA	poly(lactic acid)
PTA	purified terephthalic acid
PVC	poly(vinyl chloride)
PvOH	pivalic acid
p.	page

TCE	1,1,2,2-tetrachloroethane
TfOH	triflic acid

CHAPTER 1: INTRODUCTION

Terephthalic **1**, isophthalic **2** and phthalic **3** acids are large volume commodity chemicals manufactured from the Amoco-MidCentury oxidation of petroleum-derived xylenes.[1] Annually, an estimate of 50×10^9 kg of terephthalic acid **1** are globally manufactured from *p*-xylene and polymerized with ethylene glycol to form poly(ethylene terephthalate), PET.[2] Approximately 1.5×10^9 kg of isophthalic acid (IPA) **2** is produced globally each year from *m*-xylene.[1] The reaction conditions for oxidation of terephthalic acid and isophthalic acid are similar and enable production facilities to be used interchangeably for these two oxidations. Whereas terephthalic acid is the "straight" monomer that dominates PET formulations, isophthalic acid is the "bent" co-monomer that is typically added in much smaller concentrations.[1] The content of IPA in PET is typically only 5-7% of purified terephthalic acid (PTA). However, the "bent" IPA is critical to lowering melt process temperatures and inhibiting crystallinity in route to achieving clear, transparent PET. Phthalic acid (PA) **3**, obtained from oxidation of *o*-xylene, has been dominantly esterified to yield di(2-ethylhexyl)phthalate (DEHP) for plasticizer applications, up to 6.0×10^9 kg annually.[3] Plasticizers are not covalently attached to poly(vinyl chloride) (PVC), they can diffuse through and volatize out of the polymer. Claims have been made linking DEHP to damaged sexual development in neonatal infants and reproductive problem in rodents. This has led to replacement of phthalate esters in plasticizer applications with diisononyl cyclohexane 1,2-dicarboxylate (DINCH), which is obtained by hydrogenating diisononyl phthalate.

Not only that current manufacture of terephthalic, isophthalic, and phthalic acids are using nonrenewable xylenes, the Amoco-MidCentury oxidations to produce aromatic diacids from xylenes are also high carbon footprint processes which will be addressed later in this chapter. As

part of a larger effort to address the issue of increasing atmospheric concentration of greenhouse gases, an alternate strategy is to replace the use of petroleum-derived xylenes with abundant C1-chemical feedstock such as methane and carbon dioxide.

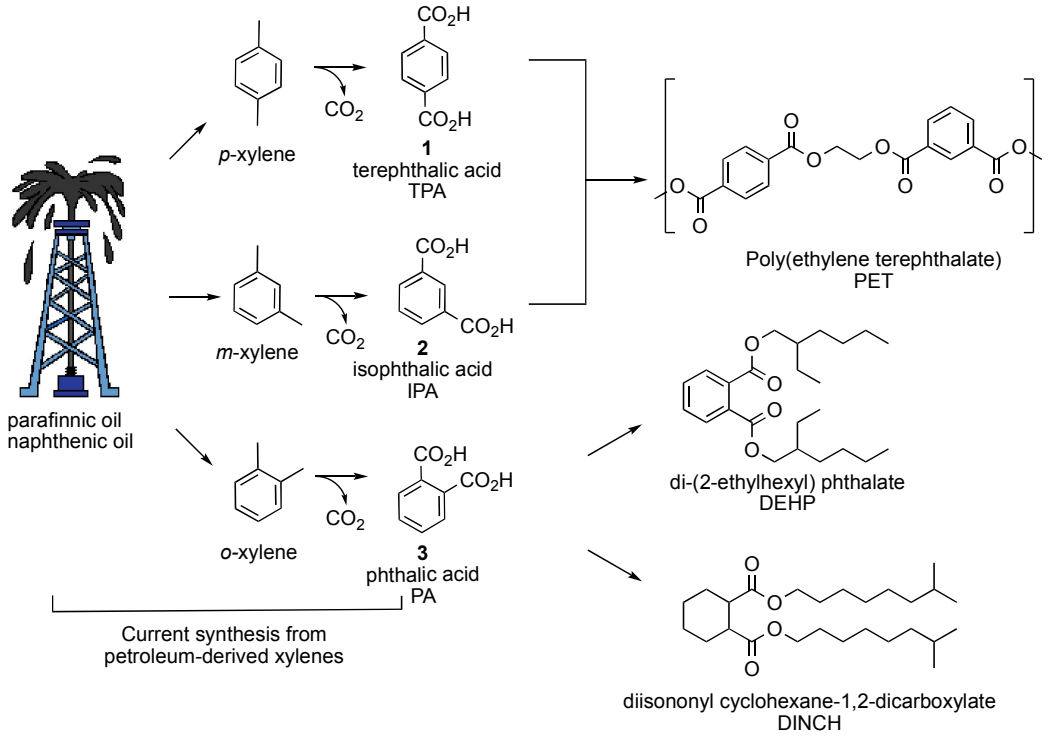


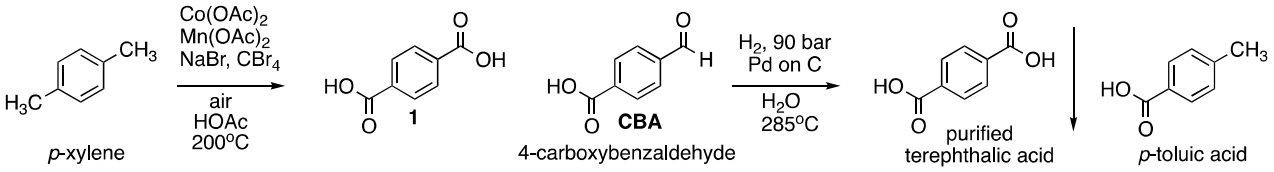
Figure 1.1. Oxidation of petroleum-derived xylenes to terephthalic, isophthalic and phthalic acids

The work carried out in this thesis focused on developing concise syntheses of terephthalic, isophthalic, and phthalic acids from methane and CO_2-derived starting materials such as isoprene and acetylenemonocarboxylic acid (AMCA). Previous work in the Frost group explored the Alder Route as a xylene-free three-step synthesis of terephthalic and isophthalic acids using isoprene and acrylic acid as C1-derived starting materials (Scheme 1.4). The Propiolate Route, presented in chapter 2, while still using isoprene as a starting material, explored AMCA instead of acrylic acid, resulted in a straightforward two-step synthesis to C-8 terephthalic and isophthalic acids. AMCA can be synthesized in two steps directly from methane and CO_2, while acrylic acid requires a multi-step synthesis. Chapter 3 presents the Pyrone Route which focuses on catalyzed conversion of

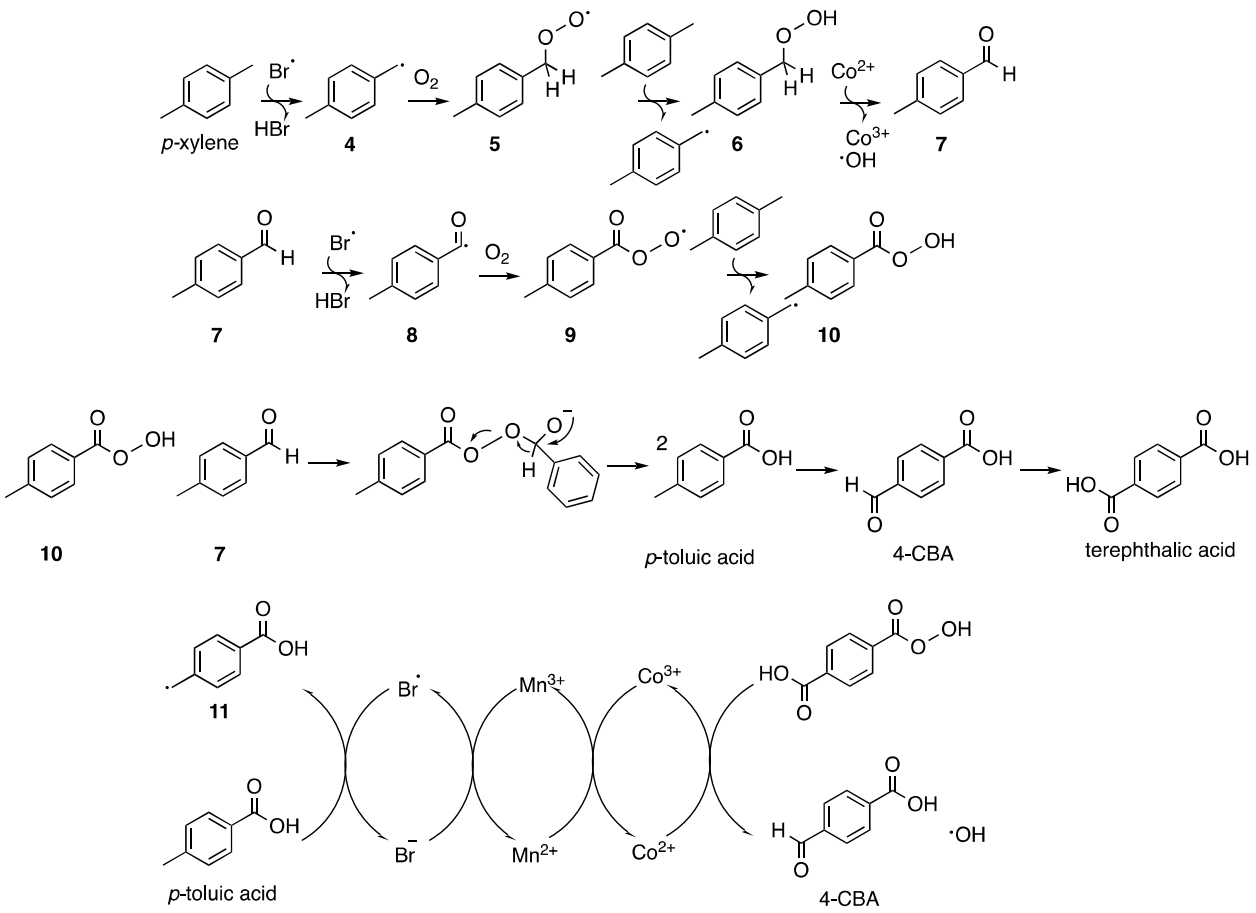
AMCA as a single starting material to all three C-8 terephthalic, isophthalic and phthalic acids via two pyrone intermediates – coumalic and isocoumalic acids. Cycloadditions of pyrones and AMCA to selectively form terephthalic and phthalic acids are also included in Chapter 3. With AMCA as the starting material, virtually all terephthalic, isophthalic and phthalic acids can be derived from methane and carbon dioxide, the Pyrone Route not only eliminates petroleum-derived xylenes as chemical feedstocks to targeted aromatic products but also eliminates the high-carbon footprint Amoco-MidCentury oxidation. Mechanistic studies of catalyzed conversion of AMCA to pyrone intermediates and byproducts trimellitic and trimesic acids via 1,3- and 1,4-hydration pathways are presented in Chapter 4. As part of an application of the 1,3-hydration pathway, synthesis of pyruvic acid from AMCA afford a pathway to lactic acids as monomers of biodegradable poly(lactic acid) (PLA).

1. Amoco-MidCentury oxidation of xylenes to terephthalic, isophthalic and phthalic acids

Terephthalic acid industrially comes from the Amoco-MidCentury oxidation of *p*-xylene.[1] The same process can be used to produce isophthalic acid from *m*-xylene.[1] Phthalic acid and phthalate anhydride can be obtained via oxidation of *o*-xylene, either based on the Amoco-MidCentury oxidation or V_2O_5 oxidation.[10]



Scheme 1.1. Amoco-MidCentury oxidation of p-xylene and purification of terephthalic acid



Scheme 1.2. Propagation and catalytic cycle of p-xylene oxidation to terephthalic acid

The Amoco-Midcentury oxidation is a radical process using Br radical as the radical initiator to abstract a H atom from the arylmethyl of *p*-xylene to from a *p*-xylene radical. Upon reacting with oxygen, *p*-xylene formed peroxide **5** which generates another *p*-xylene radical and peroxide **6**. *p*-Tolualdehyde **7** is formed as peroxide **6** collapsed to generate hydroxy radical and oxidize Co^{2+} to Co^{3+}. As Br radical abstract the aldehydic proton of **7** followed by reacting with oxygen, peroxide radical **9** is formed. Peroxide **9** abstracts a H atom from *p*-xylene to form a *p*-xylene radical and peracid **10**. *p*-Tolualdehyde **7** and peracid **10** reacts in a Baeyer-Villiger reaction to form two molecules of *p*-toluic acid which can go through another cycle of oxidation to form terephthalic acid. In order to regenerate Co^{2+}, Mn^{2+} is oxidized by Co^{3+} and formed Mn^{3+}, which in turn can be reduced by Br anion to regenerate Br radical initiator and Mn^{2+}.

Synthesis of PTA from *p*-xylene highlights many of the challenges inherent in selective oxidation of xylene arylmethyl groups. Amoco-MidCentury oxidations are radical chain reactions employing NaBr and CBr_4 as chain propagators in HOAc as solvent.[1] Use of halide reagents in the process leads to metal corrosion and therefore requires that pressure reactors required for the oxidation to be constructed from Ti^0.[1] During the catalytic oxidation of *p*-xylene, 165 kg of CO_2 is generated for each 1000 kg of purified terephthalic acid produced (Scheme 1).[4] Of this CO_2, 40% comes from over-oxidation of *p*-xylene and 60% comes from oxidation of the HOAc used as solvent.[4a] Decarboxylation of HOAc solvent leads to generation of copious quantities of CH_4, which has a 25-fold greater impact on climate change relative to CO_2 on a wt/wt basis.[4b] The Amoco-MidCentury oxidation therefore has a sizable carbon footprint.

Oxidation of terephthalic acid is never a complete process, which leads to contamination by the partially oxidized 4-carboxybenzaldehyde (CBA) (Scheme 1). In order to form high molecular weight PET, purified terephthalic acid participating in the polycondensation with ethylene glycol has to be 99.99% pure with a maximum of 25 ppm of CBA.[5] Removing CBA contamination, therefore, requires an extra step to hydrogenate CBA to *p*-toluic acid in a pressurized, continuous flow trickle bed reactor containing immobilized Pd/C with a counter flow of H_2.[11] Crude terephthalic acid solution in water is passed through the reactor, allowing purified terephthalic acid to recrystallize while *p*-toluic acid remains in solution (Scheme 3).[5]

Prior to elaboration of CBA hydrogenation/selective crystallization of terephthalic acid from water to obtain PTA, crude terephthalic acid was converted to its methyl ester, which was purified by distillation. Polymerization of dimethyl terephthalate with ethylene glycol to produce PET led to generation of flammable CH_3OH. Byproduct CH_3OH had to be collected, purified, and reused, which is problematic from an atom economy and process chemistry perspective.

Generation of nonflammable H_2O during polymerization of the free acid PTA with ethylene glycol quickly displaced use of dimethyl terephthalate in polymerization with ethylene glycol to form PET.

2. Methane and carbon dioxide as C1 chemical feedstocks

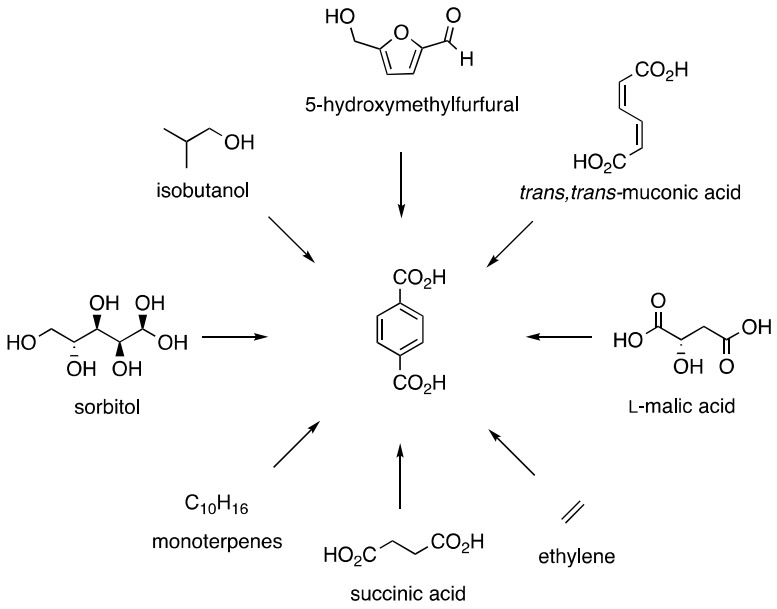
The U.S. has 16×10^{12} m^3 of proven dry natural/shale gas reserves and an estimated 474×10^{12} m^3 of total CH_4 reserves.[6] The amount of methane hydrate off the U.S. coast is estimated at 1500×10^{12} m^3. For comparison, the U.S. annually consumes 0.74×10^{12} m^3 of CH_4.[7-9] Renewable biogas production from landfill, wastewater treatment, and industrialized livestock facilities has the potential of supplying 6.0×10^{10} m^3/year of CH_4, which could serve as a source of the 4.6×10^3 m^3/year of methane consumed by the U.S. chemical industry.[4]

Human activities also introduce 22×10^{12} m^3 of CO_2 into the atmosphere annually.[4] As carbon dioxide concentration continues to rise, one of the consequential impacts is global food security.[10] The elemental chemical composition of a plant balances between carbon from atmospheric CO_2 and the remaining nutrients from soil.[10] Projected increases of CO_2 can result in an ionomic imbalance for most plant species which in turns will have critical consequences for human nutrition including protein and other micronutrients, especially in rice-dependent populations.[10] Given their abundances and impacts on global climate change, CH_4 and CO_2 are attractive C1 chemical feedstocks in place of petroleum derived- xylenes for synthesis of large volume commodity chemicals such as terephthalic, isophthalic and phthalic acids.

3. Synthesis of biobased starting materials to terephthalic, isophthalic and phthalic acids

3.1. Glucose-derived starting materials to terephthalic acid

As commercial production of PTA and IPA relies on fossil fuel cost, there has been alternative routes to bio-based PTA and IPA using glucose-derived starting materials to extend the variety of available chemical feedstocks and avoid xylene intermediacy.[11-36]



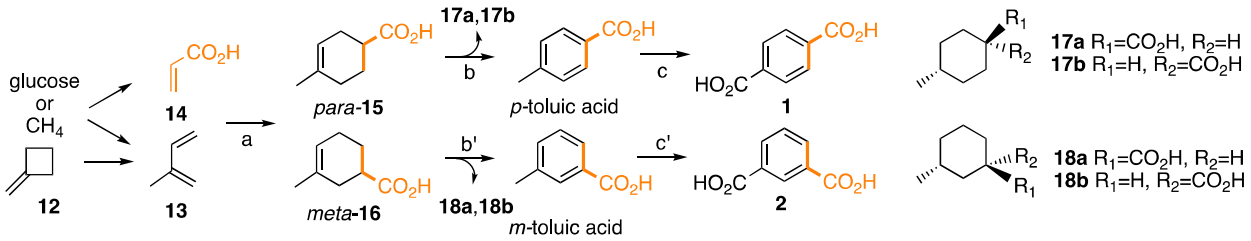
Scheme 1.3. Glucose-derived starting material to bio-based terephthalic acid.

However, as global population expected to reach 9.5-13 billion people by 2100, it is predicted that 1 out of 9 people on Earth is or will be starving.[37] Additionally, the U.S. will turn 5 billion bushels of corn into ethanol which is enough food to feed 412 million people for an entire year. As a result, converting glucose-derived starting materials to commodity chemicals was problematic consequences.

3.2. The Alder route to terephthalic and isophthalic acids

In the early 1950's, Kurt Alder investigated the electrocyclic ring-opening reaction of methylenecyclobutane **12**.[38] A cycloaddition trapping reaction using acrylic acid **14** was employed

to establish isoprene **13** as the ring-opened product. Research in the Frost group prior to the work in this thesis has established the Alder route to TPA and IPA based on the cycloaddition of isoprene **13** and acrylic acid **14** (Scheme 1.4).



Scheme 1.4. Alder route to terephthalic and isophthalic acid

[a] (a) $TiCl_4$ or $BOB(OAc)_4$, (2 mol%), neat, rt, **15**(89%),**16**(4%). (b)/(b') 5 wt% Pd on C, 240°C, 0.11 bar, *p*-toluic acid (77%), **17a**(12%), **17b**(9%),*m*-toluic acid (69%), **18a**(10%), **18b**(13%). (c)/(c') $Co(OAc)_2$ (0.5 mol%), $Mn(Oac)_2$ (0.5 mol%), *N*-hydroxysuccinimide, O_2, HOAc, 100°C, **1**(94%), **2**(88%).

$TiCl_4$-catalyzed cycloaddition of isoprene **13** and acrylic acid afforded **14** *para*-cycloadduct **15** and *meta*-cycloadduct **16**, which undergo a dehydrogenative aromatization to form *p*-toluic acid and *m*-toluic acid, subsequently. An Amoco-Midcentury Oxidation of toluic acids yielded terephthalic and isophthalic acids, respectively.

The Alder route has a number of advantageous features. (a) Acrylic acid can be synthesized via a microbial synthesis from glucose while isoprene comes from a steam reforming of methane followed by methanol to olefin (MTO) catalysis.[39-42] (b) The Alder route enables access to both PTA and IPA, with high selectivity toward higher-demanded PTA. (c) The Alder route entails a Lewis acid-catalyzed solvent free cycloaddition of unprotected acrylic acid, which leads to free acid product that is ready for polymerization with ethylene glycol to form PET. Catalyzing reaction of unesterified carboxylic acids has remained a problem in synthetic chemistry, often necessitating the use of an ester derivative in place of the free acid. However, no PET is currently produced from polymerization of diesterified terephthalate with ethylene glycol. This follows from the need to capture and recycle byproduct alcohol, which is problematic from an atom economy and process

chemistry perspective. By contrast, polymerization of PTA and with ethylene glycol produces nonflammable water, which does not require capture and recycling. With both acrylic acid and isoprene are methane-derived starting materials, the Alder route therefore is the first synthesis to terephthalic and isophthalic acids from the greenhouse gases CH_4 and CO_2.

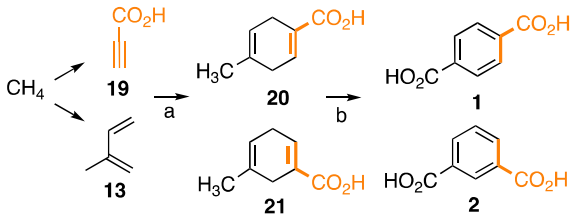
One significant challenge with the Alder route is the formation of byproduct cyclohexanedicarboxylic acid **17ab** and **18ab** during the aromatization of cycloadducts **15** and **16**. Formation of the cyclohexanedicarboxylic acid siphons away 20-25% of cycloadducts.[3] Loss of the activated allylic H atom for Pd(0) insertion means that aromatization of cyclohexanedicarboxylic acid likely requires cracking temperature (>500 ˚C) rather than the relatively mild temperatures required (240˚C) for aromatization of cyclohexenyl cycloadducts.[3] Aromatization of cyclohexenes is a long standing problem in synthetic chemistry.[43-45]

Another challenge of the Alder route is the use of Amoco-MidCentury Oxidation to convert toluic acids to terephthalic and isophthalic acids. With the Amoco-MidCentuty process as a high-carbon footprint due to overoxidation of starting material and decomposition of HOAc to methane and CO_2, as well as formation of byproduct cyclohexanedicarboxylic acids, the Propiolate route was developed in the Frost group to avoid these challenges.

3.3. The Propiolate route to terephthalic and isophthalic acids

The Propiolate route to PTA and IPA was explored based on the cycloaddition of methane- and carbon dioxide-derived AMCA **19** and isoprene **13**.[46] The more reactive 1,4- and 1,3-cyclohexadiene **20** and **21** were designed to undergo aromatization without competing formation of a cyclohexane byproduct. Trace amounts of *p*-toluic acid was detected, which promoted examination of catalyst-free oxidative aromatization of cyclohexadienes and the discovery that heating cyclohexadiene **20** with HOAc at 100˚C under O_2 led to *p*-toluic acid.[46] Accordingly,

reaction of cyclohexadiene **20** under O_2 using *N*-hydroxysuccinimide as the chain carrier catalyzed by $Co(OAc)_2$ and $Mn(OAc)_2$ lead to terephthalic acid. Synthesis of terephthalic and isophthalic acids becomes a two-step route without cyclohexanedicarboxylic acids byproduct. The cycloaddition of AMCA and isoprene will be discussed in detail in Chapter 2.

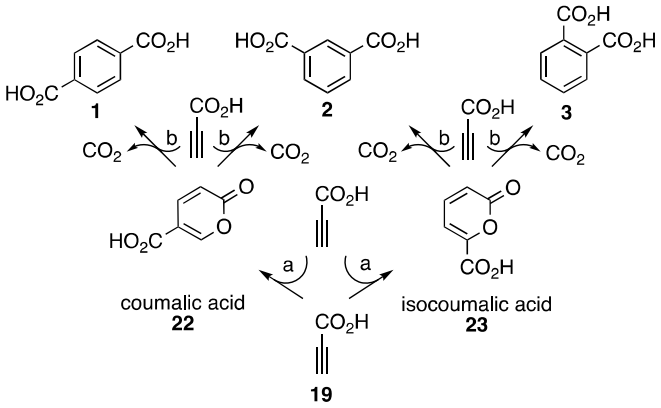


Scheme 1.0.5. The Propiolate Route to Terephthalic and Isophthalic Acids

(a) toluene, 60°C, 67%. (b) $Co(OAc)_2$ (5 mol%), $Mn(Oac)_2$ (5 mol%), *N*-hydroxy-succinimide (20 mol%), O_2, HOAc, 100°C, 85%.

While the Propiolate route is one step shorter than the Alder route, it still requires a dehydrogenative aromatization and oxidation of the methyl group derived from isoprene. Both the Alder and Propiolate Routes were not able to eliminate the use Amoco-MidCentury Oxidation and are not a route to phthalic acid. As we were exploring new route to all three C-8 diacids, the Pyrone Route was discovered which does not require oxidation of an arylmethyl group. With the Pyrone Route, terephthalic, isophthalic, and phthalic acids are all derived from a single starting material – AMCA **19**.

3.4. The Pyrone route to terephthalic, isophthalic and phthalic Acids



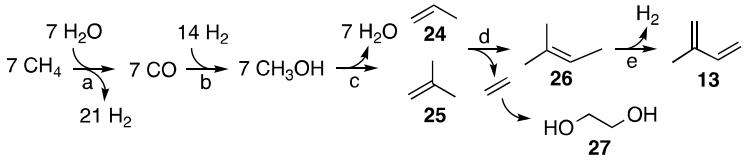
Scheme 1.6. The Pyrone route to terephthalic, isophthalic and phthalic Acids

(a) $MoCl_5$, 0.8 mol%, $AgSbF_6$, 4.0 mol%, dioxane, 100 ˚C, 12h or $[RuCl_2(p\text{-cymene})]_2$, 5.0 mol%, $AgSbF_6$, 20 mol%, HOAc, 80 ˚C, 12 h. (b) $TiCl_4$, 5.0 mol%, toluene, 110 ˚C, 12 h.

With AMCA as the single starting materials, the Pyrone Route eliminates the use of isoprene. With all carboxylic acids come from AMCA, no Amoco-MidCentury Oxidation process is required, leaving this route as a lower carbon footprint synthesis than the Alder and Propiolate Routes. Catalyzed conversion of AMCA generates all three C-8 diacids via 2 pyrone intermediates: coumalic and isocoumalic acids. The Pyrone route entails two steps: (1) conversion of AMCA to coumalic and isocoumalic acids and (2) cycloaddition of pyrone intermediate with AMCA to form terephthalic, isophthalic and phthalic acids. Screening of catalysts to optimize the pyrone route will be included in detail in Chapter 3, and mechanistic studies leading to coumalic and isocoumalic acids will be discussed in Chapter 4.

4. Synthesis of isoprene and acetylenemonocarboxylic acid from methane and carbon dioxide

4.1. Synthesis of isoprene from methane

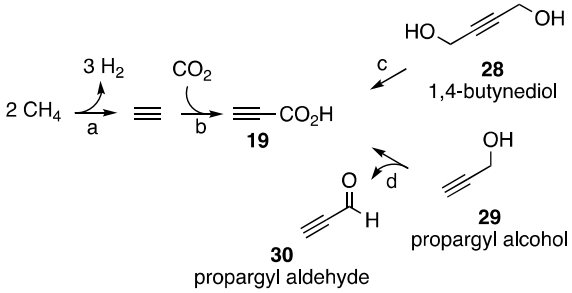


Scheme 1.7. Isoprene from methane

(a) Ni on Al_2O_3 800 °C, 35 bar. (b) CuO/ZnO on Al_2O_3, 250 °C, 50 bar. (c) SAPO-34, 460 °C, 1 bar. (d) WO_3/SiO_2 260 °C, 35 bar. (e) $Fe_2O_3/Cr_2O_3/ K_2CO_3$, 600 °C.

Synthesis of renewable isoprene **13** from biogas methane with steam-reforming of biogas methane to CO and reduction to MeOH. Propylene **24** and isopropylene **25** derived from MeOH using methanol to olefin (MTO) catalysis undergo cross metathesis to produce 2-methyl-2-butene **26**.[41,42] This cross metathesis is a modification of the original Phillips Triolefin Process and the currently practiced OCT routes to synthesis of propylene from 2-butene and ethylene.[43] Byproduct ethylene can conceivably be converted into the ethylene glycol **27** required for polymerization with terephthalic acid to form PET.

4.2. Synthesis of AMCA from methane and carbon dioxide



Scheme 1.8. AMCA from methane and carbon dioxide

(a) 1,500-1,900 °C. (b) Cu^+ or DBU. (c) PbO anodic oxidation. (d) $Na_2Cr_2O_7$, H_2SO_4.

The work completed in this thesis mainly used AMCA purchased from Sigma-Millipore. Prior to 2018, commercial AMCA were isolated as a byproduct of an anodic oxidation of 1,4-butynediol **28** using a PbO anode.[47] Main contaminants of AMCA during that period were water and HOAc, which can be removed via distillation under reduced pressure. More recently, commercial AMCA is synthesized from oxidation of propargyl alcohol **29** using Cr(VI) oxide in sulfuric acid.[48] Aside from H_2O contamination, propargyl aldehyde **30** is generated as a contaminating byproduct. The amount of aldehyde **30** contaminating AMCA varies from batch to batch. After distillation AMCA usually is contaminated with 2 mol% aldehyde. Other sources of commercial AMCA contained 10-25% ethyl acetate which poses a challenge in obtaining pure AMCA due to formation of other byproducts such as ethanol, HOAc, and ethyl acetylenemonocarboxylate during distillation.

Conversion of methane into acetylene followed by carboxylation of acetylene leads to AMCA. A variety of different approaches for synthesis of acetylene from methane have been commercialized.[40] A recently described dehydrodimerization route employs a supersonic reactor to achieve yields up to 95% for methane to acetylene conversion. Carboxylation of acetylene has been reported using (4,7-diphenylphenanthroline)-bis(triphenylphosphine) copper (I) nitrate or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst.[49] Two-step synthesis of AMCA from methane and carbon dioxide potentially avoid byproducts such as propargyl aldehyde, HOAc, and ethyl acetate. At high concentrations, these byproducts result in low yielding of aromatic products from the catalyzed conversion of AMCA.

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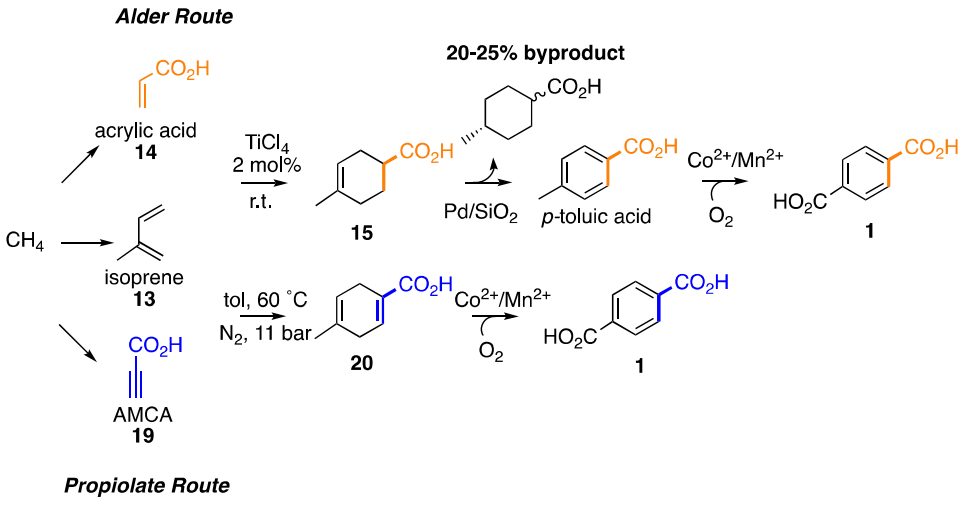
CHAPTER 2: THE PROPIOLATE ROUTE TO TEREPHTHALIC & ISOPHTHALIC ACIDS

1. Introduction

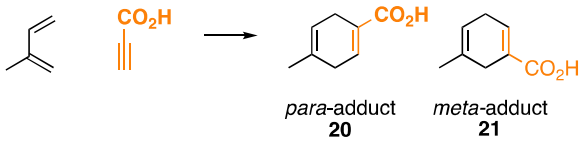
Elevation in atmospheric concentrations of greenhouse gases as well large reserves of both methane and methane hydrates could pave the way for carbon dioxide and methane to become the dominanting C-1 feedstocks in chemical synthesis and manufacture. Synthesis of large-volume, economically-important chemicals such as terephthalic acid and isophthalic acid from C-1 feedstocks CH_4 and CO_2 avoids petroleum and glucose-derived starting materials. Inspired by the challenge in the dehydrogenative aromatization of cycloadduct **15** to *p*-toluic acid in the Alder route due to loss of 20-25% formation of cyclohexane byproduct, the Propiolate Route was developed based on substitution of acetylenemonocarboxylic acid (AMCA) **19** for acrylic acid **14** to lead to cycloadduct **20** that was more reactive toward aromatization relative to cycloadduct **15** (Scheme 2.1).[1]



Scheme 2.1. The Alder and Propiolate routes to terephthalic acid

A one-pot cascade oxidation of the intermediate cyclohexadiene cycloadduct **20** in HOAc using O_2 as oxidant with *N*-hydroxysuccinimide as the chain carrier catalyzed by $Co(OAc)_2$ and

$Mn(OAc)_2$ led to terephthalic acid **1** with no cyclohexane formation.[1] Some earlier problems encountered in the Propiolate Route were conversion and selectivity of cycloadducts **20** and **21** (Scheme 2.2) and respectively terephthalic and isophthalic acids. Isophthalic acid are only at 5-7% of PET, it is necessary for the cycloaddition of isoprene and AMCA to be more selective toward *p*-cycloadduct **20**. The work described in this chapter focuses on optimization to increase selectivity in cycloadduct **20** formation via manipulation of different conditions: temperature, concentration of AMCA in solvent, and isoprene/AMCA ratios.



Scheme 2.2. Cycloaddition of isoprene and AMCA

2. Cycloaddition of isoprene and acetylenemonocarboxylic acid

2.1. Effect of temperature

As part of optimizing the cycloaddition of isoprene and AMCA, variation of reaction temperature was explored. Due to the reactive nature of AMCA and to avoid runaway polymerization in solvent-free conditions, the cycloaddition was run in a titanium vessel under nitrogen atmosphere. The Initial concentration of AMCA was chosen at 5% wt/wt in toluene (0.6M), and the relative mol/mol ratio of isoprene and AMCA was 1:1.

Table 2.1. Effect of temperature on cycloaddition of isoprene and AMCA

[a]Entry	Reaction Temp. (˚C)	% Yield [b]	
		para – **20**	*meta* - **21**
1	120	43[c]	24
2	21	0	0
3	60	30[d]	9

[a] 5% wt/wt of AMCA in toluene, 0.6M, 1:1 mol/mol ratio of isoprene **13** to AMCA **19**, 24 h.
[b] Determined by GC. [c] 15% isolated yield. [d] 21% isolated yield.

At 120 ˚C, cycloaddition of isoprene and AMCA reached 67% total yield of both **20** and **21** with 1.8:1 *para* **20**/*meta* **21**-selectivity. (Table 2.1, entry 1). However, purified *para*-cycloadduct isolated from the product mixture by recrystallization from toluene afforded only a 15% yield. At 21 ˚C, no product was formed in the reaction (Table 2.1, entry 2). While total yield of *para* **20** and *meta* **21** was only 39%, at a reaction temperature of 60 ˚C, the *para* **20**/*meta* **21**-selectivity increased to 3.3:1 with 21% of *para* **20** being isolated from the product mixture by recrystallization from toluene (Table 2.1, entry 3). Further optimization of the cycloaddition therefore was done at 60 ˚C where the *para*-selectivity and isolated yield of purified *para* **20** were improved.

2.2. Effect of concentration on cycloaddition of isoprene and AMCA

The next parameter to be evaluated in the cycloaddition of isoprene and AMCA is the concentration of starting materials in toluene. While isoprene is miscible in nonpolar solvents such as toluene, hexane, and xylenes, there is however a limit to solubility of AMCA in such solvents. At the same time, Diels-Alder cycloadditions favored by highest possible concentrations with solvent-free reaction conditions frequently being ideal. Therefore, concentration of AMCA in toluene was utilized as a parameter to optimize the cycloaddition. Two boundary conditions were set: (1) solvent-free and (2) 50% wt/wt of AMCA in toluene, where AMCA and toluene appeared to be immiscible at room temperature at the beginning and end of the reaction. The molar ratio of isoprene and AMCA was maintained at 1:1.

Solvent-free cycloaddition of isoprene and AMCA showed promising results, with a total yield of 52% and *para* **20**/*meta* **21**-selectivity of 3.7:1 (Table 2.2, entry 1). However, the product mixture appeared to be a red tacky solid from which **20** was unable to be isolated by recrystallization in toluene. Solvent-free cycloaddition of isoprene and AMCA therefore was not

pursued any further. The increase *para* **20**/*meta* **21**-selectivity in solvent-free reaction can be explained by better overlapping of HOMO-isoprene and LUMO-AMCA without interference of solvent. While there were no significant difference going from 5 to 10 wt.% of AMCA in toluene in terms of yield and *para* **20**/*meta* **21**-selectivity, at 25% wt/wt, total yield of **20** and **21** increased to 60% while maintaining *para* **20**/*meta* **21**-selectivity of 3:1 (Table 2.2, entries 2-4).

Table 2.2. Effect of concentration of AMCA on cycloaddition of isoprene and AMCA

Entry[a]	AMCA in tol		% Yield[b]	
	M	wt.%	*para* – **20**	*meta* - **21**
1	--	solvent-free	41[c]	11
2	0.6	5	30	9
3	1.2	10	30	10
4	3	25	45	15
5	6	50	19	5

[a] 1:1 mol/mol ratio of isoprene **13** to AMCA **19**, 24 h reaction.
[b] Determined by GC. [c] Unable to isolate **20** from product mixture.

At 50 wt.% of AMCA in toluene, while the *para* **20**/*meta* **21**-selectivity, the total yield of the reaction suffered (24%). AMCA precipitated from the reaction mixture and formed a thick red liquid. Therefore, 25 wt.% was chosen as the concentration of AMCA in toluene for further optimization of the cycloaddition.

2.3. The impact of isoprene and AMCA mole ratios on cycloaddition yield

In order to improve the yield of the cycloaddition, different molar ratios of isoprene and AMCA were explored. Mole ratios including a 1:1 isoprene:AMCA, 5:1 isoprene:AMCA and 1:5 isoprene:AMCA. The temperature of the reaction was set at 60 ˚C and the concentration of AMCA in toluene throughout different molar ratios was maintained at 25 wt.%.

Table 2.3. Isoprene/AMCA ratio on cycloaddition of isoprene and AMCA

Entry[a]	Isoprene:AMCA (mol/mol)	% Yield (mol/mol)[b]	
		para – **20**	*meta* – **21**
1	1:1	45	15
2	1:2.5	33	9
3	1:5	40	10
4	2.5:1	43	20
5	5:1	66	22
6	5:1	72[c]	24

[a] 25 wt.% of AMCA in toluene, 24 h reaction. [b] Determined by GC.
[c] 67% isolated yield, 36h reaction.

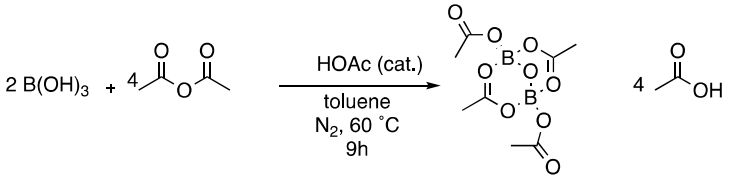
With a 1:2.5 (mol/mol) isoprene:AMCA ratio, the *para* **20**/*meta* **21**-selectivity reached 3.8:1 (mol/mol ratio) at a lower total yield of *para* **20** and *meta* **21** compared to the total yield of the reaction using equimolar of isoprene and AMCA (Table 2.3, entries 1-2). A 1:5 (mol/mol) isoprene:AMCA improved *para* **20**/*meta* **21**-selectivity further and total yield increased to 50% (Table 2.3, entry 3).

With a 2.5:1 (mol/mol) isoprene:AMCA ratio, the *para* **20**/*meta* **21**-selectivity lowered to 2.1:1 while total yield remained unchanged compared to the equimolar reaction (Table 2.3, entries 1 and 4). A 5:1 (mol/mol) isoprene:AMCA ratio led to a significant improvement observed in both total yield (88%) of cycloadducts *para* **20** and *meta* **21**. (Table 2.3, entry 5). Extended reaction time (36 h) at 5:1 (mol/mol) isoprene:AMCA ratio led to a 96% total yield of *para* **20** and *meta* **21**, with 67% isolated yield of **20**.

2.4. Tetraborylacetate and $TiCl_4$-catalyzed cycloaddition of isoprene and AMCA

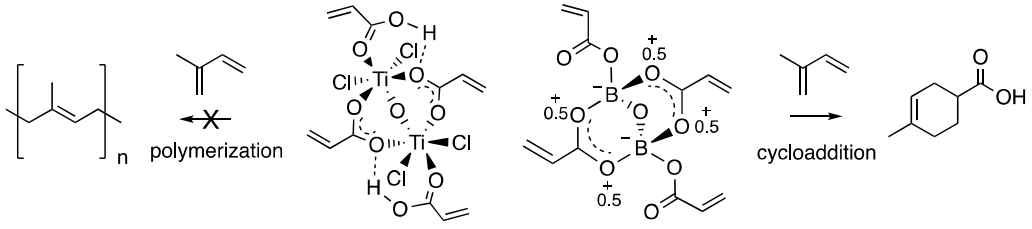
Polymerization reactions encountered during Lewis acid catalyzed cycloaddition involving substrates having an unesterified carboxylic acid has generally required esterification of carboxylic acid. However, during developing the Alder route to terephthalic and isophthalic acids from

isoprene and acrylic acid, $TiCl_4$ and tetraborylacetate ($BOB(OAc)_4$) were discovered to catalyze the cycloaddition without polymerization of isoprene, leading to high the *para:meta*-selectivity in the cycloadditions.[2-4] $BOB(OAc)_4$ was synthesized from boric acid and acetic anhydride in toluene in gram-scale.[4] HCl is a common byproduct which is corrosive to stainless steel reactors and generates halide waste in in industrial manufacture when metal halides are employed as catalyst. By contrast, $BOB(OAc)_4$ catalysis results in no halide formation while leading to yield and *para/meta* selectivity in cycloaddition of isoprene and acrylic acid comparatable to the *para/meta* selectivity and total yield of cycloaddition products observed with $TiCl_4$-catalysis.[4]



Scheme 2.3. Synthesis of $BOB(OAc)_4$

While uncatalyzed cycloaddition of isoprene and AMCA led to a high total yield of cycloaddition products in toluene, could a catalyst be used to improve *para* **20**/*meta* **21**-selectivity? Given the established impact of $TiCl_4$ and $BOB(OAc)_4$ catalysis the total yield of cycloaddition products and *para/meta* selectivity of acrylic acid reaction with isoprene, each catalyst was employed in the reaction at optimized conditions of uncatalyzed cycloaddition of isoprene and AMCA with $TiCl_4$ and $BOB(OAc)_4$ concentration of 5 mol% relative to AMCA concentration initially.



Scheme 2.4. $TiCl_4$ and $BOB(OAc)_4$ complexes with acrylic acid

$TiCl_4$ catalysis was unable to lead to formation of product. As isoprene was added into the $TiCl_4$-AMCA complex in isoprene, the reaction mixture rapidly darkened with the formation of a black precipitate and consumption of all starting materials (Table 2.4, entry 1). Higher loading of $TiCl_4$ therefore was not investigated.

$BOB(OAc)_4$ catalysis at 5 mol% led to promising 6.5:1 (mol/mol) *para* **20**/*meta* **21**-selectivity but the catalyzed reaction was low yielding. Increasing catalyst loading to 100 mol% only lead to a 36% total yield of **20** and **21** (Table 2.4, entry 4).

Table 2.4. Effect of $TiCl_4$ and $BOB(OAc)_4$ on cycloaddition of isoprene and AMCA

Entry[a]	Catalyst[c]	% Yield (mol/mol)[b]	
		para – **20**	*meta* - **21**
1	uncatalyzed	66	22
2	$TiCl_4$	0	0
3[c]	BOB(OAc)	13	2
4[d]	BOB(OAc)[d]	31	5

[a] 25 wt.% of AMCA in toluene (1.2M) isoprene/AMCA (5:1 mol/mol), 24 h reaction.
[b] Determined by GC. [c] 5 mol%. [d] 100 mol%.

Even though $BOB(OAc)_4$ catalysis led to improved *p/m* selectivity, the uncatalyzed reaction was able to achieve a significantly higher total yield (96%) (Table 2.3, entry 5). A reason could be that due to BOB-AMCA complex has low solubility in toluene and precipitated out of reaction, sequestering away AMCA needed to react with isoprene, leading to low yielding. BOB and $TiCl_4$ catalysis of isoprene and AMCA provided preliminary knowledge of dealing with catalyzed conversion of AMCA in the Pyrone Route presented in Chapter 3.

Substituting AMCA for acrylic acid as the dienophile in the reaction with isoprene eliminates formation of cyclohexane byproducts during cycloadduct aromatization in the Alder route. Aromatization and oxidation of the methylaryl group are also conveniently accomplished in a one-pot, cascade oxidation of the cyclohexadienes **20** and **21**. With both AMCA and isoprene

derived from CH_4 and CO_2, the Propiolate Route established a concise synthesis of terephthalic and isophthalic acids from abundant C-1 chemical feedstocks.

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REFERENCES

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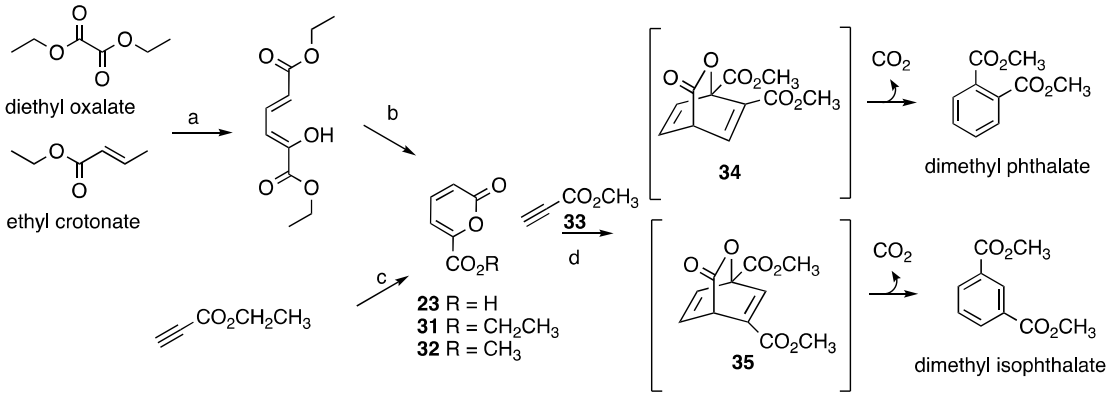
CHAPTER 3: THE PYRONE ROUTE FROM ACETYLENEMONOCARBOXYLIC ACID

Catalyzed Conversion of Acetylenemonocarboxylic Acid to Terephthalic, Isophthalic and Phthalic Acids via Pyrone Intermediacy

1. Introduction

While the Propiolate route formally established a strategy for synthesis of terephthalic and isophthalic acids from methane and CO_2-derived isoprene and acetylenemonocarboxylic acid, there are a few shortcomings in this approach: (1) An Amoco-MidCentury oxidation step in HOAc is required to convert the 4-methyl-1,4-cyclohexandiene-1-carboxylic acid **20** and 5-methyl-1,4-cyclohexadiene-1-carboxylic acid **21** to terephthalic and isophthalic acids, respectively; and (2) No phthalic acid can be produced from methane and CO_2 using the Propiolate route.

To develop an approach that can access all three aromatic diacids and avoid employing an oxidation to introduce a carboxylic acid, different diene starting materials were explored that can ensure: (1) A cyclohexadiene is the product of a cycloaddition with AMCA; (2) Aromatization of the cyclohexadiene cycloadducts is spontaneous.



Scheme 3.1. Isocoumalate to phthalate and isophthalate

(a) potassium metal, t-BuOH, diethyl ether, 4 ˚C, 12 h.[2] (b) H_2O:H_2SO_4:HOAc ratio of 5:1:4 (v/v), 90 ˚C, 6 h.[2] (c) $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), dioxane, PvOH, 110 ˚C, 12 h. (d) toluene, 140 ˚C, 16 h.[3]

To address synthesis of phthalic acid **3**, isoprene is replaced with isocoumalic acid **23**. Literature precedent showed that methyl isocoumalate **32** reacted with methyl acetylenemonocarboxylate **33** in toluene at 140 ˚C resulted in 63% yield of dimethyl phthalate and 37% yield of dimethyl isophthalate via proposed intermediacy of bicyclohexadienes **34** and **35**, respectively.[1] The conditions of esterified reaction indicates that uncatalyzed cycloaddition of isocoumalic acid **23** and AMCA will be slow and require higher temperature. However, bicyclohexadienes can undergo decarboxylative aromatization spontaneously and were not reported as part of the product mixture.[1] Therefore, utilizing isocoumalic acid **23** will eliminate the use of Amoco-MidCentury oxidation entirely. Chemical synthesis of **23** started with aldol condensation of diethyl oxalate and ethyl crotonate using potassium *t*-butyl alkoxide in diethyl ether to form diethyl hydroxymuconate.[2] Hydrolysis and lactonization of hydroxymuconate formed isocoumalic acid **23** under acidic condition.[2] It was also reported that $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$-catalyzed ethyl acetylenemonocarboxylate formed ethyl isocoumalate **31** in 45% yield.[3] However, the NMR reported indicates that the product is actually ethyl coumalate. Therefore, it was unclear which was the right product of the reaction. Replacing ethyl acetylenemonocarboxylate by AMCA resulted in a mixture of both isocoumalic and coumalic acids, among other aromatic products which will be discussed in Section 2 of this Chapter.

During catalyst screening to improve the yield and *o/m*- selectivity of cycloaddition of isocoumalic acid and AMCA, trace amounts of terephthalic acid **1** was observed in NMR spectra of $BOB(OAc)_4$, $CuCl_2$, and $Cu(OTf)_2$-catalyzed reaction (Fig. 3.1).

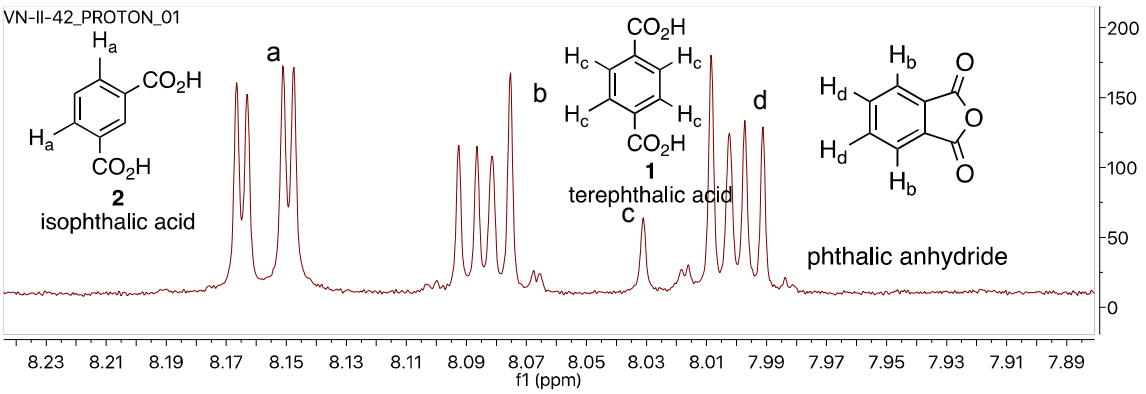
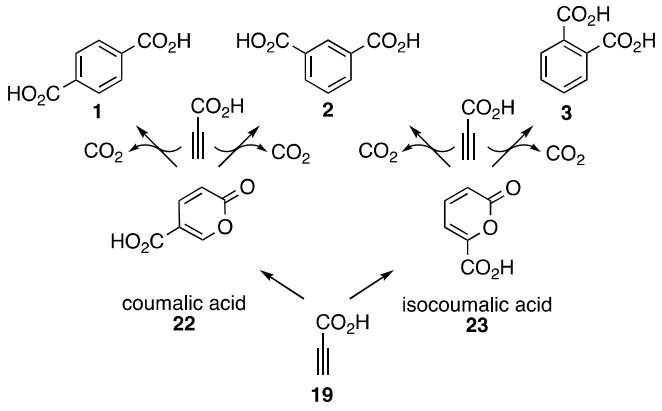


Figure 3.1. ^{1}H-NMR spectrum of BOB(OAc)$_4$-catalyzed cycloaddition of isocoumalic acid and AMCA

In theory, the reaction was supposed to only give *meta*- and *ortho*- bicyclic cycloadducts, which subsequently undergo decarboxylation to give isophthalic acid **2** and phthalic acid **3**. The presence of terephthalic acid in the reaction mixture indicated that catalyzed conversion of AMCA directly to terephthalic acid in one step is possible. Based on what was observed in the Ru-catalysis, it was hypothesized that AMCA was converted to coumalic acid **23**, which subsequently undergoes a cycloaddition with AMCA to form terephthalic and isophthalic acids. A wide range of catalysts were screened to optimize conversion of AMCA to coumalic, terephthalic, isophthalic acids, starting with AuCl based on a report indicating Au-catalyzed annulation [4+2] of AMCA and substituted alkenes to form pyrones.[4]



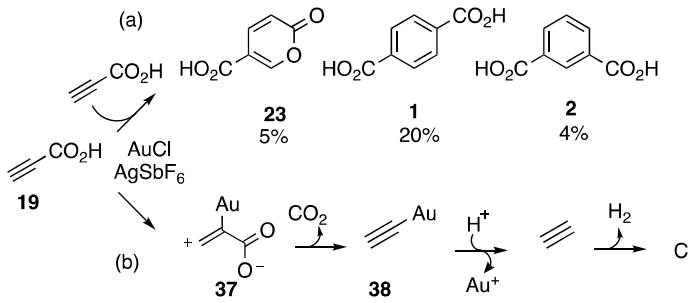
Scheme 3.2. The Pyrone route to terephthalic, isophthalic, and phthalic acids

This chapter will include two parts: (1) catalyzed conversion of AMCA **19** to terephthalic, isophthalic and phthalic acids, focusing on catalysts that can achieve higher than 50% total yield of products, and (2) cycloadditions of pyrone intermediates and AMCA.

2. Acid catalyzed conversion of AMCA to terephthalic, isophthalic and phthalic acids

It was discovered in our lab that AMCA **19** as a single starting material, catalyzed by $AuCl/AgSbF_6$, rapidly formed terephthalic and isophthalic acids (24% yield, 5:1 ratio) at 100˚C, along with coumalic acid **22** (5%) (Scheme 3.3a). Trimellitic **39** and trimesic **40** acids were also formed as byproducts (1% each). With AMCA formed in only 2 steps from methane and CO_2, this reaction opens a promising avenue to synthesize terephthalic acid **1** from abundant chemical feedstock.

Au-catalyzed reaction of AMCA is an intumescent reaction. Upon complexation with Au, a 1,4-C,O-dipole intermediate **37** is formed,[4] which can decarboxylate to form a Au-acetylide **38** (Scheme 3.3b). Au-acetylide **38** can be protodemetalated to form acetylene, which can decompose upon heating to release H_2 gas and C. The combination of evolved gas (CO_2 and H_2), heat, and carbonization could lead to the observed intumescence.



Scheme 3.3. $AuCl/AgSbF_6$-catalyzed AMCA to coumalic acid, isophthalic, and terephthalic acids.

Catalysts across the periodic table in different solvents and temperatures were explored to optimize conversion of AMCA in high yield and selectivity. Metal catalysts were screened beyond AuCl, with the exception of Group V metals. Besides coumalic, isocoumalic, terephthalic,

isophthalic acids, trimellic **39** and trimesic **40** acids were often observed at the end of reaction as byproducts. Muconic acid **41** is another byproduct only observed in using Mo and Au catalysis.

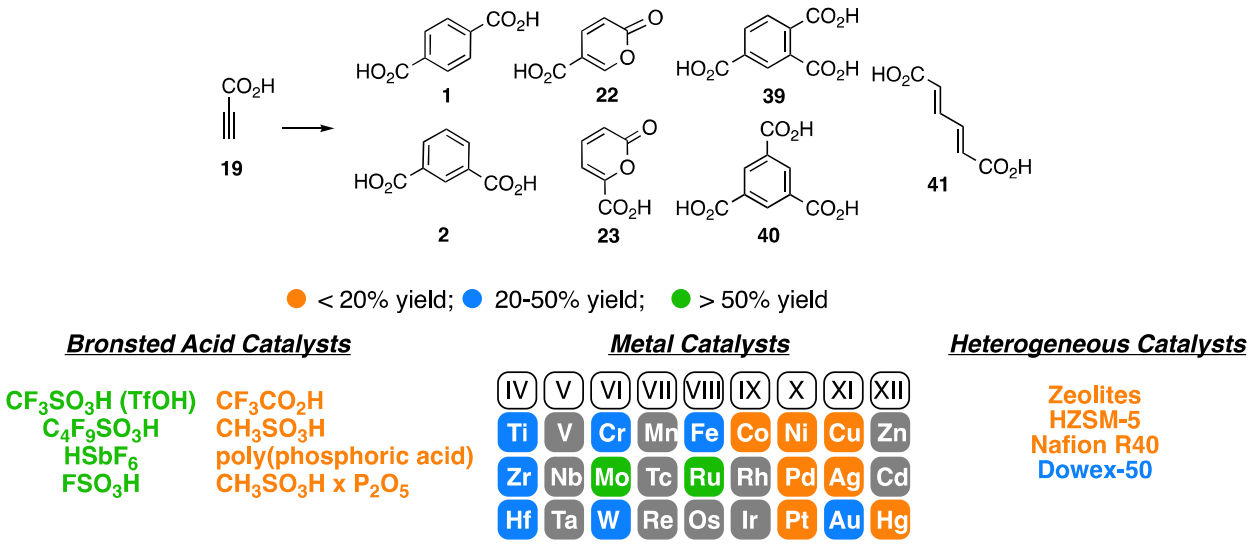


Figure 3.2. Catalysts screened to optimize conversion of acetylenemonocarboxylic acid with color coding based on total yield of pyrones and aromatic products

Aside from AuCl, other metal chlorides in Group IX to Group XII that were screened were low yielding (1-20%) of pyrones and aromatic products. $MoCl_5$ and $[RuCl_2(p\text{-cymene})]_2$ are metal catalysts with highest reactivity in terms of total yield of pyrones and aromatic products. $TiCp_2Cl_2$, $ZrCp_2Cl_2$, and $HfCp_2Cl_2$ showed moderate activity with total yield of pyrones and aromatic products ranging from 20-50%. Super acids such as fluorosulfonic, triflic (TfOH), perfluorosulfonic, and hexafluoroantimonic acids (pKa -12 to -24) showed higher reactivity compared to weaker organic acids, with the best catalyst being TfOH. Hetereogeneous catalysts had low reactivity, with the exception of Dowex-50, which is sulfonic acid with polystyrene backbone. Data obtained from catalyst screening is included in Appendix A.

Table 3.1. Acids catalyzed conversion of acetylenemonocarboxylic acid

Entry	Catalyst	Rxn Cond.	% Yield (mol/mol)							
			1[a]	**2**[a]	**22**[a]	**23**[b]	**39**[a]	**40**[a]	**41**[a]	**19**[b]
1	[c]AuCl	[d]neat	**20**	**4**	5	0	1	1	0	13
2	[c]$AgSbF_6$	[e]TCE	4	2	0	8	1	1	12	10
3	TfOH	[f]neat	**19**	**20**	15	1	0	6	0	9
4		[g]TCE	1	6	60[h]	0	0	7	0	12
5	[i]$[RuCl_2(p\text{-cymene})]_2$	[k]dioxane PvOH	0	0	6	24	1	1	0	0
6	[j]$AgSbF_6$	[k,l]HOAc	3	12	16	24	13	12	0	0
7	[c]$MoCl_5$	[n]neat	1	1	24	12	11	2	11	7
8	[m]$AgSbF_6$	[o]dioxane	0	0	30	20	10	2	6	9

[a] Determined by HPLC. [b] Yield determined by HPLC. [c] 0.8 mol%. [d] 100 ˚C,1 h. [e] 100 ˚C, 12 h, under N_2, TCE: 1,1,2,2-tetrachloroethane. [f] 15 mol%, 100 ˚C, 4 h; then 110 ˚C, 12 h. [g] 20 mol%, 25 wt%, 80 ˚C, 28 h. [h] Yield after isolation and recrystallization from MeOH. [i] 5 mol%. [j] 20 mol%. [k] 80˚C, 12 h. [l] 6% yield of benzoic acid. [m] 4.0 mol%. [n] 50 ˚C, 1 h. [o] 100 ˚C, 4 h.

Yield of products in each reaction using other metal and organo-catalysts compared to AuCl is summarized in Table 3.1. With TCE as solvent and AuCl/$AgSbF_6$ as catalyst (Table 1, entry 2), formation of terephthalic acid **1** diminished while muconic acid **41** emerged as a significant product. Higher selectivity in formation of terephthalic acid **1** in the solvent-free reaction of AMCA catalyzed by AuCl/$AgSbF_6$ could come from cycloaromatization of muconic acid **41** and acetylene.

The highest combined yield (39%) of terephthalic **1** and isophthalic **2** acids was achieved using TfOH as the catalyst under solvent-free condition (Table 3.1, entry 3). In TCE as solvent, TfOH catalysis afforded a 60% yield of coumalic acid **22** after isolation (Table 3.1, entry 4).

A recent report of dimerization of ethyl acetylenemonocarboxylate affording ethyl isocoumalate in 45% yield employed $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ as catalysts.[3] However, ^{1}H-NMR and ^{13}C-NMR reported of the product were identical to ethyl coumalate, making it uncertain

which product was formed in the reaction.[3] Duplication of the reported reaction conditions led to a mixture of products using AMCA as substrate (Table 3.1, entries 5 &6). $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalysis in dioxane/pivalic acid formed isocoumalic acid **23** selectively over coumalic acid **22** (6.5:1 ratio, 30% yield) (Table 3.1, entry 5). Byproducts trimellic **39** and trimesic **40** acids, not reported in literature,[3] were also observed (1:1 mol/mol ratio, 2% yield) (Table 3.1, entry 2). $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ was particularly sensitive to the solvent conditions used. In HOAc, $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ led to isocoumalic **23** and coumalic **22** acids (1.5:1 mol/mol ratio, 40%) (Table 3.1, entry 5). Terephthalic **1** and isophthalic **2** acids, neither observed in dioxane/PvOH reaction nor reported in literature,[3] were formed in the reaction selectively toward isophthalic acid (1:4 mol/mol ratio, 15% yield) (Table 3.1, entry 6). Significant amount of trimellitic **39** and trimesic **40** acids were also observed (1:1 mol/mol ratio, 25% yield) while no muconic acid **41** was detected in the reaction (Table 3.1, entry 6).

$MoCl_5$ was reported to catalyze polymerization of poly(acetylenemonocarboxylic acid) in dioxane via a metathesis mechanism.[6] $MoCl_5/AgSbF_6$ catalysis in solvent-free condition led to formation of coumalic **22** and isocoumalic **23** acids (2/1 mol/mol ratio, 36% yield) (Table 3.1, entry 7). Trimellitic **39** and trimesic **40** acids were also formed in the reaction (5/1 mol/mol ratio, 13% yield). Muconic acid **41** is a byproduct of the $MoCl_5/AgSbF_6$ and $AuCl/AgSbF_6$ reactions not observed in $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalysis. ^{13}C-NMR of *trans,trans*-muconic acid, however, is identical with reported poly(acetylenemonocarboxylic acid).[6] Duplication of the reported reaction conditions catalyzed by $MoCl_5$ to polymerize AMCA only resulted in muconic acid **41** and trace amounts of pyrones **22** and **23**, confirming that there was no poly(acetylenemonocarboxylic acid) in the reaction. $MoCl_5/AgSbF_6$ catalysis in dioxane increased the yield of coumalic **22** and isocoumalic **23** acids (1.5:1 mol/mol ratio, 50% yield) while reducing

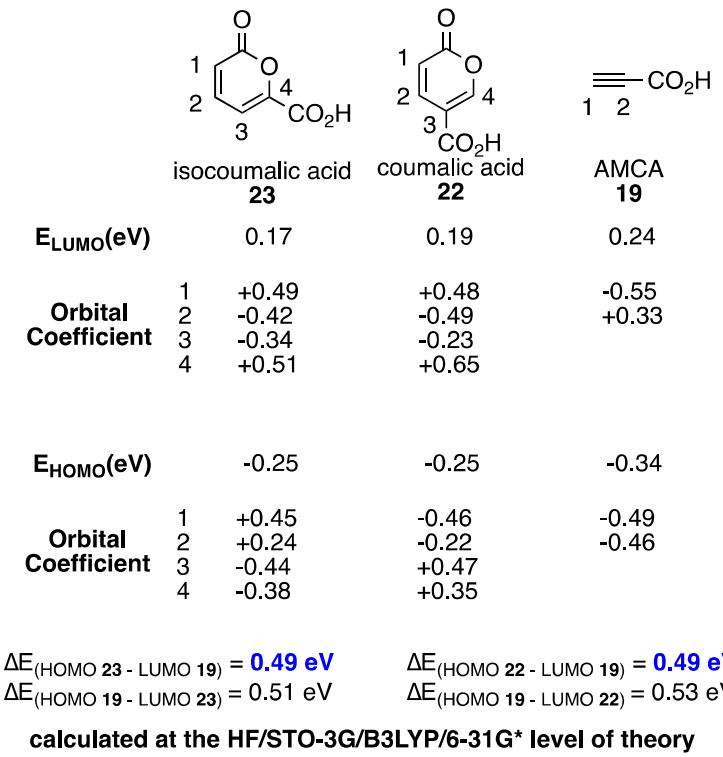
the amount of muconic acid **41** (6% yield) (Table 3.1, entry 8). Formation of **22** and **23** using $[RuCl_2(p\text{-cymene})]_2$ versus $MoCl_5$ catalysis is associated with formation of triacids **39** and **40**. Proposed mechanisms leading to different product distribution will be discussed in Chapter 4.

3. Cycloaddition of pyrones and acetylenemonocarboxylic acid 19

3.1. Computational results

HOMO-LUMO gap and orbital coefficients of methyl coumalate and methyl propiolate have also been reported, indicating that there should be no regioselectivity, same as experimental results.[9] It was unclear whether these computational results have taken in the effect of different temperatures and solvents.

However, there has been no reports in terms of reactivity, regioselectivity and HOMO-LUMO energy gap of the unesterified pyrones and AMCA. These calculations were done by Gaussian'09, at the HF/STO-3G//B3LYP/6-31G* level of theory (Scheme 9). The energy gap between HOMO-LUMO of dienes and dienophiles indicated that in the gas phase, without any adjustment in terms of temperature and solvation effects, cycloadditions of coumalic and isocoumalic with AMCA are normal electron demand Diels-Alder.



Scheme 3.4. HOMO-LUMO gaps and orbital coefficient of coumalic, isocoumalic and acetylenemonocarboxylic acids

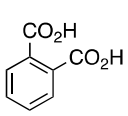
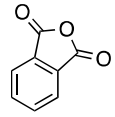
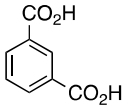
Orbital coefficients also indicated that for isocoumalic acid **23**, there should be a slight selectivity toward *ortho*-cycloadduct, since the absolute value of C-1 is marginally higher than C4 (0.45 vs. 0.38) (Scheme 3.4). Coumalic acid **22**, on the other hand, should have higher selectivity toward *meta*-cycloadduct, due to a greater difference in terms of orbital coefficients of C-1 (0.46) vs. C-4 (0.35) (Scheme 3.4).

3.2. Cycloaddition of isocoumalic acid and AMCA

Diels-Alder reactions often require Lewis acid catalysis to increase *para* selectivity and reduce cycloaddition reaction temperatures. Solvent-free cycloadditions often lead to increased cycloaddition yields and eliminate toxicity, flammability and cost issues associated with solvent use and recycling. A list of Lewis acids screened and the best yielding condition for each catalyst is summarized in Table 3.2.

Isocoumalic acid **23** has a high melting point (232 ˚C) and low solubility in AMCA at rt. Therefore, either elevated temperatures or use of a solvent was necessary. Uncatalyzed Diels-Alder reactions of isocoumalic acid and AMCA with or without solvent showed limited regioselectivity (entries 1-3, Table 3.2), as expected from computational results. Cycloaddition proceeded at a much slower rate in solvent (entry 1, Table 3.2). At 150 ˚C, under solvent-free conditions, there was only a 52% conversion, with a 2/3 (mol/mol), *ortho/meta* selectivity (entry 2, Table 3.2). Full conversion of isocoumalic acid was achieved at an elevated temperature of 200 ˚C with 100% conversion and a 3/2 (mol/mol) ratio (entry 3, Table 3.2). Elevated temperature (150- 200 ˚C) and longer reaction time (3-6 h) also dehydrated phthalic acid to form phthalic anhydride.

Table 3.2. Lewis acid-catalyzed cycloaddition of isocoumalic and acetylenemonocarboxylic acids

Entry	Catalyst	Solvent	Temp. (˚C)	Rxn time	%Yield (mol/mol)			
								**23**[d]
					3[c]	**42**[d]	**2**[c]	
1[a]	Uncatalyzed[f]	toluene	110	12 h	0	0	4	94
2[b]	Uncatalyzed	neat	150	6 h	0	19	30	48
3[a]	Uncatalyzed	neat	200	6 h	9	51	40	0
4[a]	**$TiCl_4$[f]**	**toluene**	**110**	**12 h**	**75**	**2**	**14**	**8**
5[b]	$ZrCl_4$	neat	150	3 h	5	39	37	18
6[b]	$HfCl_4$	neat	150	12 h	2	22	18	58
7[a]	$TiBr_4$[f]	toluene	110	12 h	20	2	5	60
8[b]	**$BOB(OAc)_4$**	**neat**	**150**	**6 h**	**1**	**44**	**45**	**0**
9[b]	CuOTf	neat	150	<1 h	23	0	11	58
10[a]	$Cu(OTf)_2$[f]	1,4-dioxane	200	6 h	20	7	3	65
11[b]	$PhB(OH)_2$	neat	150	6 h	23	20	40	15
12[b]	*o*-$BrPhB(OH)_2$	neat	150	6 h	2	10	15	70
13[b]	BH_3.THF	neat	150	6 h	8	20	25	40
14[a]	BCl_3[f]	toluene	110	12 h	4	35	33	20

Isocoumalic acid **23** : AMCA **19** 1:7 (mol/mol), 5 mol % catalyst. [a]Reaction in Ti vessel. [b]Reaction at 1atm N_2. [c]Determined by HPLC. [d]Determined by NMR. [f] 0.2 M Pyrone.

$TiCl_4$ at 2 mol% catalyst loading led to a 23:1 *para*/*meta* selectivity and a 94% cycloadduct yield for the solvent-free cycloaddition of unesterified acrylic acid and isoprene at rt.[23a] Solvent-free cycloaddition of isocoumalic acid and AMCA catalyzed by $TiCl_4$ led to no detectable product formation attendant with decomposition of the starting material. Results changed when the reaction was run with $TiCl_4$ in a pressurized reactor with toluene as solvent (entry 4, Table 3.2).

The *ortho/meta* selectivity improved to 5.5:1, with a 94% total yield of aromatized products. Zr^{4+} and Hf^{4+} belong to the same group of near transition metals as Ti^{4+} but did not lead to the same selectivity. Both catalysts showed a slight improvement compared to the uncatalyzed reaction at the same condition but had no effect on *ortho*- versus *meta*- selectivity (entry 5, entry 6, Table 3.2). $TiBr_4$–catalyzed reaction was run under the same conditions as entry 4 to compare with $TiCl_4$. Good selectivity (*ortho/meta*; 6/1, mol/mol) was observed, but conversion was low in this reaction (entry 7, Table 3.2). $BOB(OAc)_4$ is a less corrosive alternative to $TiCl_4$ for *para* selective cycloaddition of acrylic acid and isoprene.[7] $BOB(OAc)_4$-catalyzed reaction afforded a 90% yield, and 1/1 (mol/mol) *ortho/meta* selectivity.

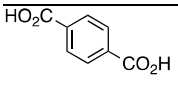
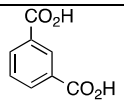
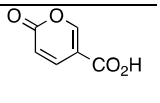
Boron catalysts (entries 11-14, Table 3.2) leading to acyloxyborane and acylboronate intermediacy can enhance *para* selectivity in the cycloaddition of isoprene and acrylic acid.[8,9] However, except $PhB(OH)_2$, boron catalysts only resulted in low yields (entries 16 and 17, Table 3.2). $PhB(OH)_2$-catalyzed reaction afforded 83% yield with a 1.1:1 (mol/mol) *ortho/meta* selectivity (entry 15, Table 3.2).

Overall, $TiCl_4$ is a catalyst that showed the best selectivity toward phthalic acid **3** formation. Even though none of the screened catalysts showed *meta*-selectivity, $BOB(OAc)_4$ was the only catalyst found to increase isophthalic acid **2** to 45%. Extended reaction time for $TiCl_4$-catalyzed reaction to 24 h under the same conditions resulted in 94% yield with a 5.7:1 *ortho/meta* selectivity. At a higher load of $TiCl_4$ (20 mol%) relative to isocoumalic acid, after 12 h, the reaction resulted in 98% yield with a 4.2/1 (mol/mol), *ortho/meta* selectivity.

3.3. Cycloaddition of coumalic acid and AMCA

Cycloaddition of coumalic acid **22** and AMCA required a lower mole ratio of pyrone **22** to AMCA (1:3) and lower temperature (Table 3.3).

Table 3.3. Cycloaddition of coumalic and acetylenemonocarboxylic acids

Entry	Catalyst[c]	Solvent	Temp. (˚C)	%Yield (mol/mol)		
						
				1[d]	**2**[d]	**5**[d]
1[a]	-	toluene	110	20	15	60
2[b]	-	neat	100	44	40	10
3[a]	$TiCl_4$	toluene	110	48	20	16
4[b]	$BOB(OAc)_4$	neat	100	40	25	30

[a]Reaction in Ti vessel. [b]Reaction at 1 atm. [c]5 mol% catalyst; coumalic acid **22**: AMCA **19:** 1:3 (mol/mol), 12 h. [d]Determined by HPLC.

Compared to uncatalyzed cycloaddition of coumalic acid and AMCA in the pressurized reactor, $TiCl_4$ catalysis showed higher *para*-selectivity. The reaction afforded a total 68% yield of terephthalic and isophthalic acids with a 2.4:1 (mol/mol) *para/meta* selectivity. Uncatalyzed reaction in solvent-free conditions resulted in an 84% yield and a 1.1:1 (mol/mol) *para/meta* selectivity (entry 2, Table 3.3), similar to computational results. $BOB(OAc)_4$–catalyzed reaction (entry 4, Table 3.3), resulted in an 65% yield but only 1.6:1 (mol/mol) *para/meta* selectivity.

A previous study of methyl coumalate and methyl acetylenemonocarboxylate/AMCA reported a 64% and 58% yield respectively with a 1:1 (mol/mol) *para/meta* selectivity in both cases.[10] Using toluene as solvent, the reaction resulted in a 35% yield with a 1.2:1 (mol/mol) *para/meta* selectivity (entry 1, Table 3.3). It was reported that cycloadditions of methyl coumalate and the two alkynes were run at 140 ˚C,[10] which was higher than the reaction temperature of entry

1 (Table 3.3). The difference in temperatures of the two reactions (110 ˚C vs. 140 ˚C) could be responsible for the difference in conversion of coumalic acid.

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CHAPTER 4: THE PYRONE ROUTE: MECHANISTIC INSIGHTS

1,3- vs. 1,4-Hydration of Acetylenemonocarboxylic Acid

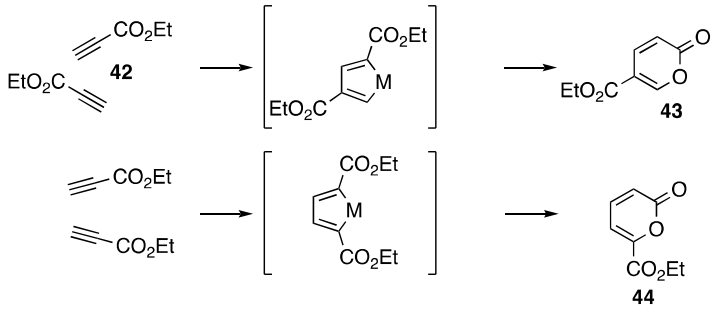
1. Introduction

The pyrone route established a concise synthesis to terephthalic, isophthalic and phthalic acids from methane- and CO_2-derived AMCA. An interesting aspect of catalyzed conversion of a thermogenic material such as AMCA[1] is that the process produced multiple products, and different catalytic systems can remarkably change the selectivity in formation of products. $MoCl_5/AgSbF_6$ catalysis in dioxane lead to total 50% yield of coumalic and isocoumalic acids which can be selectively converted to terephthalic and phthalic acids under $TiCl_4$ catalytic condition. On the other hand, $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalysis led to the highest yields of trimellitic and trimesic acids. Meanwhile, using TfOH catalysis, the major products of the process are terephthalic and isophthalic acids in one step.

The numerous products formed during catalyzed reactions of AMCA point to the challenges in improving the conversions and selectivities to increase efficiency of the pyrone route. The products also could shed light into the underlying mechanism responsible for the transformation of AMCA. This chapter focueses on possible mechanisms of the key reactions leading to coumalic, isocoumalic, trimellic, trimesic and muconic acids.

The dimerization of ethyl acetylenemonocarboxylate **42** to form ethyl isoucoumalate via a $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalyzed reaction has been reported in literature (Scheme 4.1).[2] This reaction proceeds via an oxidative cyclometallation to form intermediate metallacycles which can then undergo a reductive elimination of the metal to yield ethyl esters of coumalate **43** and isocoumalate **44** (Scheme 4). The reported yield of ethyl isocoumalate was 45%.[2] Ethyl coumalate **43** has also been observed by the Frost group although this was not reported in the literature

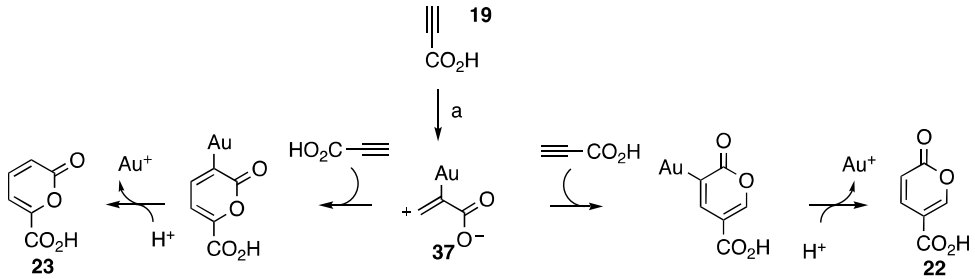
account. However, ethyl acetylenemonocarboxylate **42** will lead to esterified isophthalates, phthalates or terephthalate. Virtually no PET is produced from polymerization of diesterified terephthalate with ethylene glycol. This follows from the need to capture and recycle byproduct ethyl alcohol, which is problematic from an atom economy and process chemistry perspective. Accordingly, elaboration of the dimerization of the unesterified propiolic acid is the focus of this project.



Scheme 4.1. Ruthenium catalysis of ethyl acetylenemonocarboxylate

(a) M = Ru, $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $AgSbF_6$ (20 mol%), PvOH, dioxane, 110 ˚C.

Recent literature evidence indicates a route to synthesize coumalic and isocoumalic acids via a metal-catalyzed dimerization of derivatives of AMCA.[3] An example of this strategy includes Au-catalyzed annulation of AMCA (Scheme 5).[3]

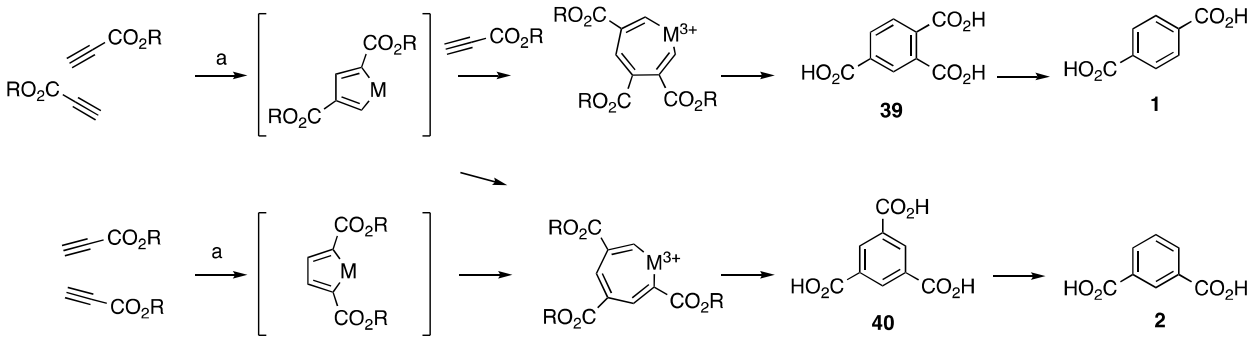


Scheme 4.2. Au-catalyzed annulation and dimerization of acetylenemonocarboxylic acid

(a) Au(*t*-BuP(*o*-biphenyl))Cl/$AgSbF_6$, $CHCl_3$, rt.

Annulation of AMCA is catalyzed by Au(*t*-BuP(*o*-biphenyl))Cl/$AgSbF_6$ at ambient temperature (Scheme 4.2).[3] A 1,4-C,O-dipole intermediate formed upon complexation of AMCA by Au(*t*-BuP(*o*-biphenyl))Cl/$AgSbF_6$ can undergo dimerization with another AMCA molecule to form coumalic and isocoumalic acids (Scheme 4.2). This can be an alternative route to dimerize AMCA without intermediacy of metallacycles (Scheme 4.1).

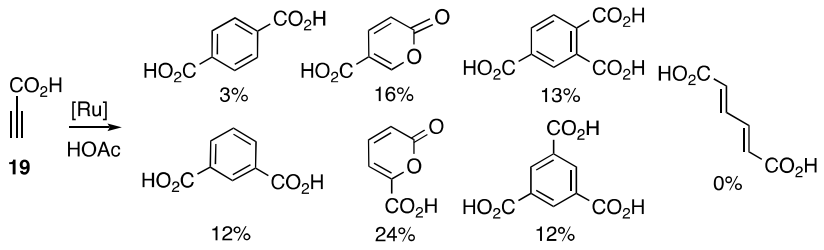
Trimerization, or Reppe mechanism, of AMCA can be a competing process with dimerization and is reported in literature (Scheme 4.3).[4] Trimellitic **39** and trimesic **40** acids (Scheme 4.3) in a 6:1 ratio results from a $Ni(cod)_2$-catalyzed trimerization of sodium acetylenemonocarboxylate.[4] Upon decarboxylation with a stochiometric amount of Cu_2O, these triacids can be converted to terephthalic and isophthalic acids in a 94:6 ratio (Scheme 4.3).[4] The use of sodium acetylenemonocarboxylate not only requires two steps from propiolic acid **4** to terephthalic acid **1** and isophthalic **2** but also results in a salt stream which can be costly in industrial settings.



Scheme 4.3. Trimerization of sodium acetylenemonocarboxylate catalyzed by Ni(cod)2
R = Na^+, M = Ni, (a) 2 mol % $Ni(cod)_2$, $P(Ph)_3$, NaH, THF, 23 ˚C, 1h. (b) Cu_2O, 1 equiv., 180 ˚C

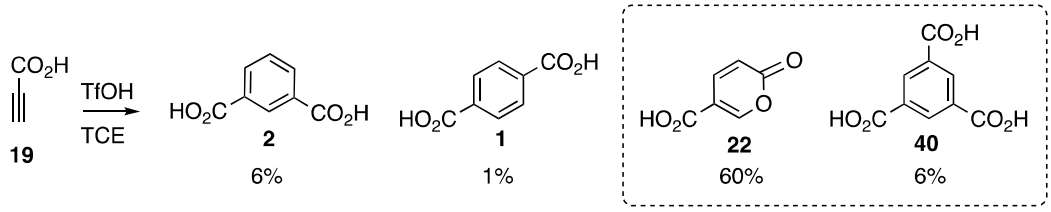
The results of uncatalyzed cycloaddition of coumalic acid **22** and AMCA and TfOH-catalysis in chapter 3 showed consistent 1:1 (mol/mol ratio) of terephthalic and isophthalic acids, indicating that coumalic acid is the key intermediate leading to **1** and **2** in the pyrone route.

Reppe-type trimerization of acetylenic compounds often employed metal catalysis, such as Co, Ni, and Rh.[4-6] The presence of trimesic and trimellitic acids in $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ – catalysis suggests that Reppe process is a possible pathway to form the triacids.



Scheme 4.4. Ruthenium catalysis of AMCA in HOAc

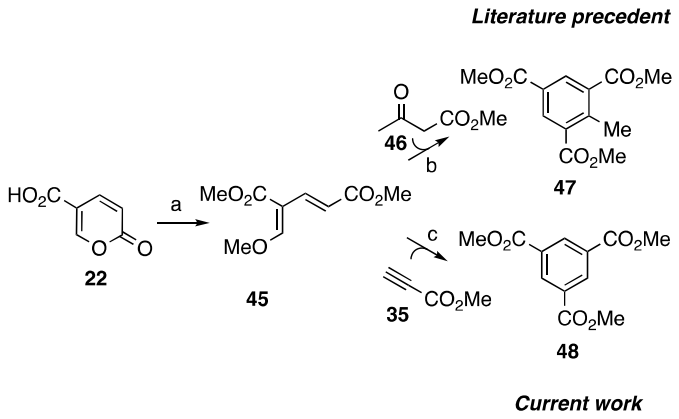
However, trimesic acid was formed in the TfOH catalyzed reaction in 6% yield even in the absence of any catalytic metal, indicating that (1) a Reppe mechanism is not necessary required for the direct formation of trimesic acid **40**, and (2) formation of coumalic acid **22** is associated with **40**.



Scheme 4.5. TfOH-catalyzed AMCA in TCE

2. Formation of coumalic acid and trimesic acid in TfOH catalysis

The presence of trimesic acid **40** as a byproduct was proposed to follow from the decomposition of coumalic acid **22**.[7] It was reported that under acidic condition, coumalic acid **22** can undergo a ring-opening methylation esterification to form **45**.[8] Base-catalyzed cycloaromatization of **45** and **46** in MeOH leads to **28** (91% yield) (Scheme 4.6).[8] Under similar condition of solvent-free TfOH catalysis of AMCA, **45** reacted with methyl acetylenemonocarboxylate **35** to form trimethyl trimesate **48** (40% yield).

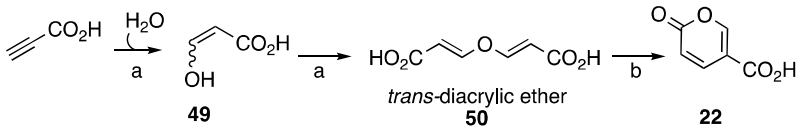


Scheme 4.6. Formation of trimethyl trimesate from coumalic acid and methyl acetylenemonocarboxylate under acidic condition

(a)MeOH:$HC(OCH_3)$ (1:3), H_2SO_4 (5%), rf, 48h, 71% yield.[8] (b) Na_2CO_3, 10 mol%, MeOH, rt, 91% yield.[8] (c)TfOH, 15 mol%,100˚ C, neat, N_2, 40% yield.

Commercial coumalic acid **22** is synthesized from malic acid under acidic conditions.[9] A key intermediate leading to formation of coumalic acid is malonic semialdehyde **49** which has never been isolated in enol form,[9] but was observed by ^{1}H NMR in TfOH catalysis. In wet TCE, TfOH catalysis results in the conversion of AMCA into *trans*-diacrylic ether **50**, which is the dimer of malonic semialdehyde. NMR studies of diacrylic ether **50** catalyzed by TfOH (20 mol%) in D_2O showed conversion of diacrylic either to trimesic acid, isophthalic acid, malonic semialdehyde-keto form, and acetaldehyde (Fig. 4.1).

In wet TCE, conversion of AMCA to diacrylic ether **50** (85% isolated yield) was achieved by employing a stoichiometric amount of TfOH in diluted concentration (1 wt% or 0.13M). TfOH-catalyzed reaction of *trans*-diacrylic ether **50** yielded 55% coumalic acid **22**, which is consistent malonic semialdehyde **49** formed via acid-catalyzed 1,4-hydration of AMCA (Scheme 4.7), being an intermediate in coumalic acid formation.



Scheme 4.7. 1,4-hydration of AMCA leading to coumalic acid

(a) TfOH (2.0 equiv.), 1 mol% H_2O, 100 ˚C, TCE, 1 wt%, N_2, 28h, 85% yield of **35**.
(b) TfOH (15 mol%), neat, 100 ˚C, N_2, 6 h, 55% yield.

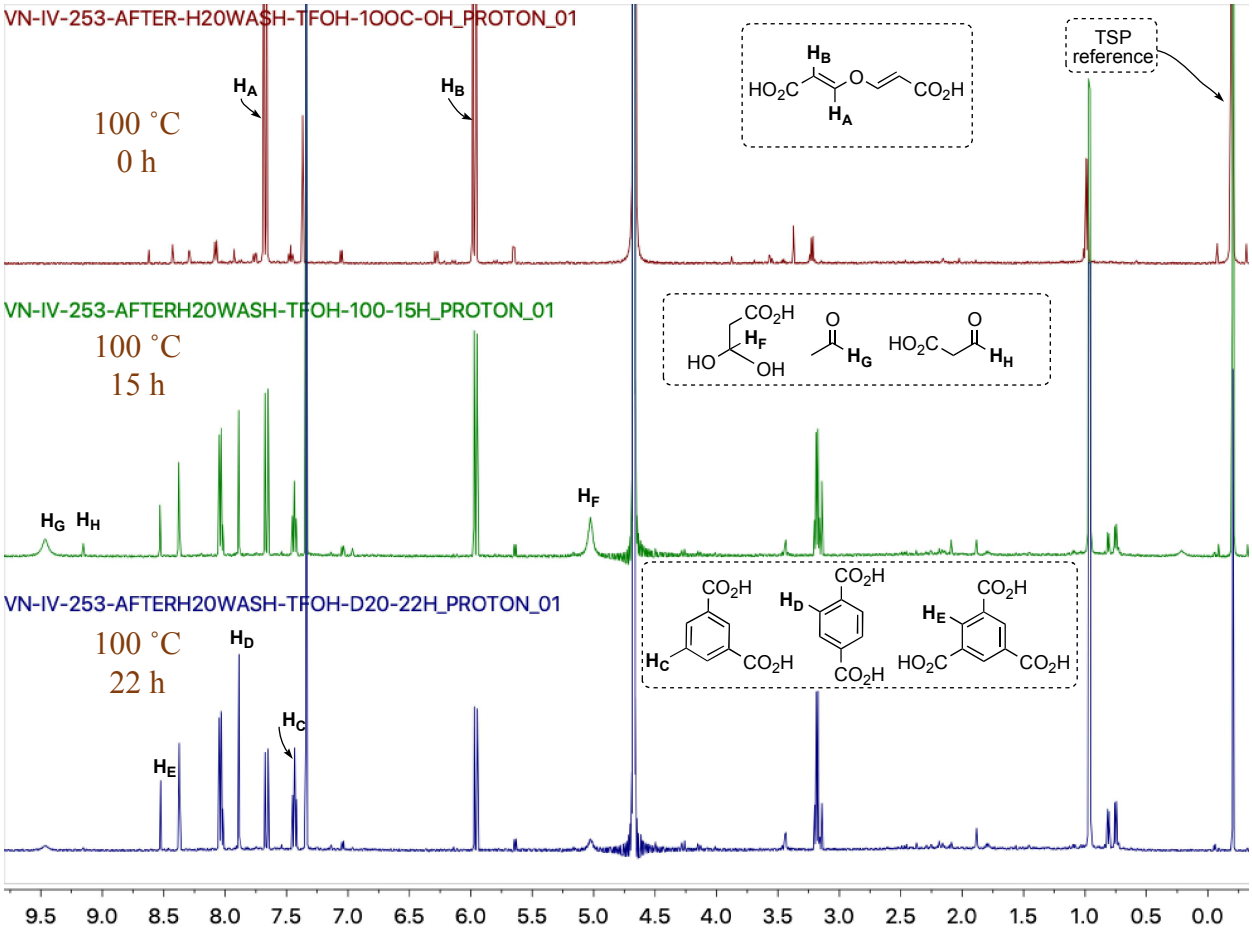
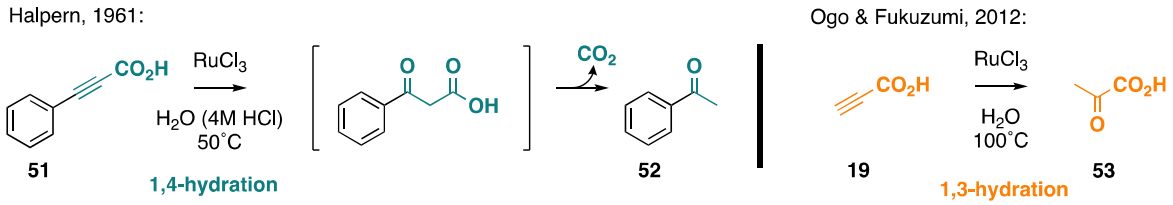


Figure 4.1. NMR studies of diacrylic ether in D_2O at 0, 15, and 22 h and 100˚C

3. Formation of coumalic, isocoumalic, and muconic acids in Ru- and Mo-catalysis

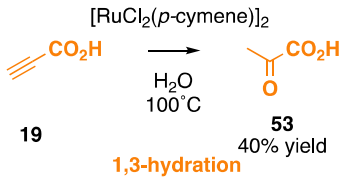
Similar to trimesic acid and coumalic acid being indicative of a 1,4-hydration pathway, formation of isocoumalic and trimellitic acid in Ru and Mo catalysis was proposed to proceed via 1,3- hydration of AMCA. Ru-catalyzed hydration of acetylenic compounds has been studied

extensively, however, there are only two relevant examples that employed free acid acetylenic substrates[11,12] (Scheme 4.7). The first example described $RuCl_3$-catalyzed 1,4-hydration of phenylpropiolic acid **51** in acidic condition. Decarboxylation of the hydrate product led to acetophenone **52** without reported yield.[11]



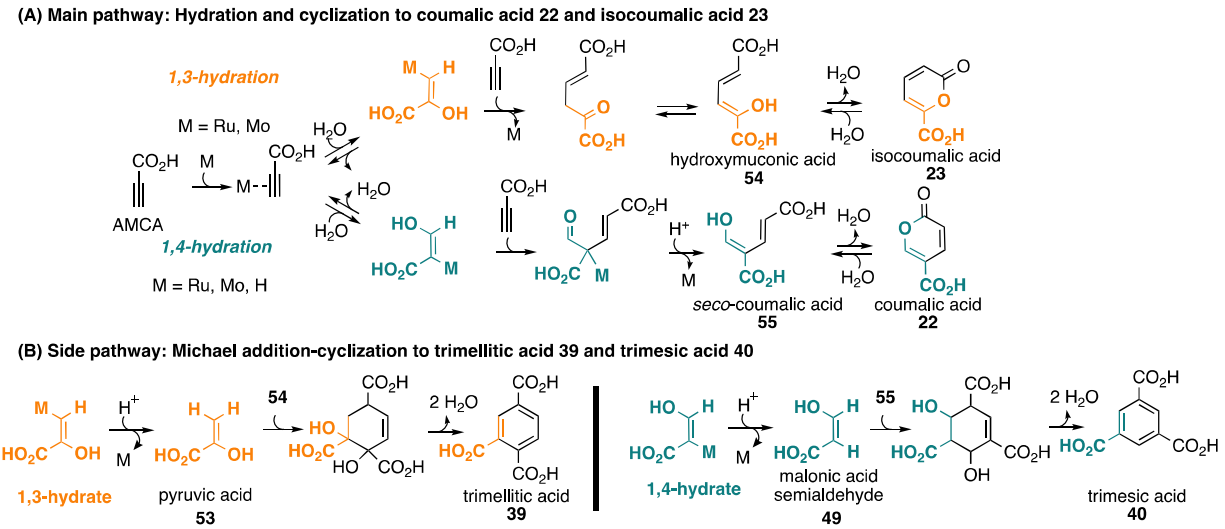
Scheme 4.8. $RuCl_3$-catalyzed 1,4- and 1,3- hydration of acetylene compounds

The second example described 1,3-hydration of AMCA which led to pyruvic acid **53** at 90% yield.[10]



Scheme 4.9. Ru-catalyzed 1,3-hydration of AMCA to pyruvic acid

Replacing $RuCl_3$ by $[RuCl_2(p\text{-cymene})]_2$ in hydration of AMCA also led to a 40% yield of pyruvic acid in water, which indicated that pyruvic acid could play intermediacy role leading to formation of isocoumalic acid as well as trimellitic acid.



Scheme 4.10. Proposed mechanism: 1,3- vs. 1,4-hydration of AMCA

When the metal complex of AMCA is formed in the presence of a catalytic amount of H_2O in the reaction, hydration can occur via a 1,4- or 1,3- hydration pathway to form 1,3-hydrate or 1,4-hydrate respectively (Scheme 4.9A). Following the 1,3-hydration pathway, addition of AMCA to 1,3-hydrate forms hydroxymuconic acid **54** which after intramolecular cyclization/esterification forms isocoumalic acid **23.** On the other hand, addition of AMCA to the 1,4-hydrate forms *seco*-coumalic acid **55**, which can cyclize to form coumalic acid **22**. Trimellitic **39** and trimesic **40** acids formation are side reactions of the main pathways leading to isocoumalic and coumalic acids. The 1,4-hydrate can undergo protodemetallation in the case of $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ and $MoCl_5/AgSbF_6$ catalysis to form malonic acid semialdehyde **49**. A Michael addition-cyclization of and **49** and **55** form cyclohexene **57** which can undergo a dehydration aromatization to form trimesic acid **40** (Scheme 4.9B). Similarly, the 1,3-hydrate can undergo a protodemetallation step to form pyruvic acid **53** (Scheme 6C). Cyclization of pyruvic acid **53** and hydroxymuconic acid **54** formed cyclohexene **56** followed by a dehydration aromatization step to form trimellitic acid **40**.

Addition of diacrylic ether **50** to $RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalysis elevated yield of coumalic acid from 16% to 24% (Table 4.1, entries 1 and 2), which is consistent with malonic acid semialdehyde **49** in a 1,4-hydration pathway and formation of coumalic acid **22** (Scheme 6A). Additional pyruvic acid **53** in $RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalysis undergoes Michael addition-cyclization with hydroxymuconic acid **54**, increasing formation of trimellitic acid **9** from 13% to 23% (Table 3, entry 3) while diminishing the yield of **22** and **23**.

Table 4.1. Impact of pyruvic acid and diacrylic ether on Lewis acid catalysis of AMCA

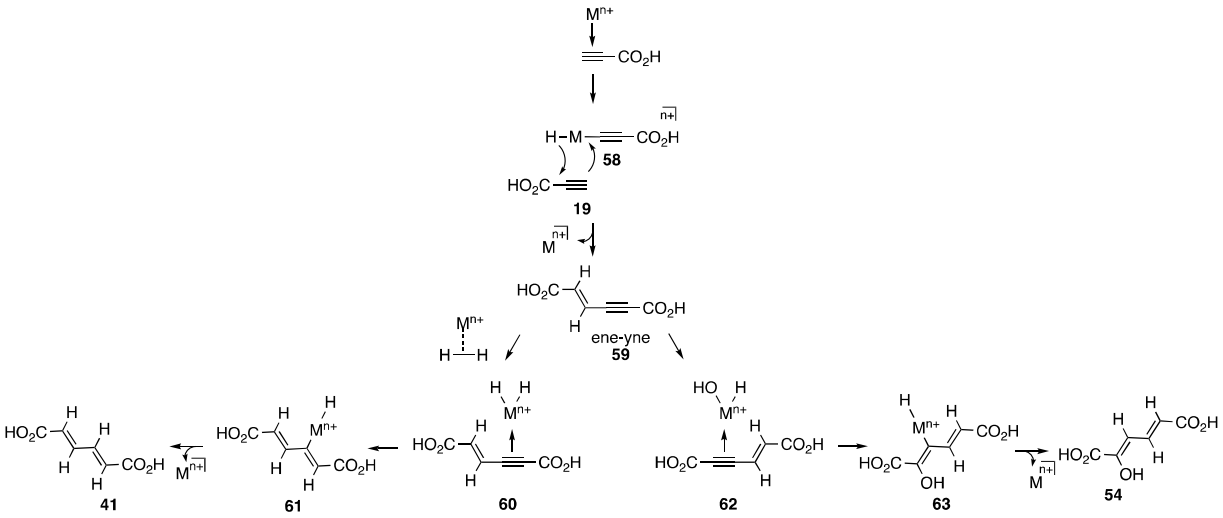
Entry	Cat.	Reaction Condition	Starting Materials	%Yield (mol/mol)			
				22[b,i]	**23**[c,i]	**39**[b,i]	**40**[b,i]
1[d]	[e]$[RuCl_2(p\text{-cymene})]_2$	HOAc	**19**	16	24	13	12
2		80˚C, N_2	**19** + **50**[f]	24	24	12	16
3	[f]$AgSbF_6$	12h	**19** + **53**[f]	8	16	23	9
4[d]	[g]$MoCl_5$ [h]$AgSbF_6$	dioxane	**4**	30	20	10	2
5		100˚C, N_2	**19** + **50**[f]	35	17[j]	6	7[k]
6		4h	**19** + **53**[f]	15	22	4	1[k]

[a]Triplicate run of each entry; yield of **1**, **2, 9** and **10** unaffected by addition of **28** and **35** under conditions mentioned above. [b]Yield determined by HPLC. [c] Yield determined by ^1H NMR. [d] Data taken from **Chapter 3, Table 3.1** for comparison. [e] 5 mol%. [f] 20 mol%. [g] 0.8 mol%. [h] 4.0 mol%. [i] ±1%. [j] ±2%. [k] ±0%.

In $MoCl_5/AgSbF_6$ catalysis, addition of diacrylic ether **50** improves the yield of coumalic acid and trimesic acid while slightly inhibiting formation of isocoumalic and trimellitic acids (Table 4.1, entry 5). To a small extent, addition of pyruvic acid **53** to $MoCl_5/AgSbF_6$ catalysis shifted selectivity of pyrone formation toward isocoumalic acid. The minimal impact of pyruvic acid on $MoCl_5/AgSbF_6$ catalysis suggested that pyruvic acid might not be an intermediate leading to isocoumalic acid in this particular reaction.

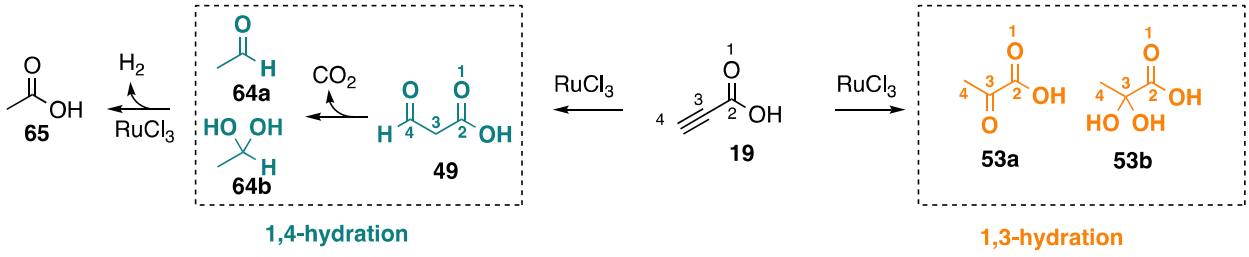
Another side product formed in $MoCl_5/AgSbF_6$ and $AuCl/AgSbF_6$ in TCE was *trans,trans*-muconic acid **41**. Complexation of metal catalyst and AMCA affords metal acetylide **58** (Scheme 10)[12]. Reppe reactions of acetylenes can lead to ene-yne **59**. Mo and Au catalysts are known for

catalyzing homogenous and heterogeneous hydrogenation.[15] Coordination of the alkyne to the metal-H_2 complex **60** is followed by insertion into a metal-hydrogen bond to form hydrogenated product **61** which undergo protodemetallation to afford *trans,trans*-muconic acid **41** (Scheme 10). Instead of complexing with metal-H_2, ene-yne **57** could complex with a metal-hydroxy complex to form **62**. 1,3-hydration of ene-yne complex **62** leads to **63** which can undergo protodemetallation to form hydroxymuconic **54**. Cyclization of **54** led to isocoumalic acid observed in Mo catalysis. This proposed mechanism could explain why addition of pyruvic acid had little to no impact on $MoCl_5/AgSbF_6$ catalysis.



Scheme 4.11. Mechanism to muconic and hydroxymuconic acid in Mo catalysis

4. RuCl3 - catalyzed 1,3-hydration of AMCA – Synthesis of pyruvic acid



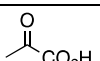
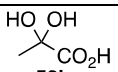
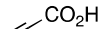
Scheme 4.12. Hydration of AMCA catalyzed by $RuCl_3$

As part of our collaboration with Prof. Karen Draths, we developed a strategy to synthesize lactic acids from methane and CO_2-derived AMCA. While the reduction of pyruvic acid **53** to lactic acids catalyzed by lactate dehydrogenase (LDH) using NADH as co-factor is well-known, there are only two relevant examples to hydration of AMCA.[10.11]

Reaction of 0.25 M concentrations of AMCA with H_2O (Fig 6) catalyzed by $RuCl_3$ (1 mol%) was examined under a variety of solvent conditions (Table 4.2). Products formed (Scheme 4.11) included pyruvic acid **53a**, hydrated pyruvic acid **53b**, acetaldehyde **64a**, hydrated acetaldehyde **64b**, and acetic acid **65**. Pyruvic acid **53a** and its hydrate **53b** are the products of the desired 1,3-addition of H_2O to AMCA (Scheme 4.11). Competing, undesired 1,4-addition of water leads to malonic semialdehyde **49**, which decarboxylates to form acetaldehyde **64a** and acetaldehyde hydrate **64b** (Fig. 6). Wacker-style oxidation of **64a** and **64b** leads to acetic acid **65** (Scheme 4.11).

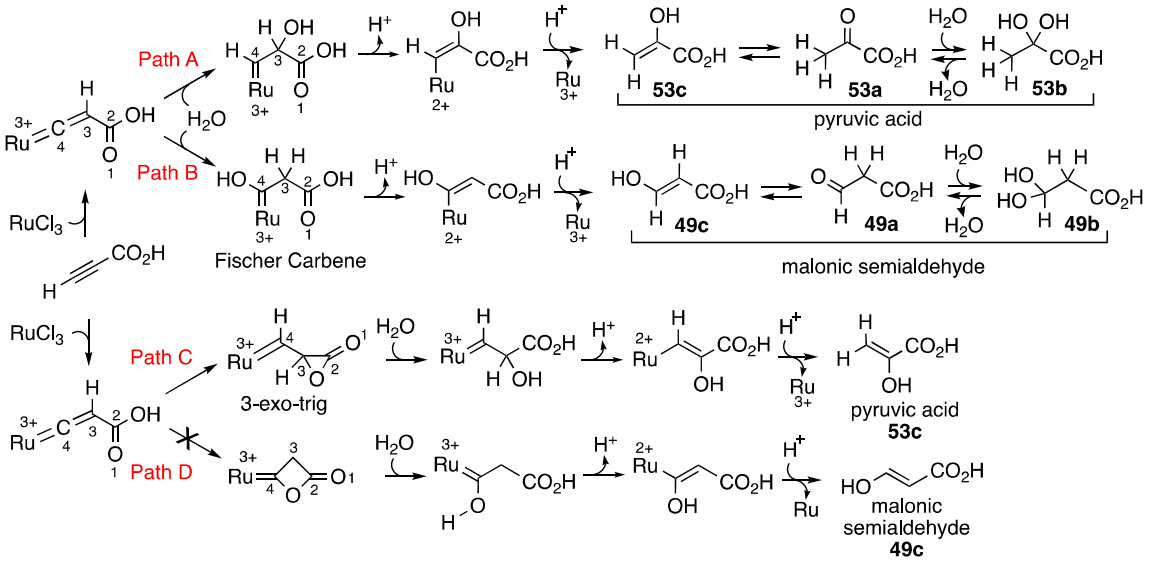
In H_2O as solvent at 100 ºC (entry 1, Table 4.2), $RuCl_3$-catalyzed the hydration of AMCA to produce a 64% combined yield of pyruvate **53a** and its hydrate **53b**. Significant yields of acetaldehyde **64a** (5%), its hydrate **64b** (5%) and acetic acid **65** (15%) were also formed (entry 1, Table 4.2). Only trace quantities of pyruvic acid **53a** and its hydrate **53b** were observed in THF at 65 ºC (entry 2, Table 4.2). Dioxane as solvent at 100 ºC (entry 3, Table 4.2) afforded a combined yield of 51% yield of pyruvic acid **53a** and its hydrate **53b** along with formation of acetic acid **63** (17%). Dioxane at 100 ºC with 10 equiv. of pivalic acid (PvOH) and 1 equiv of H_2O relative to AMCA (entry 4, Table 4.2) afforded a 54% combined yield of pyruvic acid **53a** and its hydrate **53b** along with a 7% yield of acetic acid. The highest combined yields at 92% of pyruvic acid **53a** and its hydrate **53b** were observed when $RuCl_3$-catalyzed hydration was run in HOAc as solvent with 1 equiv. of H_2O relative to AMCA (entry 5, Table 4.2).

Table 4.2. RuCl3-catalyzed hydration of AMCA in various solvents

Entry[a]	Solvent	Temp	 **53a**	 **53b**	 **64a**	 **64b**	 **65**	unreacted  **19**
			%Yield[b] (mol/mol)					
1	H_2O	100 ºC	34	30	5	5	15	0
2[c]	THF	65 ºC	1	1	0	0	0	90
3[c]	dioxane	100 ºC	31	20	0	0	17	0
4[d]	dioxane/ PvOH	100 ºC	48	6	0	0	7	0
5[d]	HOAc	100 ºC	75	17	0	0	-	0

[a] All hydrations contained 0.25 M AMCA and 1 mol% $RuCl_3$ and were run under N_2 for 12 h in solvents containing the indicated number of equivalents of H_2O. [b] Yields determined by ^1H NMR. [c] 10 equiv. of H_2O. [d] 1 equiv. of H_2O.

Hydration of AMCA in HOAc and H_2O catalyzed by $RuCl_3$ likely begins (Scheme 4.13) with formation of a Ru-vinylidine complex (Paths A, B, C, D). Given the preferred attack of protic nucleophiles such as water and alcohols at the carbon atom attached to the metal of metal-vinylidene complexes to yield Fischer carbenes (Path B), malonic semialdehyde **49a-c** would be expected to dominate as the hydration product over formation of pyruvic acid **53a-c** (Scheme 4.13). An extensive literature covers Ru-catalyzed hydration of terminal alkynes. This literature predicts (Scheme 4.13) that Ru-catalyzed hydration of AMCA (a terminal alkyne) would yield the 1,4-hydrate (Path B), which is malonic acid semialdehyde **49a-c** and not the 1,3-hydrate, which is pyruvic acid **53a-c** (Path A). Preferred formation, let alone exclusive formation of pyruvic acid **53a-c**, is an unexpected result.

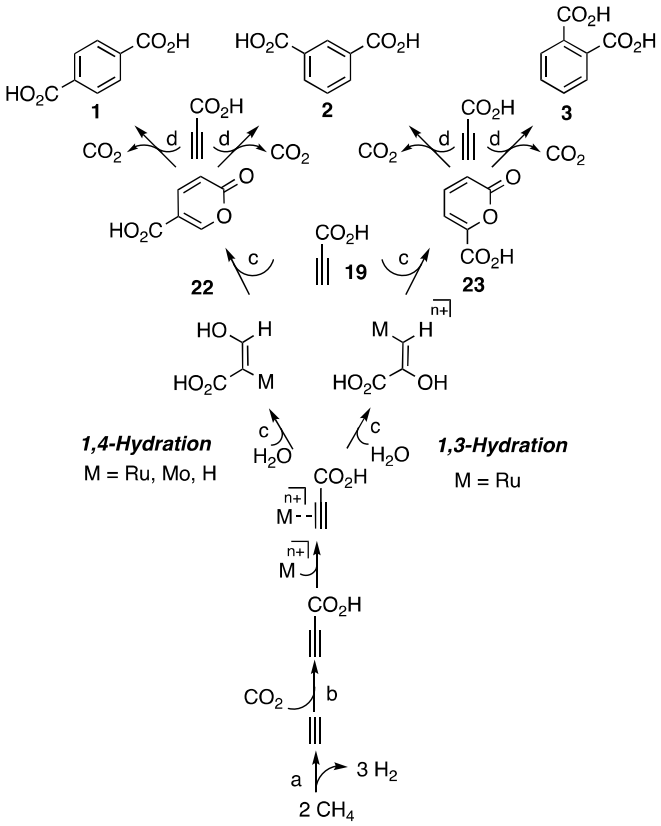


Scheme 4.13. Mechanistic analysis of Ru-catalyzed hydration of AMCA

Exclusive formation of pyruvic acid **53a-c** can possibly be explained (Scheme 4.13) by invoking anchimeric (neighboring group) participation of the C-1 carboxylic acid (Path C, D). Such anchimeric assistance could lead to a three-membered α-lactone (Path C) or a four-membered β-lactone (Path D). Formation of an α-lactone is a 3-exo-trig cyclization (Path C) that is predicted to be a favored cyclization. Formation of a β-lactone is a 4-endo-dig cyclization (Path D) that is predicted by the Alabugin, Gilmore, Manoharan modification of Baldwin's rules to be a disfavored cyclization.[13] Rules for predicting the course of cyclizations involving metal vinylidenes have not yet been formulated using a combination of extensive literature examples and computational analysis. Nonetheless, Baldwin's rules provide an initial hypothesis explaining exclusive formation of pyruvic acid **53a-c** over malonic acid **49a-c** resulting from $RuCl_3$-catalyzed hydration of AMCA in HOAc and H_2O (entry 5, Table 4.2).

Catalysis of methane and CO_2-derived AMCA opens a new route to terephthalic **1**, isophthalic **2** and phthalic **3** acids without the necessity of (a) petroleum-derived xylenes as starting material and (b) sizeable carbon footprint of Amoco-Midcentury oxidation. TfOH catalysis

proceeds via 1,4-hydration of AMCA, allowing a one-step process to highest total combined yield of terephthalic and isophthalic acids. $MoCl_5/AgSbF_6$ and $RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalyzed both 1,3- and 1,4- hydration of AMCA are pivotal intermediates leading to isocoumalic **23** and coumalic **22** acids. Cycloaddition of coumalic **22** and isocoumalic **23** acids with AMCA, catalyzed by $TiCl_4$, afford selective formation of terephthalic **1** and phthalic **3** acids. 1,3-hydration of AMCA catalyzed by $RuCl_3$ also enable an efficient route to methane and CO_2-derived pyruvic acid. Chemoenzymatic step converts pyruvic to lactic acids will establish a sustainable synthesis of poly(lactic acid) PLA.



Scheme 4.14. The pyrone route leading to terephthalic, isophthalic and phthalic acids from methane and carbon dioxide

(a) 1200-3200 ˚C plasma jet, 95%. (b) Cu(I) or Ag(I), ligand, Cs_2CO_3, 1 atm. (c) $MoCl_5$, 0.8 mol%, $AgSbF_6$, 4.0 mol%, dioxane, 100 ˚C, 12h or $[RuCl_2(p\text{-cymene})]_2$, 5.0 mol%, $AgSbF_6$, 20 mol%, HOAc, 80 ˚C, 12 h. (c) $TiCl_4$, 5.0 mol%, toluene, 110 ˚C, 12 h.

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CHAPTER 5: EXPERIMENTAL

1. General

Cycloadditions of acetylenemonocarboxylic acid **19** with isoprene **13**, coumalic acid **22** or isocoumalic acid **23** were run in a 25 mL Titanium Parr series 4590-Bench Top Micro Reactor. ^{1}H NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are reported (in parts per million) relative to $CDCl_3$ (δ = 7.26 ppm) or to DMSO-d_6 (δ = 2.62 ppm). When D_2O was used as the solvent, chemical shifts are reported (in parts per million) relative to sodium 3-(trimethylsilyl)propiomate-2,2,3,3-d_4 (TSP, δ = 0.00 ppm). ^{13}C NMR spectra were recorded at 125 MHz and the shifts for these spectra are reported (in parts per million) relative to $CDCl_3$ (δ = 77.0 ppm). When D_2O was used as the solvent, chemical shifts are reported (in parts per million) relative to sodium 3-(trimethylsilyl)propiomate-2,2,3,3-d_4 (TSP, δ = 0.00 ppm). HPLC spectra were recorded on an Agilent HPLC 1100 chromatograph equipped with an autosampler. $PtCl_2$, $PtCl_4$, $HgCl_2$, Hg_2Cl_2, and $AuCl_3$ were purchased from Strem. All other catalysts used in catalyst screening for conversion of acetylenemonocarboxylic acid to coumalic, isocoumalic, terephthalic, isophthalic, and phthalic acids were purchased from Millipore-Sigma. Acetylenemonocarboxylic acid was purchased from Millipore-Sigma and distilled at 83 mmHg and 85 ˚C before used. Solvents were purified via distillation before used.

2. Product Analyses

Reaction crude was dissolved in 50 mL of *N,N*-dimethylacetamide (DMA) in a 50 mL volumetric flask. Filtration (0.45 μm Whatman filter) was followed by analysis to determine crude yield of terephthalic **1**, isophthalic **2**, phthalic **3**, coumalic **22**, trimellitic **39**, trimesic **40** acids using an Agilent Zorbax SB-C18 column (4.6 x 150 mm, 5 µm particle size) and isocratic elution with 12/88, (v/v); CH_3CN/H_2O (100 mM $NH_4^+HCO_2^-$, pH 2.5). Muconic acid **41** was analyzed using

Grace Alltima Amino column (4.6 x 250 mm, 5 μm particle size) and isocratic elution with 80/20 (v/v); CH_3CN/H_2O (100 mM $NH_4^+HCO_2^-$, pH 2.5). Requisite buffers were prepared with degassed, deionized, distilled water which had been filtered through a DURAPORE 0.45 μm HV filter (Millipore) Terephthalic, isophthalic, phthalic, coumalic, trimellitic and trimesic acids used for the HPLC standard calibration curve are commercially available from Sigma.

Crude yield of isocoumalic acid **23** (δ 6.62, d, 1H) and unreacted acetylenemonocarboxylic acid **19** (δ 4.3, s, 1H) was analyzed by ^{1}H-NMR using maleic acid as standard (δ 6.32, s, 2H) as standard. Crude yield of pyruvic acid **53a** (δ 2.5, s, 3H) and pyruvate hydrate **53b** (δ 1.7, s, 3H) was analyzed by ^{1}H-NMR using TSP as standard. Response factors were determined by adding a known quantity of each compound in 0.7 mL of 10mM maleic acid in DMSO-d_6 or 0.7 mL of 10 mM TSP in D_2O stock solutions.

The concentration of isocoumalic acid **23** was calculated by application of a calibration formula derived from standard taken using laboratory-synthesized isocoumalic acid **23**:

$$[\text{mM}]_{\text{actual}} = 1.03\ [\text{mM}]_{\text{NMR}}$$

The concentration of acetylenemonocarboxylic acid **19** was calculated by application of a calibration formula derived from distilled acetylenemonocarboxylic acid **19**:

$$[\text{mM}]_{\text{actual}} = 0.97\ [\text{mM}]_{\text{NMR}}$$

The total concentration of pyruvic acid **53a** and pyruvic hydrate **53b** were calculated by application of a calibration formula derived from distilled pyruvic acid **53**:

$$[\text{mM}]_{\text{actual}} = 0.95\ [\text{mM}]_{\text{NMR}}$$

3. 4-Methyl-1,4-cyclohexadiene-1-carboxylic acid 16 from cycloaddition of AMCA 19 with isoprene 13

To a solution of propiolic acid **2** (1.0 g, 95%, 13 mmol) in a 25 mL Titanium Parr was added 4.0 mL of toluene and isoprene **3** (7.1 mL, 71 mmol) at rt. The reactor was flushed with N_2 (3x) and then pressurized to 10.3 bar under N_2. The reaction was heated at 60°C for 36 h. After completion of the reaction, the reactor was cooled to rt. The *para* product that crystallized as a white solid was vacuum filtrated and washed with 7 mL of toluene. After one recrystallization, 1.3 g of pure *para*-product was obtained in 67% yield, and 0.7 g of *para/meta* product mixture (1:4.4 *para*:*meta* ratio) was recovered in 29% yield from the mother liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.70 (s, 3H), 2.80 (m, 2H), 2.90 (m, 2H), 5.48 (s, 1H), 7.11 (s, 1H), 11.70 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 22.8, 25.7, 32.0, 118.5, 127.1, 129.2, 139.2, 172.4.

4. Solvent-free conversion of AMCA 19 catalyzed by AuCl/$AgSbF_6$

To a 5 mL one-neck round bottom flask under N_2 was added AuCl (17 mg, 7.2 μmol) and $AgSbF_6$ (25 mg, 7.2 μmol) followed by acetylenemonocarboxylic acid **19** (633 mg, 9.0 mmol). The stirred reaction mixture was heated at 100 ˚C for 5 min under N_2. The crude reaction was cooled to rt, dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column. Products formed in the reaction included: 100 mg of terephthalic acid **1** (20 %), 19 mg of isophthalic acid (4%), 63 mg of coumalic acid **22**, 6 mg of trimesic acid **40** (1%), and 4 mg of trimellitic acid **39** (1%). The amount of unreacted acetylenemonocarboxylic acid **19** was 83 mg (13%). Terephthalic acid **1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 129.7, 131.4, 133.3, 166.9. Isophthalic acid **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, 1H), 8.16 (dd, 2H), 8.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ129.2, 130.4, 131.5, 133.8, 167.3. Coumalic acid **22**: ^{1}H NMR (500

MHz, DMSO-d_6) δ 6.42 (dd, 1H), 7.86 (dd, 1H), 8.42 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 112.2, 114.9, 142.8, 159.1, 160.2, 166.3. Trimellitic acid **39**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, 1H), 8.12 (dd, 1H), 8.21 (d, 1H). Trimesic acid **40**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 3H), 13.42 (br s, 3H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 132.74, 134.43, 166.7.

5. Conversion of AMCA 19 catalyzed by AuCl/$AgSbF_6$ in TCE

To a 5 mL one-neck round bottom flask under N_2 was added AuCl (17 mg, 7.2 μmol) and $AgSbF_6$ (25 mg, 7.2 μmol) followed by addition of TCE (1.7 mL). Acetylenemonocarboxylic acid **19** (633 mg, 9.0 mmol) was added to the reaction mixture. The stirred reaction mixture was heated at 100 ˚C for 12h under N_2. The crude reaction was cooled to rt, dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column. Products formed in the reaction included: 20 mg of terephthalic acid **1** (4%), 9 mg of isophthalic acid **2** (2%), 50 mg of coumalic acid **22** (8%), 6 mg of trimesic acid **40** (1%), 5 mg of trimellitic acid **39** (1%), and 75 mg of muconic acid **41** (12%). The amount of unreacted acetylenemonocarboxylic acid **19** was 63 mg (10%). Terephthalic acid **1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 129.7, 131.4, 133.3, 166.9. Isophthalic acid **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, 1H), 8.16 (dd, 2H), 8.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ129.2, 130.4, 131.5, 133.8, 167.3. Coumalic acid **22**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.42 (dd, 1H), 7.86 (dd, 1H), 8.42 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 112.2, 114.9, 142.8, 159.1, 160.2, 166.3. Trimellitic acid **39**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, 1H), 8.12 (dd, 1H), 8.21 (d, 1H). Trimesic acid **40**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 3H), 13.42 (br s, 3H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 132.74, 134.43, 166.7. Muconic acid **11**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.30 (ddd, 2H), 7.27 (ddd, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 129.6, 141.5, 167.4.

6. Solvent-free conversion of AMCA 19 catalyzed by $MoCl_5/AgSbF_6$

To a 5 mL one-neck round bottom flask under N_2 was added $MoCl_5$ (20 mg, 7.2 μmol) and $AgSbF_6$ (140 mg, 36 μmol) followed by acetylenemonocarboxylic acid **19** (633 mg, 9.0 mmol). The stirred reaction mixture was heated at 50 ˚C for 1h under N_2. The crude reaction was cooled to rt, dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using Agilent Zorbax SB-C18 and Grace Alltima Amino columns. Products formed in the reaction included: 5 mg of terephthalic acid **1** (1%), 4 mg of isophthalic acid **2** (1%), 151 mg of coumalic acid **22** (24%), 76 mg of isocoumalic acid **23** (12%), 70 mg of trimellitic acid **39** (11%), 12 mg of trimesic acid **40** (2%), 73 mg of muconic acid **41** (11%). The unreacted acetylenemonocarboxylic acid **19** was 43 mg (7%). Terephthalic acid **1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 129.7, 131.4, 133.3, 166.9. Isophthalic acid **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, 1H), 8.16 (dd, 2H), 8.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ129.2, 130.4, 131.5, 133.8, 167.3. Coumalic acid **22**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.42 (dd, 1H), 7.86 (dd, 1H), 8.42 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 112.2, 114.9, 142.8, 159.1, 160.2, 166.3. Isocoumalic acid **23**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.62 (d, 1H), 7.12 (d, 1H), 7.67 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 110.4, 120.3, 143.9, 149.9, 160.4, 160.9. Trimellitic acid **39**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, 1H), 8.12 (dd, 1H), 8.21 (d, 1H). Trimesic acid **40**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 3H), 13.42 (br s, 3H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 132.74, 134.43, 166.7. Muconic acid **41**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.30 (ddd, 2H), 7.27 (ddd, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 129.6, 141.5, 167.4.

7. Conversion of AMCA 19 catalyzed by $MoCl_5/AgSbF_6$ in dioxane

To a 10 mL one-neck round bottom flask under N_2 was added $MoCl_5$ (20 mg, 7.2 μmol) and $AgSbF_6$ (140 mg, 36 μmol) followed by addition of dioxane (2.5 mL). The reaction turned dark green and white precipitate formed immediately. After 5 minutes, acetylenemonocarboxylic acid **19** (633 mg, 9.0 mmol) was added to the reaction mixture. The stirred reaction mixture was heated at 100 ˚C for 4h. The crude reaction was cooled to rt, dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18. Products formed in the reaction included: 191 mg of coumalic acid **22** (30%), 76 mg of isocoumalic acid **23** (20%), 63 mg of trimellitic acid **39** (10%), 11 mg of trimesic acid **40** (2%), 37 mg of muconic acid **41** (6%). The unreacted acetylenemonocarboxylic acid **19** was 56 mg (9%).

8. Conversion of AMCA 19 catalyzed by $RuCl_2(p\text{-cymene})]_2/AgSbF_6$ in dioxane/PvOH

To a 25 mL one-neck round bottom flask under N_2 was added $[RuCl_2(p\text{-cymene})]_2$ (77 mg, 12.5 μmol) and $AgSbF_6$ (170 mg, 50 μmol) followed by addition of dioxane (2.5 mL) and pivalic acid (1.02 g, 25 mmol). The reaction turned bright orange and white precipitate formed immediately. After 10 minutes, acetylenemonocarboxylic acid **19** (170 mg, 2.5 mmol) was added to the reaction mixture. The stirred reaction mixture heated at 80 ˚C for 12h. The crude reaction was cooled to rt, dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using Agilent Zorbax SB-C18 and Grace Alltima Amino columns. Products formed in the reaction included: 10 mg of coumalic acid **22** (6%), 42 mg of isocoumalic acid **23** (24%), 1.7 mg of trimellitic acid **39** (1%), and 2 mg of trimesic acid **40** (1%). Coumalic acid **22**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.42 (dd, 1H), 7.86 (dd, 1H), 8.42 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 112.2, 114.9, 142.8, 159.1, 160.2, 166.3. Isocoumalic acid **23**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.62 (d, 1H), 7.12 (d, 1H), 7.67 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 110.4, 120.3, 143.9, 149.9, 160.4, 160.9.

Trimellitic acid **39**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, 1H), 8.12 (dd, 1H), 8.21 (d, 1H). Trimesic acid **40**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 3H), 13.42 (br s, 3H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 132.74, 134.43, 166.7.

9. Conversion of AMCA 19 catalyzed by $RuCl_2$(p-cymene)]$_2$/$AgSbF_6$ in HOAc

To a 25 mL one-neck round bottom flask under N_2 was added [$RuCl_2$(*p*-cymene)]$_2$ (77 mg, 12.5 μmol) and $AgSbF_6$ (170 mg, 50 μmol) followed by addition of HOAc (4.0 mL). The reaction turned bright orange and white precipitate formed immediately. After 10 minutes, acetylenemonocarboxylic acid **19** (170 mg, 2.5 mmol) was added to the reaction mixture. The stirred reaction mixture was heated at 80 ˚C for 12 h under N_2. The crude reaction was cooled to rt, dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column. Products formed in the reaction included: 4 mg of terephthalic acid **1** (3%), 16 mg of isophthalic acid **2** (12%), 27 mg of coumalic acid **22** (16%), 41 mg of isocoumalic acid **23** (24%), 22 mg of trimellitic acid **39** (13%), 20 mg of trimesic acid **40** (12%). Terephthalic acid **1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 129.7, 131.4, 133.3, 166.9. Isophthalic acid **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, 1H), 8.16 (dd, 2H), 8.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ129.2, 130.4, 131.5, 133.8, 167.3. Coumalic acid **22**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.42 (dd, 1H), 7.86 (dd, 1H), 8.42 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 112.2, 114.9, 142.8, 159.1, 160.2, 166.3. Isocoumalic acid **23**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.62 (d, 1H), 7.12 (d, 1H), 7.67 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 110.4, 120.3, 143.9, 149.9, 160.4, 160.9. Trimellitic acid **39**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, 1H), 8.12 (dd, 1H), 8.21 (d, 1H). Trimesic acid **40**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 3H), 13.42 (br s, 3H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 132.74, 134.43, 166.7.

10. Solvent-free conversion of AMCA 19 catalyzed by TfOH

To a 25 mL one-neck round bottom flask under Ar was added acetylenemonocarboxylic acid **19** (1.1 g, 15.7 mmol). TfOH (208 μL, 350 mg, 0.24 mmol) was added dropwise over 3 min. The stirred reaction mixture heated at 100˚C for 4h until solidified. Temperature was increased to 110˚C for 12h. The crude reaction was cooled to rt, dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column. Products formed in the reaction included: 165 mg of terephthalic acid **1** (19%), 173 mg of isophthalic acid **2** (20%), 165 mg of coumalic acid **22** (15%), and 66 mg of trimesic acid **40** (62%). Unreacted acetylenemonocarboxylic acid **19** was 132 mg (12%). Terephthalic acid **1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 129.7, 131.4, 133.3, 166.9. Isophthalic acid **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, 1H), 8.16 (dd, 2H), 8.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ129.2, 130.4, 131.5, 133.8, 167.3. Coumalic acid **22**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.42 (dd, 1H), 7.86 (dd, 1H), 8.42 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 112.2, 114.9, 142.8, 159.1, 160.2, 166.3. Trimesic acid **40**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 3H), 13.42 (br s, 3H), ^{13}C NMR (125 MHz, DMSO-d_6) δ 132.74, 134.43, 166.7.

11. Isolation of terephthalic acid 1 and isophthalic 2 from the solvent-free conversion of AMCA 19 catalyzed by TfOH

To a 50 mL one-neck round bottom flask under Ar was added acetylenemonocarboxylic acid **19** (2.2 g, 31.4 mmol). TfOH (416 μL, 700 mg, 0.48 mmol) was added dropwise over 10 min. The stirred reaction mixture heated at 100˚C for 4h until solidified. Temperature was increased to 110˚C for 16h. The crude reaction was cooled to rt and suspended in 50 mL of ice water in a 100 mL beaker, and a white solid precipitated from the solution. This white solid was collected by filtration and dried overnight *in vacuo*. Suspension of the solid in 30 mL EtOAc followed by a

filtration removed terephthalic acid **1** (890 mg, 17%). The filtrated was concentrated and dried to afford isophthalic acid **2** (1.09 g, 21%) and trimesic acid (350 mg, 7%).

12. Conversion of AMCA 19 to coumalic acid 22 catalyzed by TfOH in TCE

To a 50 mL one neck round bottom flask under Ar was added acetylenemonocarboxylic acid **19** (2.2 g, 31.4 mmol), followed by addition of TCE (5.5 mL). TfOH (555 µL, 0.94 g, 6.3 mmol, 20 mol%) was added dropwise to the reaction mixture over 5 min. The stirred reaction mixture was heated at 80˚C for 28h. The crude product was filtered and washed with cold EtOAc to afford 1.3 g of coumalic acid **22** (61%). The filtrate was extracted with EtOAc (100 mL x3), and the combined organic layer was dried over Na_2SO_4. The organic layer was concentrated to yield 310 mg of coumalic acid **22** (14%). The combined coumalic acid **22** was recrystallized in dry MeOH to form off white crystal (1.3 g, 60%), mp(dec): 234-236˚C.

13. Conversion of AMCA 19 to diacrylic ether 50 catalyzed by TfOH in TCE

To a 250 mL three-neck round bottom flask under Ar was added acetylenemonocarboxylic acid **4** (2.1 g, 30 mmol), followed by addition of TCE (131.2 mL). TfOH (5.3 mL, 9.0 g, 60 mmol) was added dropwise to the stirred reaction mixture over 20 min, followed by filtered DI H_2O (5.4 µL, 1 mol%). The reaction was heated at 100˚C for 20h under N_2. The crude product was isolated from the reaction mixture via extraction with cold EtOAc (4 x 250 mL). The combined organic layer was dried over Na_2SO_4 overnight. EtOAc was removed and the crude product was dried in vacuo, followed by recrystallization in hot hexanes to give diacrylic ether **50** in the form of white rod-shaped crystal (1.8 g, 85%), mp:85-88˚C. Anal. calc.: C: 45.56%, H: 3.83%. Found: C: 45.05%, H: 3.95%.

14. Uncatalyzed cycloaddition of isocoumalic acid 23 and AMCA 19

Toluene (6.0 mL), isocoumalic acid **23** (168 mg, 1.2 mmol), and acetylenemonocarboxylic acid **19** (544 μL, 8.4 mmol) were added to a 25 mL Ti Parr reactor. The reactor was flushed with N_2 (3x) and then pressurized to 10 bar under N_2. The reaction was heated at 110 ˚C for 12h. The crude reaction was cooled to rt slowly. The crude product mixture was collected via vacuum filtration and dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column in which the formation of phthalic acid **3** was 8 mg (4%) and the unreacted isocoumalic acid **23** was 159 mg (94%). Phthalic acid **3**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59 (m, 2H), 7.66 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 128.8, 131.4, 133.2, 169.0. Isophthalic acid **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, 1H), 8.16 (dd, 2H), 8.47 (s, 1H), 13.1 (br s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 129.2, 130.4, 131.5, 133.8, 167.3.

15. $TiCl_4$-catalyzed cycloaddition of isocoumalic acid 23 and AMCA 19

Toluene (3.0 mL), isocoumalic acid **23** (168 mg, 1.2 mmol), $TiCl_4$ (6.5 μL, 0.06 mmol), and acetylenemonocarboxylic acid **19** (544 μL, 8.4 mmol) were added to 25 mL Parr reactor. The reactor was flushed with N_2 (3x) and then pressurized to 10 bar under N_2. The reaction was heated at 110 ˚C for 12h. The crude reaction was cooled to rt slowly. The crude product mixture was collected via vacuum filtration and dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column, in which the formation of phthalic acid **3** was 149 mg (75%) and the formation of isophthalic acid **2** was 30 mg (15%). The unreacted isocoumalic acid **23** was 11 mg (6%).

16. Isolation of phthalic acid 3 and isophthalic acid 2 from the $TiCl_4$-catalyzed cycloaddition of isocoumalic 23 and AMCA 19

Toluene (6.0 mL), isocoumalic acid **6** (336 mg, 2.4 mmol), $TiCl_4$ (13 μL, 0.12 mmol), and acetylenemonocarboxylic acid **19** (1090 μL, 16.8 mmol) were added to 25 mL Parr reactor. The reactor was flushed with N_2 (3x) and then pressurized to 10 bar under N_2. The reaction was heated at 110 ˚C for 24h. The crude reaction was cooled to rt slowly. The crude product mixture was collected via vacuum filtration and dried overnight *in vacuo* at 50˚C to convert phthalic acid **3** to phthalic anhydride. The product mixture was added into 10 mL of diethyl ether in a 50 mL beaker, and a white solid precipitate from the solution. The solid was collected by filtration to afford 45 mg of isophthalic acid **2** (11%). The filtrate was concentrated to afford a white solid containing isocoumalic acid **6** (14 mg, 4%) and phthalic anhydride (255 mg, 72%). The solid was dissolved in 10 mL of hot water, recrystallized at rt, filtered and dried to afford phthalic acid **3** (278 mg, 70%).

17. Uncatalyzed cycloaddition of coumalic acid 22 and AMCA 19

Toluene (6.0 mL), coumalic acid **5** (140 mg, 1.0 mmol), and acetylenemonocarboxylic acid **19** (195 μL, 3.0 mmol) were added to a 25 mL Ti Parr reactor. The reactor was flushed with N_2 (3x) and then pressurized to 10 bar under N_2. The reaction was heated at 110 ˚C for 12 h. The crude product mixture was collected via vacuum filtration and dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column, in which the formation of terephthalic acid **1** was 33 mg (20%) and the formation of isophthalic acid **2** was 25 mg (15%). The unreacted coumalic acid **22** was 84 mg (60%). Terephthalic acid **1**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04 (s, 4H), 13.3 (br s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 129.7, 131.4, 133.3, 166.9. Isophthalic acid **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, 1H), 8.16

(dd, 2H), 8.47 (s, 1H), 13.2 (br s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 129.2, 130.4, 131.5, 133.8, 167.3.

18. $TiCl_4$-catalyzed cycloaddition of coumalic acid 22 and AMCA 19

Toluene (6.0 mL), coumalic acid **5** (140, 1.0 mmol), $TiCl_4$ (6.5 μL, 0.06 mmol), and acetylenemonocarboxylic acid **4** (195 μL, 3.0 mmol) were added to a 25 mL Ti Parr reactor. The reactor was flushed with N_2 (3x) and then pressurized to 10 bar under N_2. The reaction was heated at 110 ˚C for 12 h. The crude product mixture was collected via vacuum filtration and dissolved in 50 mL of DMA in a 50 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column, in which the formation of terephthalic acid **1** was 80 mg (48%) and the formation of isophthalic acid **2** was 33 mg (20%). The unreacted coumalic acid **22** was 23 mg (16%).

19. Synthesis of methyl 4-carbomethoxy-5-methoxy-penta-2E, 4Z-dienoate 45

45 was prepared using a modified procedure Nantz and Fuch.[1] To a solution of coumalic acid **22** (500 mg, 3.5 mmol) in 9 mL of trimethylorthoformate and 3 mL of methanol was added conc. H_2SO_4 (0.6 mL, 11 mmol) at room temperature. The reaction mixture was refluxed for 18 h after which it was cooled to 0˚C and diluted with 10 mL of EtOAc. The solution was then extracted with sat. $NaHCO_3$. The organic layer was then washed with brine and dried over Na_2SO_4. EtOAc was removed *in vacuo* to yield crude products which were separated by plug filtration (4:1, $CHCl_3$: hexane) to yield **26** (0.5 g, 71% yield). mp 54-56˚C.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.59 (d, J = 16.2 Hz, 1H), 6.64 (d, J = 16.2 Hz, 1H), 4.30 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 166.6, 164.7, 134.4, 119.3, 106.8, 63.0, 51.5, 51.3. Anal. calcd for $C_9H_{12}O_5$: C, 53.98%, H, 6.04%. Found: C, 54.48%, H, 6.24%.

20. Cycloaromatization of methyl 4-carbomethoxy-5-methoxy-penta-2E, 4Z-dienoate 45 and methyl acetylenemonocarboxylate to trimethyl trimesate 48

To a 5 mL one neck round bottom flask was added **45** (100 mg, 0.5 mmol) and methyl acetylenemonocarboxylate (47 mg, 0.56 mmol). TfOH (7.5 μL, 15 mol%) was added to the reaction mixture under Ar at rt. The stirred reaction mixture was heated under N_2 at 100 ˚C for 2h. After cooled down to rt, the reaction mixture was dissolved in 5 mL of ACN in a 5 mL volumetric flask to be analyzed by GC-HP5 column, in which the formation of trimethyl trimesate was 50 mg (40%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.62, 133.48, 131.0, 52.97.

21. Solvent-free conversion of diacrylic ether 50 to coumalic acid 22 catalyzed by TfOH

To a 5 mL one neck round bottom flask was added diacrylic ether **30** (47 mg, 0.3 mmol). TfOH (5.5 μL, 20 mol%) was added to the reaction mixture under Ar. The stirred reaction mixture was heated under N_2 at 100 ˚C for 2h. After cooled down to rt, the crude product was dissolved in 25 mL of DMA in a 25 mL volumetric flask, followed by HPLC analysis using the Agilent Zorbax SB-C18 column, in which the formation of terephthalic acid **1** was 3 mg (11%) and the formation of isophthalic acid **2** was 2 mg (8%). The unreacted coumalic acid **22** was 23 mg (55%).

22. Synthesis of isocoumalic acid 23 from diethyl oxalate and ethyl crotonate

Chemically synthesized isocoumalic acid **23** was used to facilitate cycloaddition of isocoumalic acid **23** and acetylenemonocarboxylic acid **19**. The synthesis is a two-step process from commercially available ethyl crotonate and diethyl oxalate. Procedures of these reactions are provided below. [2,3]

22.a. Diethyl-2-hydroxy-2,4-hexadien-1,6-dioate

The diester was prepared using a modified procedure of Lapworth[2] and Dawson.[3] Potassium (4.1 g, 0.11 mol) was slowly added to *tert*-butyl alcohol (40 mL) under Nitrogen. The reaction mixture was stirred for 1 h. Diethyl ether (25 mL) was added to the mixture and stirred for 15 min at 0 ˚C. A solution of diethyl oxalate (14.0 mL, 0.1 mol) in 10 mL of diethyl ether was added slowly at the same temperature and stirred for 1h. Ethyl crotonate (12.5 mL, 0.1 mol) in 10 mL of diethyl ether was added slowly to the reaction mixture at the same temperature. The reaction was kept at 0˚C for 6h to allow precipitation of the potassium salt of the diester. Crude product was collected by filtration and then dissolved in 400 mL of ice water. Glacial acetic acid (20 mL) was added and the resultant precipitate was collected by filtration and washed with cold water to give diester in the form of a yellow crystalline powder (16.3 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, 3H), 1.34 (t, 3H), 4.20 (q, 2H), 4.32 (q, 2H), 5.96 (d, 1H), 6.26 (d, 1H), 6.43 (br s, 1H), 7.61 (dd, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 60.1, 63.4, 108.4, 123.2, 136.7, 143.7, 164.5, 166.4

22.b. Isocoumalic acid 23

Diethyl 2-hydroxy-2,4-hexadien-1,6-dioate (1.1 g, 0.5 mmol) was dissolved in 10 mL of water, 8 mL of glacial acetic acid, and 2 mL of concentrated H_2SO_4. The reaction mixture was heated up to 95˚C for 3h. Reaction mixture was cooled down to rt, and solvents was removed to stimulate precipitation of product. Product was collected by filtration, and recrystallized in H_2O (0.6g, 84%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.62 (d, 1H), 7.12 (d, 1H), 7.67 (dd, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 110.4, 120.3, 143.9, 149.9, 160.4, 160.9.

23. General procedure for screening of metal catalysts for conversion of AMCA 19 to terephthalic 1, isophthalic 2, coumalic 22, and isocoumalic 23 acids

Screening of catalysts for the conversion of acetylenemonocarboxylic acid **19** to terephthalic, isophthalic, coumalic and isocoumalic acids employed a 5 mL flask equipped with a magnetic stir bar that was charged with a metal catalyst MX_n (26 μmol) and a AgX (n x 26 μmol) (X = OTf, OTFA, SbF_6, PF_6, BF_4, OAc). A solvent (0.8 mL) was then added if necessary. Acetylenemonocarboxylic acid **19** (211 mg, 3 mmol) was added dropwise via syringe. A color change was often observed immediately after addition of acetylenemonocarboxylic acid **19** to the catalysts. The stirred reaction mixture was run for 12 h under N_2 at an indicated temperature. The crude reaction mixture was then dissolved in 25 mL DMA in a 25 mL volumetric flask, followed by NMR and HPLC analysis. Catalysts, solvents, temperatures and data are included in Appendix A for each reaction.

24. General procedure for solvent screening for hydration of acetylenemonocarboxylic acid 19 catalyzed by $RuCl_3$

Screening of solvents for the hydration of acetylenemonocarboxylic acid **19** employed a 50 mL flask equipped with a magnetic stir bar that was charged with $RuCl_3$ (11 mg, 50 μmol). An organic solvent or H_2O (20 mL) was added to the flask to form black suspension. When an organic solvent was employed for the reaction, H_2O (90 μL, 5 mmol) was added to the reaction mixture. Acetylenemonocarboxylic acid **19** (350 mg, 5 mmol) was added to the reaction mixture. The stirred reaction mixture was run under N_2 for 12 h at 100 ˚C. When THF was used, the reaction temperature was 65 ˚C. The reaction was cooled down to rt. A 0.5 mL aliquot of the reaction mixture was used to NMR analysis using 10 mM TSP in D_2O as standard. Data for each reaction is included in Chapter 4, Table 4.2.

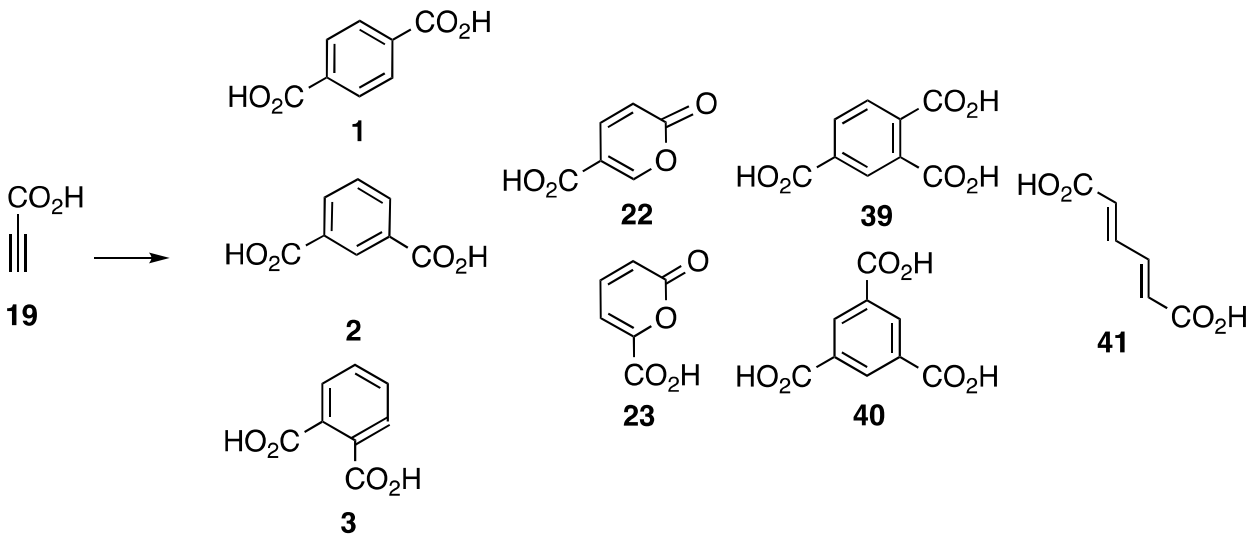
25. Isolation of pyruvic acid 53 from the hydration of AMCA 19 catalyzed by $RuCl_3$

To a 50 mL two neck flask was added 11 mg of $RuCl_3.xH_2O$ (22 mg, 1 mol%) and 40 mL of DI H_2O. Acetylenemonocarboxylic acid **19** (620 μL, 10 mmol) was added to the reaction mixture at rt. The reaction was heated under N_2 at 100 ˚C for 12 h. After cooled down to rt, pyruvic acid was isolated via extraction using MTBE (60 mL x 3). Removal of MTBE *in vacuo* yielded 484 mg (55%) of pyruvic acid **53**. Pyruvic acid **53**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.5 (s, 3H), 13.75 (br s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.0, 167.7, 194.0.

APPENDICES

APPENDIX A: CATALYST SCREENING DATA

Screening of Catalysts for Conversion of AMCA to pyrone and aromatic products



Scheme 5.1. Conversion of AMCA to pyrone and aromatic products

Table 5.1. Acid catalyzed conversion of AMCA to pyrone and aromatic products

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
Group IV																	
1	200 mg	$TiCp_2Cl_2$	0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	56	57
2	200 mg	$TiCp_2Cl_2$	0.8	neat	--	50	12 h	0	0	0	1	0	0	0	0	25	26
3	200 mg	$TiCp_2Cl_2$	0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	15	17
4	200 mg	$TiCp_2Cl_2$	0.8	neat	--	100	12 h	0	0	0	2	0	0	0	0	10	12
5	200 mg	$TiCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	0	0	1	0	0	88	89
6	200 mg	$TiCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	0	0	8	0	1	0	0	35	44
7	200 mg	$TiCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	0	1	0	14	0	2	1	0	20	38
8	200 mg	$TiCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	0	5	0	16	0	3	0	0	15	39
9	200 mg	$TiCp_2Cl_2$ $AgSbF_6$	0.8 1.6	DCE	25	100	12 h	0	2	0	28	0	1	0	0	15	46
10	200 mg	$TiCp_2Cl_2$ $AgSbF_6$	0.8 1.6	dioxane	25	100	12 h	0	0	0	0	0	0	0	0	15	15

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
11	200 mg	$ZrCp_2Cl_2$	0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	50	51
12	200 mg	$ZrCp_2Cl_2$	0.8	neat	--	50	12 h	0	0	0	1	0	0	0	0	35	36
13	200 mg	$ZrCp_2Cl_2$	0.8	neat	--	75	12 h	0	0	0	1	0	0	0	0	20	21
14	200 mg	$ZrCp_2Cl_2$	0.8	neat	--	100	12 h	0	0	0	3	0	0	0	0	7	10
15	200 mg	$ZrCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	0	0	1	0	0	85	86
16	200 mg	$ZrCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	0	0	0	0	1	0	0	53	54
17	200 mg	$ZrCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	0	0	0	2	0	2	1	0	20	25
18	200 mg	$ZrCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	1	5	0	16	0	3	0	0	15	40
19	200 mg	$ZrCp_2Cl_2$ $AgSbF_6$	0.8 1.6	DCE	25	100	12 h	1	2	0	28	0	1	0	0	15	47
20	200 mg	$ZrCp_2Cl_2$ $AgSbF_6$	0.8 1.6	dioxane	25	100	12 h	1	0	0	0	0	0	0	0	15	16
21	200 mg	$HfCp_2Cl_2$	0.8	neat	--	21	12 h	1	0	0	1	0	1	1	0	40	44

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
22	200 mg	HfCp2Cl2	0.8	neat	--	50	12 h	4	0	0	1	0	2	1	0	32	40
23	200 mg	$HfCp_2Cl_2$	0.8	neat	--	75	12 h	4	0	0	3	0	3	1	0	20	31
24	200 mg	$HfCp_2Cl_2$	0.8	neat	--	100	12 h	4	0	0	0	0	0	1	0	15	20
25	200 mg	$HfCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	3	0	1	0	0	30	34
26	200 mg	$HfCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	0	0	6	0	2	1	0	24	33
27	200 mg	$HfCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	0	1	0	3	0	3	0	0	13	20
28	200 mg	$HfCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	1	3	0	18	0	1	0	0	5	28
Group VI																	
29	200 mg	$CrCl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	0	0	1	0	0	49	50
30	200 mg	$CrCl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	0	0	0	0	1	0	0	30	31
31	200 mg	$CrCl_2$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	0	0	0	0	0	1	0	0	21	22

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
32	200 mg	$CrCl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	0	0	0	0	0	2	0	0	10	12
33	200 mg	$CrCl_3$ $AgSbF_6$	0.8 2.4	neat	--	21	12 h	0	0	0	0	0	1	0	0	15	16
34	200 mg	$CrCl_3$ $AgSbF_6$	0.8 2.4	neat	--	50	12 h	0	0	0	0	0	1	0	0	10	11
35	200 mg	$CrCl_3$ $AgSbF_6$	0.8 2.4	neat	--	75	12 h	0	0	0	0	0	3	0	0	7	10
36	200 mg	$CrCl_3$ $AgSbF_6$	0.8 2.4	neat	--	100	12 h	0	0	0	0	0	2	0	0	0	2
37	200 mg	$MoCl_3$	0.8	neat	--	21	12 h	0	0	0	0	0	1	0	0	38	39
38	200 mg	$MoCl_3$	0.8	neat	--	50	12 h	0	0	0	0	0	1	0	0	21	22
39	200 mg	$MoCl_3$	0.8	neat	--	75	12 h	0	0	0	0	0	1	0	0	7	8
40	200 mg	$MoCl_3$	0.8	neat	--	100	12 h	0	0	0	3	0	1	0	0	0	4
41	200 mg	$MoCl_3$ $AgSbF_6$	0.8 2.4	neat	--	21	12 h	1	1	0	4	0	1	0	0	20	27
42	200 mg	$MoCl_3$ $AgSbF_6$	0.8 2.4	neat	--	50	12 h	0	0	0	0	0	1	0	0	10	11

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
43	200 mg	$MoCl_3$ $AgSbF_6$	0.8 2.4	neat	--	75	12 h	1	2	0	6	0	1	0	0	5	15
44	200 mg	$MoCl_3$ $AgSbF_6$	0.8 2.4	neat	--	100	12 h	1	3	0	7	0	1	0	0	3	15
45	200 mg	$MoCl_5$	0.8	neat	--	21	12 h	0	0	0	0	0	0	2	1	19	22
46	200 mg	$MoCl_5$	0.8	neat	--	50	12 h	0	0	0	0	0	1	2	2	19	24
47	200 mg	$MoCl_5$	0.8	neat	--	75	12 h	0	1	0	0	0	1	2	4	27	35
48	200 mg	$MoCl_5$	0.8	neat	--	100	12 h	2	2	0	2	1	2	8	11	17	45
49	200 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	neat	--	21	12 h	1	0	0	16	0	0	5	8	16	46
50	200 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	neat	--	50	1 h	1	1	0	21	7	1	10	11	13	65
51	200 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	neat	--	75	1 h	1	2	0	19	8	1	11	10	7	59
52	200 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	neat	--	100	1 h	5	8	0	16	8	2	13	9	7	68
53	600 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	neat	--	50	1 h	1	1	0	22	13	2	11	11	10	71

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
54	200 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	DCE	25	100	12 h	1	1	0	19	10	2	11	13	9	66
55	200 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	dioxane	25	100	12 h	1	1	0	29	17	2	10	6	9	75
56	400 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	dioxane	25	100	12 h	0	0	0	30	20	2	11	6	10	79
57	400 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	dioxane	5	100	12 h	0	0	0	0	0	0	0	3	20	23
58	400 mg	$MoCl_5$ $AgSbF_6$	0.8 4.0	dioxane	50	100	12 h	0	0	0	24	15	2	8	7	7	63
59	200 mg	$MoCp_2Cl_2$	0.8	neat	--	100	12 h	0	0	0	2	0	1	1	15	8	27
60	200 mg	$MoCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	1	0	1	1	1	25	29
61	200 mg	$MoCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	0	0	7	0	1	4	10	16	38
62	200 mg	$MoCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	1	1	0	14	9	1	8	22	13	69
63	200 mg	$MoCp_2Cl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	1	1	0	14	10	1	7	12	5	51
64	200 mg	WCl_4	0.8	neat	--	21	12 h	0	0	0	1	0	1	1	0	34	37

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
65	200 mg	WCl_4	0.8	neat	--	50	12 h	0	0	0	2	0	1	1	0	15	19
66	200 mg	WCl_4	0.8	neat	--	75	12 h	0	0	0	2	0	1	1	0	10	14
67	200 mg	WCl_4	0.8	neat	--	100	12 h	0	0	0	3	0	1	1	0	7	12
68	200 mg	WCl_4 $AgSbF_6$	0.8 3.2	neat	--	21	12 h	1	0	0	2	0	1	1	0	19	24
69	200 mg	WCl_4 $AgSbF_6$	0.8 3.2	neat	--	50	12 h	5	1	0	14	0	1	1	0	4	26
70	200 mg	WCl_4 $AgSbF_6$	0.8 3.2	neat	--	75	12 h	3	1	0	8	0	1	0	0	18	31
71	200 mg	WCl_4 $AgSbF_6$	0.8 3.2	neat	--	100	12 h	14	12	0	16	0	2	0	0	7	51
72	200 mg	WCp_2Cl_2 $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	2	0	1	0	0	26	29
73	200 mg	WCp_2Cl_2 $AgSbF_6$	0.8 1.6	neat	--	50	12 h	4	0	0	7	0	2	0	0	15	28
74	200 mg	WCp_2Cl_2 $AgSbF_6$	0.8 1.6	neat	--	75	12 h	10	2	0	13	0	1	0	0	10	36
75	200 mg	WCp_2Cl_2 $AgSbF_6$	0.8 1.6	neat	--	100	12 h	5	5	0	7	0	1	1	0	5	24

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
76	200 mg	WCl_6	0.8	neat	--	21	12 h	0	0	0	1	0	1	0	0	21	23
77	200 mg	WCl_6	0.8	neat	--	50	12 h	0	0	0	1	0	1	0	0	15	17
78	200 mg	WCl_6	0.8	neat	--	75	12 h	0	0	0	3	0	1	0	0	8	12
79	200 mg	WCl_6	0.8	neat	--	100	12 h	0	0	0	3	0	11	0	0	4	18
80	200 mg	WCl_6 $AgSbF_6$	0.8 4.8	neat	--	21	12 h	1	0	0	2	0	1	0	0	19	23
81	200 mg	WCl_6 $AgSbF_6$	0.8 4.8	neat	--	50	12 h	2	1	0	14	0	1	1	0	11	30
82	200 mg	WCl_6 $AgSbF_6$	0.8 4.8	neat	--	75	12 h	3	3	0	20	0	1	0	0	4	31
83	200 mg	WCl_6 $AgSbF_6$	0.8 4.8	neat	--	100	12 h	7	3	0	34	0	2	1	0	4	51
84	600 mg	WCl_6 $AgSbF_6$	0.8 4.8	neat	--	100	12 h	10	12	0	18	0	3	1	0	10	54
								Group VII									
85	200 mg	$CoCl_2$	0.8	neat	--	100	12 h	1	0	0	1	0	1	0	0	14	17

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
86	200 mg	$CoCl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	8	2	0	5	0	1	0	0	5	21
87	200 mg	$(PPh_3)_3$ CoCl	5	THF	50	65	24 h	0	0	0	0	0	1	10	0	0	11
88	200 mg	$(PPh_3)_3$ CoCl $AgSbF_6$	5.0 5.0	THF	50	65	24 h	0	0	0	1	0	0	1	0	0	2
								Group VIII									
89	200 mg	$FeCl_2$	0.8	neat	--	100	12 h	1	0	0	1	0	1	0	0	10	13
90	200 mg	$FeCl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	2	1	0	1	0	1	0	0	19	24
91	200 mg	$FeCl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	3	6	0	1	0	1	1	0	11	23
92	200 mg	$FeCl_3$	0.8	neat	--	21	12 h	0	0	0	0	0	0	0	0	27	27
93	200 mg	$FeCl_3$	0.8	neat	--	50	12 h	0	0	0	0	0	0	0	0	15	15
94	200 mg	$FeCl_3$	0.8	neat	--	75	12 h	0	0	0	0	0	0	0	0	0	0

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
95	200 mg	$FeCl_3$	0.8	neat	--	100	12 h	0	0	0	0	0	0	0	0	0	0
96	200 mg	$FeCl_3$ $AgSbF_6$	0.8 0.8	neat	--	21	12 h	0	0	0	0	0	0	0	0	20	20
97	200 mg	$FeCl_3$ $AgSbF_6$	0.8 0.8	neat	--	50	12 h	0	0	0	0	0	0	0	0	14	14
98	200 mg	$FeCl_3$ $AgSbF_6$	0.8 0.8	neat	--	75	12 h	0	0	0	0	0	0	0	0	13	13
99	200 mg	$FeCl_3$ $AgSbF_6$	0.8 0.8	neat	--	100	12 h	1	1	0	0	0	0	0	0	10	12
100	600 mg	$FeCl_3$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	0	0	0	0	0	16	16
101	200 mg	$FeCl_3$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	0	0	1	0	0	0	0	12	13
102	200 mg	$FeCl_3$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	0	0	0	1	0	0	0	0	7	8
103	200 mg	$FeCl_3$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	1	1	0	1	0	0	0	0	7	10
104	200 mg	$FeCl_3$ $AgSbF_6$	0.8 2.4	neat	--	21	12 h	0	0	0	0	0	0	0	0	15	15
105	200 mg	$FeCl_3$ $AgSbF_6$	0.8 2.4	neat	--	50	12 h	4	1	0	6	0	3	1	0	3	18

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
106	200 mg	$FeCl_3$ $AgSbF_6$	0.8 2.4	neat	--	75	12 h	1	0	0	2	0	1	0	0	6	10
107	200 mg	$FeCl_3$ $AgSbF_6$	0.8 2.4	neat	--	100	12 h	1	1	0	10	0	0	0	0	2	14
108	200 mg	$FeCl_3$ $AgSbF_6$	4.0 12.0	neat	--	100	12 h	4	4	0	6	0	1	1	0	0	16
109	200 mg	$FeCl_3$ $AgSbF_6$	20.0 60.0	neat	--	100	12 h	2	3	1	20	0	3	1	0	0	30
110	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	HOAc	4	110	12 h	5	16	0	21	24	8	9	0	0	83
111	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	HOAc	4	110	12 h	4	10	0	23	26	9	19	0	0	91
112	100 mg	$[RuCl_2(p\text{-cymene})]_2$ AuCl $AgSbF_6$	5.0 1.0 21.0	HOAc	4	110	12 h	2	0	0	11	10	8	4	0	0	35
113	100 mg	$[RuCl_2(p\text{-cymene})]_2$ AuCl $AgSbF_6$	1.0 1.0 5.0	HOAc	4	110	12 h	3	1	0	2	3	4	2	0	0	15
114	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	1.0 4.0	HOAc	4	110	12 h	5	0	0	1	2	1	1	0	0	10

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
115	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 1.0 21.0	HOAc	4	110	12 h	1	0	0	7	21	5	6	0	0	40
116	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	1.0 1.0 5.0	HOAc	4	110	12 h	1	0	0	3	9	3	3	0	5	24
117	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	dioxane PvOH	4	110	12 h	0	1	0	3	21	2	2	0	0	29
118	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	dioxane PvOH	4	110	12 h	1	4	2	6	8	30	9	0	0	60
119	100 mg	$[RuCl_2(p\text{-cymene})]_2$ KPF_6	5.0 20.0	dioxane PvOH	4	110	12 h	1	12	1	5	0	30	7	0	0	81
120	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	dioxane PvOH	4	80	4 h	0	0	0	4	26	1	1	0	8	40
121	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	DCE PvOH	4	110	12 h	1	5	1	15	9	34	5	0	0	70
122	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	DCE PvOH	4	80	4 h	0	0	0	8	6	2	0	0	14	30
123	100 mg	$[RuCl_2(p\text{-cymene})]_2$ $AgSbF_6$	5.0 20.0	TCE PvOH	4	110	12 h	1	10	1	16	7	24	3	0	0	62

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
124	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	TCE PvOH	4	80	4 h	0	0	0	12	4	4	1	0	15	36
125	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	PvOH	4	110	12 h	1	5	0	4	4	0	1	0	0	15
126	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	dioxane	4	110	12 h	1	0	0	1	8	0	2	0	0	13
127	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	dioxane PvOH	4	110	12 h	1	1	0	2	21	4	5	0	0	34
128	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	HOAC dioxane	4	110	12 h	1	0	0	6	13	0	5	0	0	25
129	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	TFA	4	110	12 h	0	0	0	2	8	0	7	0	0	17
130	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	TFA dioxane	4	110	12 h	1	0	0	1	12	0	3	0	0	17
131	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	TCA	4	110	12 h	0	0	0	2	12	0	1	0	0	15
132	100 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	TCA dioxane	4	110	12 h	1	0	0	2	4	0	3	0	0	10

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
133	200 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	HOAc	4	50	12 h	0	0	0	5	0	1	1	0	0	7
134	200 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	HOAc	4	110	12 h	0	0	0	8	13	6	4	0	0	31
135	400 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	HOAc	8	110	12 h	3	12	0	15	19	12	13	0	0	80
136	200 mg	[$RuCl_2$(*p*-cymene)]$_2$ $AgSbF_6$	5.0 20.0	HOAc	4	80	12 h	4	2	0	8	24	7	9	0	0	61
								Group X									
137	200 mg	$NiCl_2$	0.8	neat	--	100	12 h	1	0	0	1	0	1	0	0	1	4
138	200 mg	$NiCl_2$ $AgSbF_6$	0.8 0.8	neat	--	100	12 h	1	3	0	1	0	1	0	0	30	36
139	200 mg	$NiCl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	1	0	0	1	0	1	0	0	20	23
140	200 mg	$NiCl_2$ AgSbF6	0.8 1.6	neat	--	100	12 h	4	2	0	1	0	1	0	0	0	8
141	200 mg	$PdCl_2$	0.8	neat	--	100	12 h	1	0	0	1	0	3	0	0	10	15

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
142	200 mg	$PdCl_2$ $AgSbF_6$	0.8 0.8	neat	--	21	12 h	2	2	0	1	0	1	0	0	30	36
143	200 mg	$PdCl_2$ $AgSbF_6$	0.8 0.8	neat	--	100	12 h	2	0	0	1	0	4	0	0	1	8
144	200 mg	$PtCl_2$	0.8	neat	--	100	4 h	0	0	0	1	1	2	1	0	10	15
145	200 mg	$PtCl_2$	0.8	neat	--	50	12 h	0	0	0	0	0	0	0	0	60	60
146	200 mg	$PtCl_2$	0.8	neat	--	100	4 h	0	1	0	1	1	2	1	0	13	19
147	200 mg	$PtCl_2$ $AgSbF_6$	0.8 0.8	neat	--	100	1 h	0	2	0	3	0	1	1	0	2	9
148	200 mg	$PtCl_2$ $AgSbF_6$	0.8 0.8	neat	--	100	1 h	0	0	0	3	0	1	0	0	2	6
149	200 mg	$PtCl_2$ $AgSbF_6$	0.8 0.8	neat	--	50	12 h	0	1	0	5	0	1	0	0	0	7
150	200 mg	$PtCl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	1 h	0	2	0	4	0	1	0	0	0	7
151	200 mg	$PtCl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	1 h	0	1	0	13	0	1	0	0	0	15
152	200 mg	$PtCl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	0	0	4	0	1	0	0	0	5

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
153	200 mg	$PtCl_2$ $AgSbF_6$	0.8 0.8	PvOH	10	100	12 h	1	3	0	2	0	1	0	0	0	7
154	200 mg	$PtCl_2$ $AgSbF_6$	0.8 1.6	PvOH	10	100	12 h	0	2	0	4	0	1	0	0	0	7
155	200 mg	$PtCl_4$	0.8	neat	--	50	12 h	0	0	0	2	0	6	1	0	10	19
156	200 mg	$PtCl_4$ $AgSbF_6$	0.8 0.8	neat	--	50	12 h	1	1	0	6	0	1	0	0	0	9
157	200 mg	$PtCl_4$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	1	1	0	5	0	1	0	0	0	8
158	200 mg	$PtCl_4$ $AgSbF_6$	0.8 2.4	neat	--	50	12 h	1	1	0	6	0	1	1	0	0	10
159	200 mg	$PtCl_4$ $AgSbF_6$	0.8 3.2	neat	--	50	12 h	1	5	0	9	0	1	1	0	0	17
160	200 mg	$PtCl_4$ $AgSbF_6$	0.8 3.2	neat	--	100	1 h	1	0	0	8	0	1	1	0	0	11
161	200 mg	$PtCl_4$ $AgSbF_6$	0.8 3.2	neat	--	50	12 h	1	5	0	11	0	1	0	0	0	18
Group XI																	
162	200 mg	CuCl	0.8	neat	--	100	12 h	1	0	0	1	0	1	1	0	2	6
163	200 mg	CuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	1	1	0	1	0	1	1	0	0	5

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
164	200 mg	$AgPF_6$	0.8	neat	--	100	12 h	0	0	0	1	0	1	1	0	0	3
165	200 mg	$AgBF_4$	0.8	neat	--	100	12 h	0	0	0	1	0	1	1	0	0	3
166	200 mg	AgOTf	0.8	neat	--	100	12 h	0	0	0	1	0	1	1	0	0	3
167	200 mg	$AgNTf_2$	0.8	neat	--	100	12 h	0	0	0	1	0	1	1	0	0	3
168	200 mg	$AgSbF_6$	0.8	neat	--	21	12 h	1	1	0	1	0	1	1	0	0	5
169	200 mg	$AgSbF_6$	0.8	neat	--	21	24 h	2	1	0	1	0	1	1	0	0	6
170	200 mg	AuCl	0.8	neat	--	21	48 h	0	0	0	0	0	0	0	0	31	31
171	200 mg	AuCl	0.8	neat	--	100	12 h	4	1	0	1	0	1	1	0	31	39
172	200 mg	AuCl $AgSbF_6$	0.8 0.8	neat	--	21	12 h	1	1	0	1	0	1	1	0	--	5
173	200 mg 2 runs	AuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	24	5	0	1	0	1	1	0	--	32
174	200 mg	AuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	20	4	0	5	0	1	1	0	15	46

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
175	200 mg 6 runs	AuCl $AgSbF_6$	0.8 0.8	neat	--	75	12 h	7	3	0	16	0	1	1	0	10	38
176	200 mg 5 runs	AuCl $AgSbF_6$	0.8 0.8	neat	--	50	12 h	8	2	0	14	0	1	1	0	10	36
177	200 mg	AuCl $AgSbF_6$	0.4 0.4	neat	--	100	12 h	1	1	0	1	0	1	0	0	1	5
178[c]	7 g	AuCl $AgSbF_6$	0.03 0.03	neat	--	100	12 h	3	2	0	1	0	1	1	0	15	26
179	200 mg	AuCl AgSbF6	0.08	neat	--	100	12 h	1	0	0	1	0	1	1	0	14	18
180	200 mg	AuCl	0.08	neat	--	50	12 h	0	0	0	1	0	1	1	0	17	20
181	200 mg	AuCl	8	neat	--	50	12 h	2	1	0	2	0	1	1	0	5	12
182	200 mg	AuCl $AgSbF_6$	0.08 0.08	neat	--	100	12 h	1	0	0	1	0	1	1	0	10	14
183	200 mg	AuCl $AgSbF_6$	0.08 0.8	neat	--	100	12 h	1	3	0	2	0	1	1	0	0	8
184	200 mg	AuCl $AgSbF_6$	0.8 4.0	neat	--	100	12 h	1	1	0	3	0	1	1	0	0	7

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
185	200 mg	AuCl $AgSbF_6$	8.0 8.0	neat	--	100	12 h	1	1	0	3	0	1	2	0	0	8
186	200 mg	AuCl $AgSbF_6$	8.0 8.0	neat	--	50	12 h	1	2	0	3	0	1	2	0	0	9
187	200 mg	AuCl $AgSbF_6$	8.0 8.0	neat	--	21	12 h	1	0	0	1	0	1	1	0	0	4
188	800 mg	AuCl $AgSbF_6$	0.2 0.2	neat	--	100	12 h	5	1	0	1	0	1	1	0	0	10
189	600 mg	AuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	4	1	0	8	0	1	1	0	0	16
190	800 mg	AuCl $AgSbF_6$	0.2 0.2	neat	--	100	12 h	5	1	0	9	0	1	2	0	0	32
191	200 mg	AuCl $AgSbF_6$ $TiCl_4$	0.8 0.8 0.8	neat	--	100	12 h	0	0	0	0	0	1	1	0	0	2
192	200 mg	AuCl $AgSbF_6$	0.8 0.8	PvOH	10	100	12 h	0	4	0	1	0	1	1	0	0	7
193	200 mg	AuCl $AgSbF_6$	0.8 0.8	PvOH	50	100	12 h	4	3	0	11	0	1	1	0	0	20
194	200 mg	AuCl $AgSbF_6$	0.8 0.8	anisole	50	100	12 h	0	0	0	0	0	0	0	0	0	0
195	200 mg	AuCl $AgSbF_6$	0.8 0.8	cyclopentane	10	100	12 h	0	0	0	2	0	2	1	0	15	20

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
196	200 mg	AuCl $AgSbF_6$	0.8 0.8	cyclopentane	25	100	12 h	1	1	0	6	0	2	5	0	0	15
197	200 mg	AuCl $AgSbF_6$	0.8 0.8	cyclopentane	50	100	12 h	1	1	0	9	0	2	2	0	0	15
198	200 mg	AuCl $AgSbF_6$	0.8 0.8	DCM	25	21	12 h	0	0	0	0	0	0	0	0	27	27
199	200 mg	AuCl $AgSbF_6$	0.8 0.8	DCM	25	50	12 h	1	1	0	1	0	1	1	0	20	25
200	200 mg	AuCl $AgSbF_6$	0.8 0.8	DCM	25	75	12 h	3	1	0	2	0	1	1	0	15	23
201	200 mg	AuCl $AgSbF_6$	0.8 0.8	DCM	25	100	12 h	0	0	0	0	0	0	0	0	10	10
202	200 mg	AuCl $AgSbF_6$	0.8 0.8	dioxane	25	21	12 h	0	0	0	0	0	0	0	0	0	0
203	200 mg	AuCl $AgSbF_6$	0.8 0.8	dioxane	25	50	12 h	0	0	0	0	0	0	0	0	0	0
204	200 mg	AuCl $AgSbF_6$	0.8 0.8	dioxane	25	75	12 h	0	0	0	0	0	0	0	0	0	0
205	200 mg	AuCl $AgSbF_6$	0.8 0.8	dioxane	25	100	12 h	1	1	0	1	0	1	1	0	0	5
206	200 mg	AuCl $AgSbF_6$	0.8 0.8	toluene	25	21	12 h	0	0	0	0	0	0	0	0	7	7

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
207	200 mg	AuCl $AgSbF_6$	0.8 0.8	toluene	25	50	12 h	0	0	0	0	0	0	0	0	5	5
208	200 mg	AuCl $AgSbF_6$	0.8 0.8	toluene	25	75	12 h	0	1	0	1	0	1	0	0	2	5
209	200 mg	AuCl $AgSbF_6$	0.8 0.8	toluene	25	100	12 h	0	0	0	1	0	0	0	0	0	2
210	200 mg	AuCl $AgSbF_6$	0.8 0.8	toluene	50	100	12 h	6	6	0	1	0	1	1	0	0	19
211	200 mg	AuCl $AgSbF_6$	0.8 0.8	DMA	25	100	12 h	0	0	0	0	0	0	0	0	0	0
212	200 mg	AuCl $AgSbF_6$	0.8 0.8	DMA	50	100	12 h	0	0	0	0	0	0	0	0	0	0
213	400 mg	AuCl $AgSbF_6$	0.8 0.8	TCE	25	100	12 h	4	2	0	8	0	1	1	12	10	38
214	200 mg	AuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	1	1	0	1	0	1	1	0	0	5
215	200 mg	AuCl AgOTf	0.8 0.8	neat	--	100	12 h	3	2	0	1	0	1	8	0	10	25
216	200 mg	AuCl $AgBF_4$	0.8 0.8	neat	--	100	12 h	3	2	0	1	0	1	8	0	10	25
217	200 mg	AuCl $AgNTf_2$	0.8 0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	15	16

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
218	200 mg	AuCl $AgNTf_2$	0.8 0.8	neat	--	50	12 h	0	0	0	2	0	1	0	0	12	15
219	200 mg	AuCl $AgNTf_2$	0.8 0.8	neat	--	75	12 h	0	2	0	2	0	0	0	0	0	4
220	200 mg	AuCl $AgNTf_2$	0.8 0.8	neat	--	100	12 h	0	4	0	2	0	0	0	0	0	6
221	200 mg	AuCl AgOTFA	0.8 0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	15	16
222	200 mg	AuCl AgOTFA	0.8 0.8	neat	--	50	12 h	0	3	0	1	0	0	0	0	0	4
223	200 mg	AuCl AgOTFA	0.8 0.8	neat	--	75	12 h	0	2	0	1	0	0	0	0	0	3
224	200 mg	AuCl AgOTFA	0.8 0.8	neat	--	100	12 h	0	0	0	1	0	0	0	0	0	1
225	200 mg	AuCl AgOAc	0.8 0.8	neat	--	21	12 h	0	3	0	1	0	0	0	0	7	12
226	200 mg	AuCl AgOAc	0.8 0.8	neat	--	50	12 h	0	3	0	0	0	0	0	0	5	8
227	200 mg	AuCl AgOAc	0.8 0.8	neat	--	75	12 h	0	3	0	0	0	0	0	0	0	3
228	200 mg	AuCl AgOAc	0.8 0.8	neat	--	100	12 h	0	2	0	1	0	0	0	0	0	3

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
229	200 mg	AuCl $HNTf_2$	0.8 1.6	neat	--	50	12 h	1	2	0	1	0	1	1	0	15	21
230	200 mg	AuCl $HNTf_2$	0.8 1.6	neat	--	100	12 h	1	1	0	1	0	1	1	0	10	15
231	200 mg	(PPh_3) AuCl $AgBF_4$	0.8 0.8	neat	--	100	12 h	1	1	0	1	0	1	0	0	4	8
232	200 mg	(PPh_3) AuCl $AgSbF_6$	0.8 0.8	neat	--	21	12 h	0	0	0	0	0	1	1	0	0	2
233	200 mg	(PPh_3) AuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	0	0	0	0	0	1	1	0	0	2
234	200 mg	(PPh_3) AuCl $AgSbF_6$	0.8 0.8	toluene	--	21	24 h	0	0	0	1	0	1	1	0	14	17
235	200 mg	(PPh_3) AuCl $AgSbF_6$	0.8 0.8	toluene	--	50	12 h	0	0	0	4	0	1	0	0	2	7
236	200 mg	(PPh_3) AuCl $AgSbF_6$	0.8 0.8	neat	--	21	12 h	0	1	0	2	0	1	0	0	5	9
237	200 mg	(PPh_3) AuCl AgOTf	0.8 0.8	neat	--	100	12 h	1	6	0	4	0	1	1	0	4	17

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
238	200 mg	(PPh_3) AuCl AgOTf	0.8 0.8	toluene	--	21	12 h	0	0	0	1	0	1	0	0	15	17
239	200 mg	(PPh_3) AuCl AgOTf	0.8 0.8	toluene	--	50	12 h	0	0	0	1	0	1	0	0	1	3
240	200 mg	$P(OMe)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	21	72 h	3	0	0	4	0	0	0	0	0	7
241	200 mg	$P(OMe)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	50	12 h	2	0	0	7	0	1	0	0	0	10
242	200 mg	$P(OMe)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	75	12 h	2	1	0	13	0	0	0	0	0	16
243	200 mg	$P(OMe)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	100	12 h	0	1	0	4	0	0	0	0	0	5
244	200 mg	$P(OPh)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	10	11
245	200 mg	$P(OPh)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	50	12 h	0	0	0	2	0	0	0	0	5	11
246	200 mg	$P(OPh)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	75	12 h	0	0	0	4	0	0	0	0	3	7

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
247	200 mg	$P(OPh)_3$ AuCl $AgSbF_6$	0.8 0.8 0.8	neat	--	100	12 h	0	0	0	2	0	0	0	0	2	4
248	200 mg	JohnPhos AuCl	0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	0	1
249	200 mg	JohnPhos AuCl	0.8	neat	--	50	12 h	0	0	0	0	0	0	0	0	0	0
250	200 mg	JohnPhos AuCl	0.8	neat	--	75	12 h	0	0	0	0	0	0	0	0	0	0
251	200 mg	JohnPhos AuCl	0.8	neat	--	100	12 h	0	0	0	1	0	0	0	0	0	1
252	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	neat	--	21	12 h	0	0	0	3	0	0	0	0	0	3
253	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	neat	--	50	12 h	0	0	0	2	0	0	0	0	0	2
254	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	0	2
255	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	0	0	0	5	0	0	0	0	0	5
256	200 mg	JohnPhos AuCl AgOTf	0.8 0.8	neat	--	21	12 h	0	0	0	2	0	0	0	0	0	2

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
257	200 mg	JohnPhos AuCl AgOTf	0.8 0.8	neat	--	50	12 h	0	0	0	1	0	0	0	0	0	1
258	200 mg	JohnPhos AuCl AgOTf	0.8 0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	0	4
259	200 mg	JohnPhos AuCl AgOTf	0.8 0.8	neat	--	100	12 h	0	0	0	2	0	0	0	0	0	2
260	200 mg	JohnPhos AuCl $AgNTf_2$	0.8 0.8	neat	--	21	12 h	0	1	0	2	0	0	0	0	0	4
261	200 mg	JohnPhos AuCl $AgNTf_2$	0.8 0.8	neat	--	50	12 h	0	1	0	2	0	0	0	0	0	3
262	200 mg	JohnPhos AuCl $AgNTf_2$	0.8 0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	0	2
263	200 mg	JohnPhos AuCl $AgNTf_2$	0.8 0.8	neat	--	100	12 h	2	0	0	2	0	0	0	0	0	4
264	200 mg	JohnPhos AuCl $AgPF_6$	0.8 0.8	neat	--	21	12 h	0	0	0	1	0	1	1	0	0	3
265	200 mg	JohnPhos AuCl $AgPF_6$	0.8 0.8	neat	--	50	12 h	0	0	0	1	0	1	0	0	0	2

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
266	200 mg	JohnPhos AuCl $AgPF_6$	0.8 0.8	neat	--	75	12 h	0	0	0	1	0	1	0	0	0	2
267	200 mg	JohnPhos AuCl $AgPF_6$	0.8 0.8	neat	--	100	12 h	0	0	0	1	0	0	0	0	0	1
268	200 mg	JohnPhos AuCl $AgBF_4$	0.8 0.8	neat	--	21	12 h	0	0	0	2	0	1	0	0	0	3
269	200 mg	JohnPhos AuCl $AgBF_4$	0.8 0.8	neat	--	50	12 h	0	0	0	2	0	0	0	0	0	2
270	200 mg	JohnPhos AuCl $AgBF_4$	0.8 0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	0	2
271	200 mg	JohnPhos AuCl $AgBF_4$	0.8 0.8	neat	--	100	12 h	0	0	0	2	0	0	0	0	0	2
272	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	DCM	25	21	12 h	0	0	0	1	0	0	0	0	8	9
273	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	DCM	25	50	12 h	0	0	0	1	0	0	0	0	0	1
274	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	DCM	25	75	12 h	1	0	0	3	0	0	0	0	0	4

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
275	200 mg	JohnPhos AuCl $AgSbF_6$	0.8 0.8	DCM	25	100	12 h	1	0	0	6	0	0	0	0	0	7
276	200 mg	IPrAuCl	0.8	neat	--	21	12 h	0	0	0	2	0	0	0	0	0	2
277	200 mg	IPrAuCl	0.8	neat	--	50	12 h	0	0	0	2	0	1	0	0	0	3
278	200 mg	IPrAuCl	0.8	neat	--	75	12 h	0	0	0	1	0	0	0	0	0	1
279	200 mg	IPrAuCl	0.8	neat	--	100	12 h	0	0	0	1	0	0	0	0	0	1
280	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	neat	--	21	12 h	0	0	0	2	0	1	0	0	0	3
281	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	neat	--	50	12 h	0	0	0	2	0	0	0	0	0	2
282	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	neat	--	75	12 h	0	2	0	4	0	1	0	0	0	7
283	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	0	2	0	5	0	1	0	0	0	8
284	200 mg	IPrAuCl AgOTf	0.8 0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	0	1
285	200 mg	IPrAuCl AgOTf	0.8 0.8	neat	--	50	12 h	0	0	0	1	0	0	0	0	0	1

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
286	200 mg	IPrAuCl AgOTf	0.8 0.8	neat	--	75	12 h	0	1	0	2	0	0	0	0	0	3
287	200 mg	IPrAuCl AgOTf	0.8 0.8	neat	--	100	12 h	0	0	0	2	0	0	0	0	0	2
288	200 mg	IPrAuCl $AgNTf_2$	0.8 0.8	neat	--	21	12 h	0	0	0	2	0	0	0	0	0	2
289	200 mg	IPrAuCl $AgNTf_2$	0.8 0.8	neat	--	50	12 h	0	0	0	3	0	1	0	0	0	4
290	200 mg	IPrAuCl $AgNTf_2$	0.8 0.8	neat	--	75	12 h	0	0	0	3	0	1	0	0	0	4
291	200 mg	IPrAuCl $AgNTf_2$	0.8 0.8	neat	--	100	12 h	0	0	0	3	0	1	0	0	0	4
292	200 mg	IPrAuCl $AgNTf_2$	0.8 0.8	neat	--	21	12 h	0	0	0	2	0	0	0	0	0	2
293	200 mg	IPrAuCl $AgPF_6$	0.8 0.8	neat	--	50	12 h	0	0	0	2	0	0	0	0	0	2
294	200 mg	IPrAuCl $AgPF_6$	0.8 0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	0	2
295	200 mg	IPrAuCl $AgPF_6$	0.8 0.8	neat	--	100	12 h	0	0	0	2	0	0	0	0	0	2
296	200 mg	IPrAuCl $AgBF_4$	0.8 0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	0	1

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
297	200 mg	IPrAuCl $AgBF_4$	0.8 0.8	neat	--	50	12 h	0	0	0	2	0	0	0	0	0	2
298	200 mg	IPrAuCl $AgBF_4$	0.8 0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	0	2
299	200 mg	IPrAuCl $AgBF_4$	0.8 0.8	neat	--	100	12 h	0	0	0	2	0	0	0	0	0	2
300	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	DCM	25	21	12 h	0	0	0	1	0	0	0	0	0	1
301	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	DCM	25	50	12 h	0	0	0	1	0	0	0	0	0	1
302	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	DCM	25	75	12 h	0	0	0	2	0	0	0	0	0	2
303	200 mg	IPrAuCl $AgSbF_6$	0.8 0.8	DCM	25	100	12 h	0	0	0	2	0	0	0	0	0	2
304	200 mg	$(PhF_5)_3$ AuCl	0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	6	7
305	200 mg	$(PhF_5)_3$ AuCl	0.8	neat	--	50	12 h	0	0	0	1	0	0	1	0	5	7
306	200 mg	$(PhF_5)_3$ AuCl	0.8	neat	--	75	12 h	0	0	0	1	0	0	1	0	3	5
307	200 mg	$(PhF_5)_3$ AuCl	0.8	neat	--	100	12 h	0	1	0	1	0	0	1	0	0	3

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
308	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	neat	--	21	12 h	2	0	0	2	0	1	1	0	8	14
309	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	neat	--	50	12 h	1	0	0	3	0	0	0	0	0	4
310	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	neat	--	75	12 h	1	1	0	3	0	0	0	0	0	5
311	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	neat	--	100	12 h	0	2	0	3	0	0	0	0	0	5
312	200 mg	$(PhF_5)_3$ AuCl AgOTf	0.8 0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	9	10
313	200 mg	$(PhF_5)_3$ AuCl AgOTf	0.8 0.8	neat	--	50	12 h	0	0	0	1	0	0	0	0	5	6
314	200 mg	$(PhF_5)_3$ AuCl AgOTf	0.8 0.8	neat	--	75	12 h	0	0	0	1	0	0	0	0	0	1
315	200 mg	$(PhF_5)_3$ AuCl AgOTf	0.8 0.8	neat	--	100	12 h	0	1	0	4	0	0	0	0	0	5
316	200 mg	$(PhF_5)_3$ AuCl $AgNTf_2$	0.8 0.8	neat	--	21	12 h	1	0	0	1	0	1	0	0	13	16

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
317	200 mg	$(PhF_5)_3$ AuCl $AgNTf_2$	0.8 0.8	neat	--	50	12 h	1	0	0	5	0	2	0	0	0	8
318	200 mg	$(PhF_5)_3$ AuCl $AgNTf_2$	0.8 0.8	neat	--	75	12 h	0	0	0	2	0	0	0	0	0	2
319	200 mg	$(PhF_5)_3$ AuCl $AgNTf_2$	0.8 0.8	neat	--	100	12 h	0	1	0	5	0	0	0	0	0	6
320	200 mg	$(PhF_5)_3$ AuCl $AgPF_6$	0.8 0.8	neat	--	21	12 h	0	1	0	1	0	0	0	0	15	17
321	200 mg	$(PhF_5)_3$ AuCl $AgPF_6$	0.8 0.8	neat	--	50	12 h	0	1	0	2	0	0	0	0	6	9
322	200 mg	$(PhF_5)_3$ AuCl $AgPF_6$	0.8 0.8	neat	--	75	12 h	0	1	0	2	0	0	0	0	3	6
323	200 mg	$(PhF_5)_3$ AuCl $AgPF_6$	0.8 0.8	neat	--	100	12 h	0	0	0	1	0	0	0	0	0	1
324	200 mg	$(PhF_5)_3$ AuCl $AgBF_4$	0.8 0.8	neat	--	21	12 h	0	0	0	1	0	0	0	0	7	8
325	200 mg	$(PhF_5)_3$ AuCl $AgBF_4$	0.8 0.8	neat	--	50	12 h	0	0	0	1	0	0	0	0	0	1

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
326	200 mg	$(PhF_5)_3$ AuCl $AgBF_4$	0.8 0.8	neat	--	75	12 h	0	0	0	5	0	0	0	0	0	5
327	200 mg	$(PhF_5)_3$ AuCl $AgBF_4$	0.8 0.8	neat	--	100	12 h	1	0	0	3	0	1	0	0	0	5
328	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	DCM	25	21	12 h	0	0	0	1	0	0	0	0	10	11
329	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	DCM	25	50	12 h	0	0	0	1	0	0	0	0	0	1
330	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	DCM	25	75	12 h	0	0	0	3	0	0	0	0	0	3
331	200 mg	$(PhF_5)_3$ AuCl $AgSbF_6$	0.8 0.8	DCM	25	100	12 h	0	0	0	3	0	0	0	0	0	3
332	200 mg	$AuBr_3$	0.8	neat	--	100	12 h	1	0	0	1	0	1	1	0	9	13
333	200 mg	$AuBr_3$ $AgSbF_6$	0.8 2.4	neat	--	100	12 h	12	4	0	5	0	1	1	0	0	23
334	200 mg	$AuCl_3$	0.8	neat	--	21	12 h	1	0	0	1	0	0	5	0	14	21
335	200 mg	$AuCl_3$	0.8	neat	--	50	12 h	0	2	0	2	0	1	0	0	13	18

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
336	200 mg	$AuCl_3$	0.8	neat	--	75	12 h	0	3	0	2	0	2	1	0	6	14
337	200 mg	$AuCl_3$	0.8	neat	--	100	12 h	1	1	0	0	0	1	0	0	2	5
338	200 mg	$AuCl_3$ $AgSbF_6$	0.8 0.8	neat	--	21	12 h	0	0	0	2	0	3	1	0	10	16
339	200 mg	$AuCl_3$ $AgSbF_6$	0.8 0.8	neat	--	50	12 h	6	0	0	5	0	4	2	0	6	26
340	200 mg	$AuCl_3$ $AgSbF_6$	0.8 0.8	neat	--	75	12 h	1	0	0	2	0	2	2	0	5	12
341	200 mg	$AuCl_3$ $AgSbF_6$	0.8 0.8	neat	--	100	12 h	3	0	0	1	0	0	0	0	0	4
342	200 mg	$AuCl_3$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	2	0	4	0	0	9	15
343	200 mg	$AuCl_3$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	1	0	0	9	0	0	0	0	7	21
344	200 mg	$AuCl_3$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	0	0	0	13	0	1	1	0	3	24
345	200 mg	$AuCl_3$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	6	0	0	2	0	0	0	0	0	11
346	200 mg	$AuCl_3$ $AgSbF_6$	0.8 2.4	neat	--	21	12 h	1	0	0	2	0	0	1	0	7	11

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
347	200 mg	$AuCl_3$ $AgSbF_6$	0.8 2.4	neat	--	50	12 h	1	0	0	4	0	0	0	0	5	11
348	200 mg	$AuCl_3$ $AgSbF_6$	0.8 2.4	neat	--	75	12 h	1	0	0	8	0	0	1	0	3	13
349	200 mg	$AuCl_3$ $AgSbF_6$	0.8 2.4	neat	--	100	12 h	2	0	0	11	0	1	1	0	0	16
350	200 mg	C_6H_4N $AuCl_2O_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	1	0	5	0	3	0	0	14	23
351	200 mg	C_6H_4N $AuCl_2O_2$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	14	2	0	13	0	1	1	0	7	38
352	200 mg	C_6H_4N $AuCl_2O_2$ $AgSbF_6$	0.8 1.6	neat	--	100	10 min	1	1	0	13	0	1	1	0	2	20
								Group XII									
353	200 mg	$Zn(OTf)_2$	0.8	neat	--	100	12 h	0	0	0	0	0	0	1	0	30	31
354	200 mg	Hg_2Cl_2	0.4	neat	--	21	12 h	0	0	0	0	0	0	0	0	90	90
355	200 mg	Hg_2Cl_2	0.4	neat	--	50	12 h	0	0	0	0	0	0	0	0	80	80

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
356	200 mg	Hg_2Cl_2	0.4	neat	--	75	12 h	0	0	0	0	0	0	0	0	50	50
357	200 mg	Hg_2Cl_2	0.4	neat	--	100	12 h	0	0	0	0	0	0	0	0	20	22
358	200 mg	Hg_2Cl_2 $AgSbF_6$	0.4 0.8	neat	--	21	12 h	1	0	0	5	0	0	1	0	15	22
359	200 mg	Hg_2Cl_2 $AgSbF_6$	0.4 0.8	neat	--	50	12 h	1	1	0	10	0	0	1	0	0	13
360	200 mg	Hg_2Cl_2 $AgSbF_6$	0.4 0.8	neat	--	75	12 h	1	2	0	4	0	0	1	0	0	8
361	200 mg	Hg_2Cl_2 $AgSbF_6$	0.4 0.8	neat	--	100	12 h	0	1	0	3	0	0	1	0	0	5
362	200 mg	$HgCl_2$	0.8	neat	--	21	12 h	0	0	0	0	0	0	0	0	70	70
363	200 mg	$HgCl_2$	0.8	neat	--	50	12 h	0	0	0	0	0	0	0	0	26	26
364	200 mg	$HgCl_2$	0.8	neat	--	75	12 h	0	0	0	0	0	0	0	0	10	10
365	200 mg	$HgCl_2$	0.8	neat	--	100	12 h	0	0	0	0	0	0	0	0	7	19
366	200 mg	$HgCl_2$ $AgSbF_6$	0.8 0.8	neat	--	21	12 h	1	0	0	4	0	0	1	0	15	21

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
367	200 mg	$HgCl_2$ $AgSbF_6$	0.8 0.8	neat	--	50	12 h	1	1	0	10	0	0	1	0	0	13
368	200 mg	$HgCl_2$ $AgSbF_6$	0.8 0.8	neat	--	75	12 h	1	2	0	4	0	0	1	0	0	8
369	200 mg	$HgCl_2$ $AgSbF_6$	0.8 0.8	neat	--	100	12 h	0	1	0	0	0	0	1	0	0	2
370	200 mg	$HgCl_2$ $AgSbF_6$	0.8 1.6	neat	--	21	12 h	0	0	0	2	0	0	1	0	1	4
371	200 mg	$HgCl_2$ $AgSbF_6$	0.8 1.6	neat	--	50	12 h	0	1	0	6	0	0	1	0	7	15
372	200 mg	$HgCl_2$ $AgSbF_6$	0.8 1.6	neat	--	75	12 h	0	1	0	3	0	0	0	0	3	7
373	200 mg	$HgCl_2$ $AgSbF_6$	0.8 1.6	neat	--	100	12 h	0	0	0	3	0	0	1	0	3	7
								Bronsted Acids									
374	200 mg	$HSbF_6$ $x6H_20$	2	neat	--	100	7 h	0	0	0	1	0	1	1	0	40	43
375	200 mg	$HSbF_6$ $x6H_20$	10	neat	--	100	7 h	1	0	0	0	0	1	1	0	34	37
376	200 mg	$HSbF_6$ $x6H_20$	20	neat	--	100	7 h	1	1	0	0	0	1	1	0	25	29

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
377	200 mg	MsOH	20	neat	--	100	7 h	3	3	0	6	0	1	1	0	20	34
378	200 mg	TsOH	20	neat	--	100	7 h	4	0	0	4	0	1	1	0	10	20
379	200 mg	7%P_2O_5. MsOH	10	neat	--	100	12 h	1	1	0	1	0	1	0	0	26	33
380	200 mg	7%P_2O_5. MsOH	20	neat	--	100	12 h	3	5	0	4	0	1	1	0	15	31
381	200 mg	xP_2O_5. H_3PO_4	10	neat	--	100	12 h	0	0	0	0	0	1	1	0	30	32
382	200 mg	xP_2O_5. H_3PO_4	20	neat	--	100	12 h	1	1	0	1	0	1	1	0	29	36
383	200 mg	TFA	20	neat	--	100	12 h	0	0	0	3	0	2	1	0	27	33
384	200 mg	$C_4F_9SO_3H$	10	neat	--	100	12 h	0	0	0	0	0	1	1	0	30	32
385	200 mg	$C_4F_9SO_3H$	10	neat	--	100	12 h	11	12	0	15	0	3	0	0	15	56
386	200 mg	$C_4F_9SO_3H$	20	neat	--	100	12 h	13	12	0	25	0	4	0	0	18	72
387	1 g	$C_4F_9SO_3H$	20	neat	--	100	12 h	14	13	0	22	0	4	0	0	17	70

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
388[d]	1 g	$C_4F_9SO_3H$ Kugelrohr	20	neat	--	100 - 140	12 h	20	21	0	23	0	6	0	0	17	87
389	1 g	$C_4F_9SO_3H$	20	TCE	25	100	20 h	3	4	0	13	0	5	0	0	36	61
390	200 mg	TfOH	2	neat	--	100	12 h	2	3	0	5	0	1	0	0	15	26
391	200 mg	TfOH	10	neat	--	100	7 h	10	10	0	15	0	3	1	0	18	57
392	600 mg	TfOH	10	neat	--	100	7 h	10	10	0	15	0	3	1	0	17	56
393	200 mg	TfOH	15	neat	--	100	7 h	12	12	0	19	0	4	1	0	17	65
394	600 mg	TfOH	15	neat	--	100	7 h	13	14	0	25	0	6	1	0	15	74
395	200 mg	TfOH	20	neat	--	100	2 h	11	10	0	32	0	4	1	0	15	73
396	200 mg	TfOH	40	neat	--	100	12 h	12	12	0	40	0	4	3	0	14	65
397	600 mg	TfOH	20	neat	--	100	3 h	10	10	0	18	0	6	0	0	10	54

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
398[d]	600 mg	TfOH Kugelrohr	20	neat	--	100 - 180	3 h	19	26	0	32	0	6	6	0	7	96
399[d]	1 g	TfOH Kugelrohr	20	neat	--	180	20 h	21	20	0	27	0	6	3	0	1	84
400	1 g	TfOH	15	neat	--	100	3.5 h	13	14	0	25	0	6	1	0	15	74
401[d]	1 g	TfOH sublime	15	neat	--	240	4 h	10	5	0	18	1	4	1	0	38	77
402[d]	1 g	TfOH sublime	15	neat	--	140	3 h	16	19	0	14	1	6	1	0	36	93
403[d]	2 g	TfOH	15	neat	--	100	4.5 h	10	9	0	25	0	4	0	0	25	73
404[d]	2 g	TfOH Kugelrohr	15	neat	--	100 - 140	8.5 h	20	22	0	12	0	6	2	0	36	98
405	2 g	TfOH	15	neat	--	100 - 110	16 h	19	20	0	15	0	6	0	0	12	72
406	3g	TfOH MS 3A	15	neat	--	100	9 h	16	18	0	13	0	4	0	0	15	66
407	3 g	TfOH MS 3A Kugelrohr	15	neat	--	140	4 h	18	20	0	10	0	6	2	0	29	85

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
408	6 g	TfOH	15	neat	--	100	7 h	18	14	0	28	0	4	0	0	20	84
409[d]	6 g	TfOH Kugelrohr	15	neat	--	100 - 140	7 h	23	24	0	15	0	7	0	0	19	88
410	6 g	TfOH	10	neat	--	100	7 h	12	12	0	33	0	4	0	0	25	86
411[d]	6 g	TfOH Kugelrohr	10	neat	--	100 - 140	7 h	25	30	0	11	0	5	0	0	21	92
412	6 g	TfOH	10	neat	--	100	7 h	13	14	0	30	0	4	0	0	22	83
413[d]	6 g	TfOH Kugelrohr	10	neat	--	100 - 160	7 h	26	32	0	10	0	6	0	0	19	93
414	6 g	TfOH	2	neat	--	100	24 h	6	7	0	4	0	3	0	0	35	55
415[d]	6 g	TfOH Kugelrohr	2	neat	--	100 - 140	24 h	10	13	0	1	0	3	0	0	30	57
416	200 mg	TfOH	20	dioxane	25	100	12 h	0	0	0	4	0	3	0	0	37	44
417	200 mg	TfOH	20	HOAc	25	100	12 h	0	0	0	5	0	6	2	0	26	39

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
418	200 mg	TfOH	20	DCE	25	100	12 h	1	1	0	29	0	1	0	0	30	62
419	600 mg	TfOH	20	DCE	25	100	12 h	3	4	0	14	0	1	0	0	23	45
420	600 mg	TfOH	20	TCE	25	100	12 h	4	4	0	26	0	2	0	0	10	46
421	6 g	TfOH	20	TCE	25	80	28 h	1	6	0	60	0	7	0	0	12	86
422[d]	6 g	TfOH Kugelrohr	20	TCE	25	100	18 h	8	14	0	41	0	6	0	0	12	81
423[d]	6 g	TfOH Kugelrohr	20	TCE	10	100	18 h	4	6	0	30	0	5	0	0	37	82
424[d]	6 g	TfOH Kugelrohr	20	TCE	5	100	18 h	0	1	0	5	0	2	0	0	65	73
425[d]	6 g	TfOH Kugelrohr	20	TCE	2	100	18 h	0	0	0	3	0	1	0	0	75	79
426[d]	3 g	TfOH Kugelrohr	20	DCB	25	100	18 h	11	9	0	20	0	4	0	0	30	74
427	400 mg	FSO_3H	1	neat	--	100	24 h	1	1	0	1	0	1	0	0	80	84
428	400 mg	FSO_3H	10	neat	--	100	20 h	9	10	0	3	0	1	0	0	0	23

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
429	2 g	FSO_3H	10	neat	--	100	20 h	11	12	0	6	0	2	0	0	16	53
430	2 g	FSO_3H	15	neat	--	100	20 h	8	11	0	18	0	3	0	0	24	64
431	2 g	FSO_3H	10	TCE	25	100	20 h	1	2	0	5	0	1	0	0	70	79
432	400 mg	$HSbF_6$	1	neat	--	100	24 h	3	3	0	2	0	1	0	0	60	67
433	400 mg	$HSbF_6$	5	neat	--	100	20 h	12	11	0	5	0	2	0	0	0	42
434	2 g	$HSbF_6$	5	neat	--	100	20 h	14	17	0	11	0	2	0	0	11	55
435	2 g	$HSbF_6$	10	neat	--	100	20 h	6	9	0	21	0	1	0	0	20	57
436	2 g	$HSbF_6$	15	neat	--	100	20 h	9	13	0	28	0	2	0	0	21	73
437	2 g	$HSbF_6$	5	TCE	25	100	20 h	2	2	0	3	0	2	0	0	76	85
Heterogenous Catalysts																	
438	200 mg	Zeolite B-H	--	neat	100	100	12 h	1	1	0	1	0	1	0	0	0	4
439	200 mg	Zeolite Y-H	--	neat	100	100	12 h	0	0	0	1	0	0	0	0	0	1

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

Table 5.1. (cont'd)

	Scale	Catalysts	Mol %	Solv.	wt %	T (˚C)	Time	% Yield (mol/mol)									
								1[a]	**2**[a]	**3**[a]	**22**[a]	**23**[b]	**40**[a]	**39**[a]	**41**[a]	**19**[b]	Total
440	200 mg	HZSM-5	--	neat	100	100	12 h	1	1	0	0	0	1	0	0	0	3
441	200 mg	Nafion	--	neat	100	100	12 h	1	0	0	0	0	0	0	0	0	1
442	200 mg	Dowex-50	--	neat	100	100	12 h	3	4	0	12	0	4	0	0	0	23

[a] Determined by HPLC. [b] Determined by NMR. [c] Run in Ti vessel. [d] Rxn run at 100 ˚C, 1atm, 4.5h. Kugelrohr started at 80 ˚C, 83 mmHg, ended at indicated temp., 2 mmHg. All reactions run under 1 atm N_2 unless indicated otherwise.

APPENDIX B: NMR Spectra

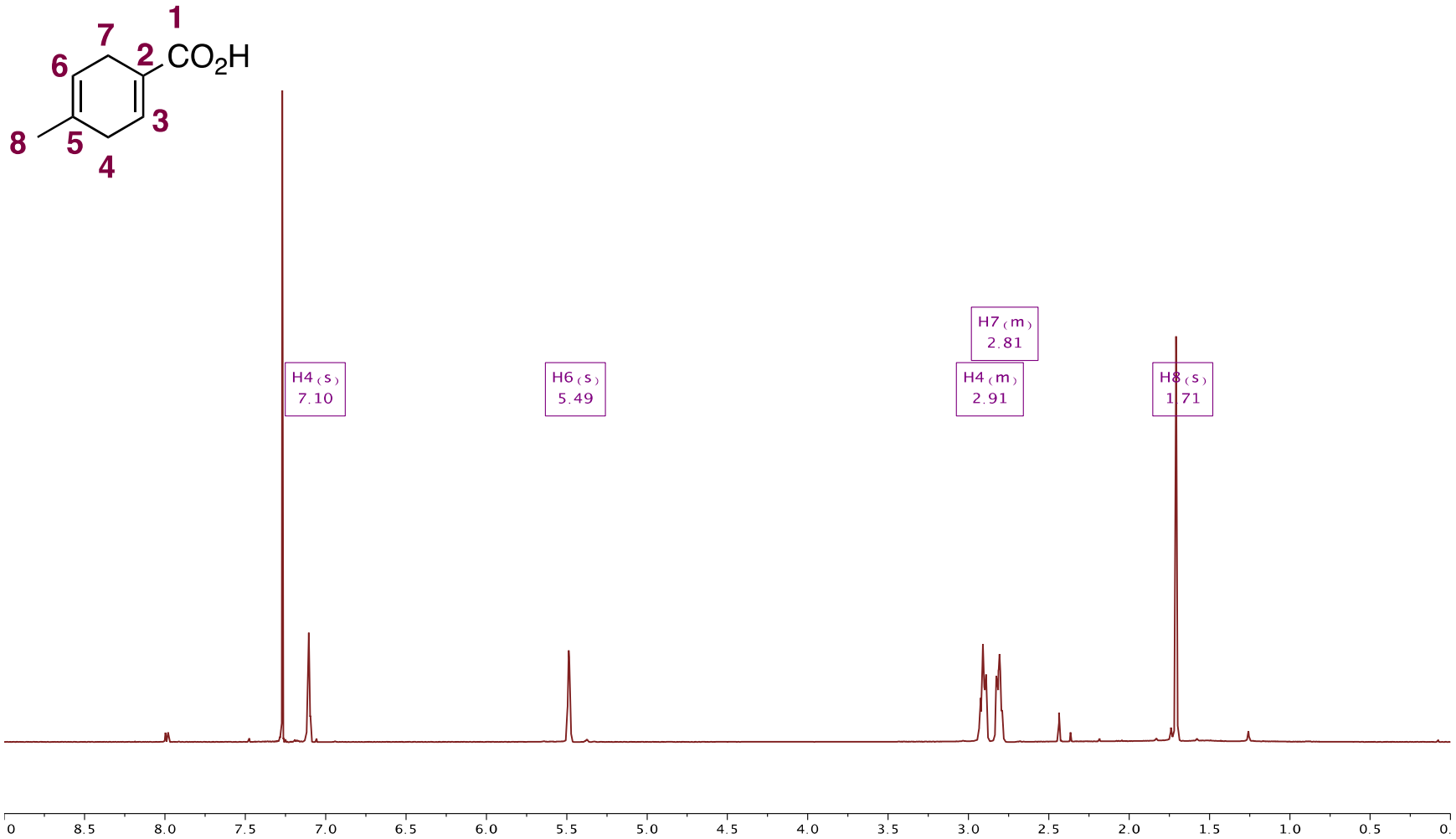


Figure 5.1. ^{1}H - NMR spectrum of solated 4-methyl 1,4-cyclohexadiene carboxylic acid **20**

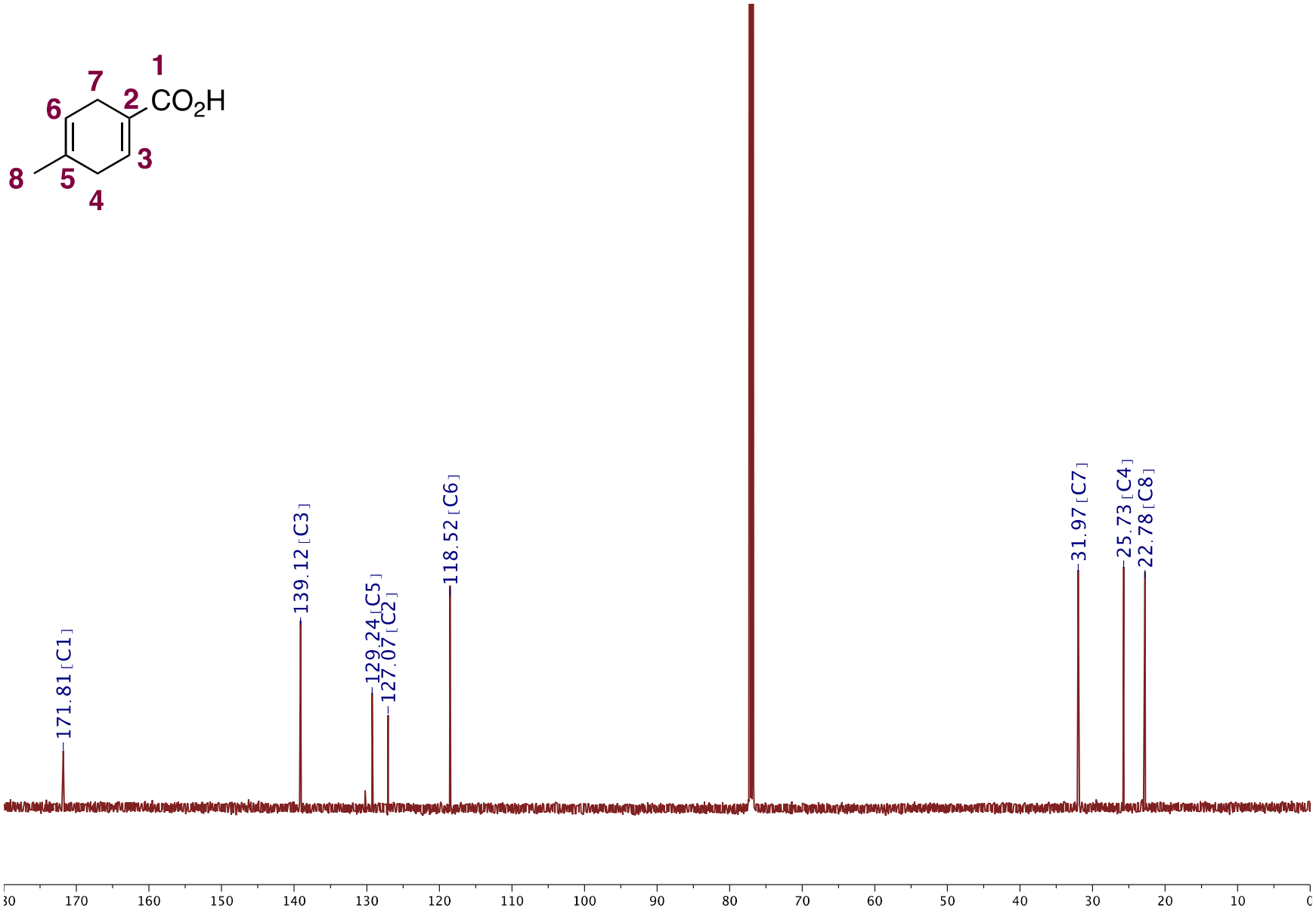


Figure 5.2. 13C- NMR spectrum of solated 4-methyl 1,4-cyclohexadiene carboxylic acid **20**

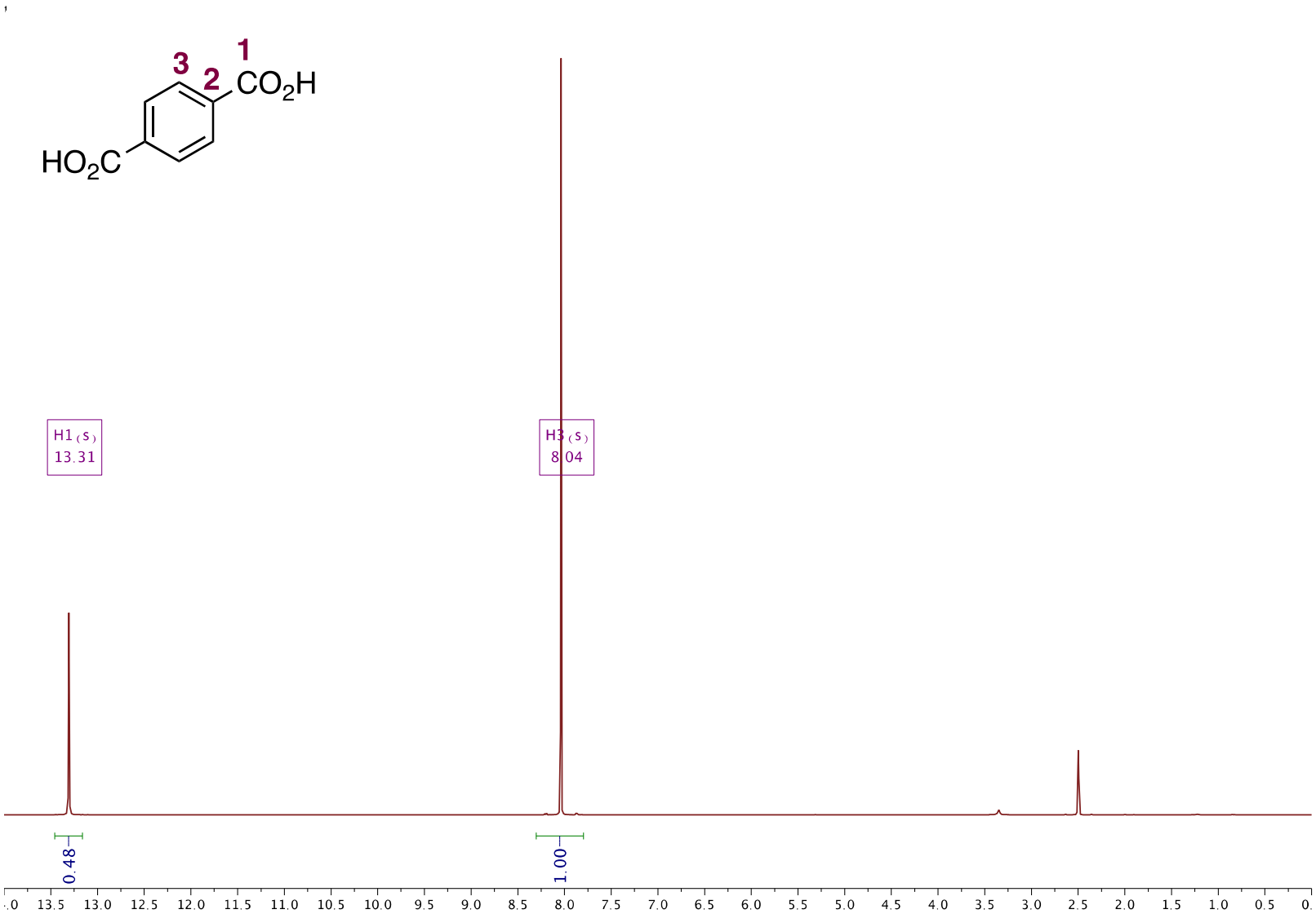


Figure 5.3. ^{1}H-NMR spectrum of isolated terephthalic acid **1**

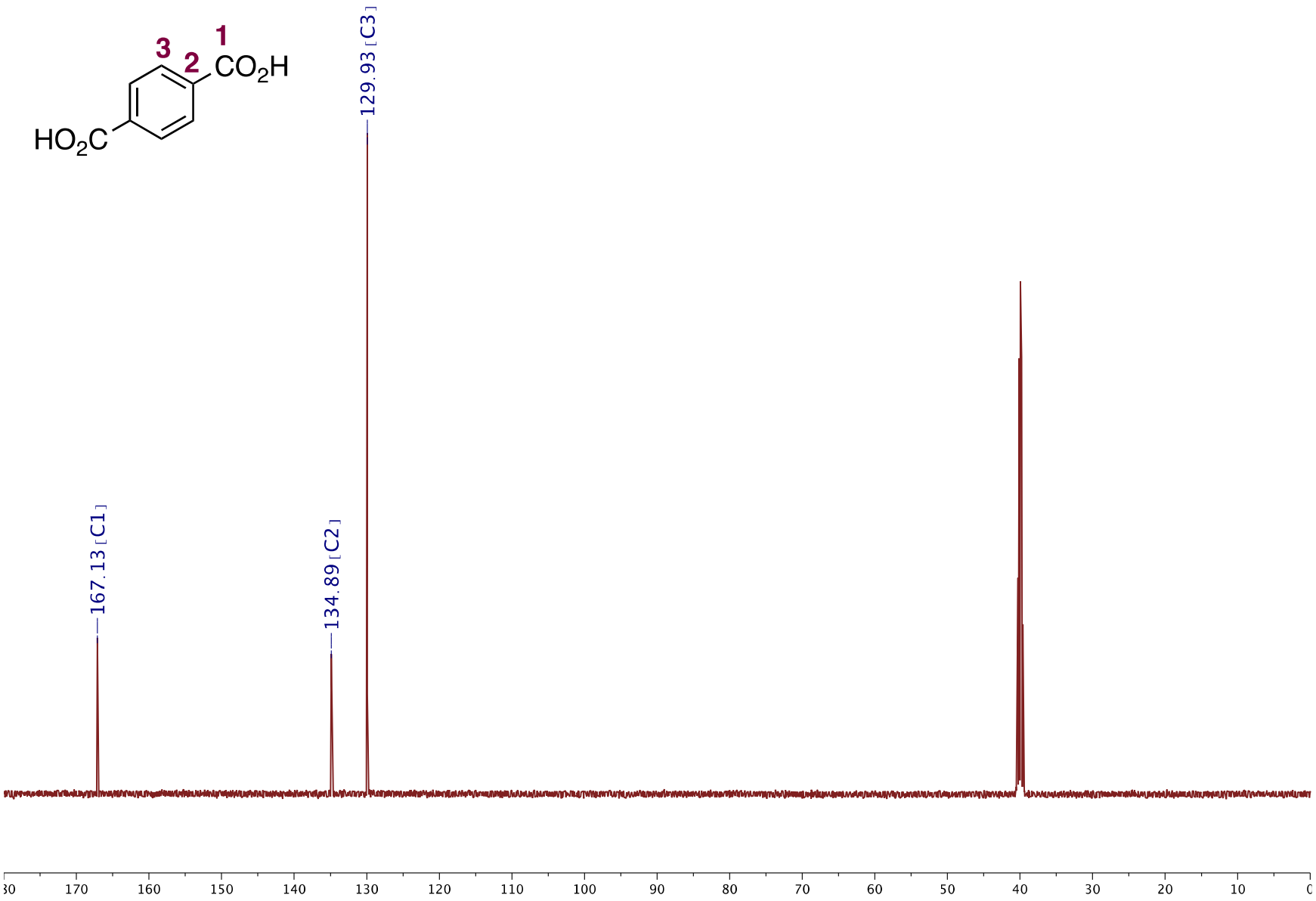


Figure 5.4. ^{13}C-NMR spectrum of isolated terephthalic acid **1**

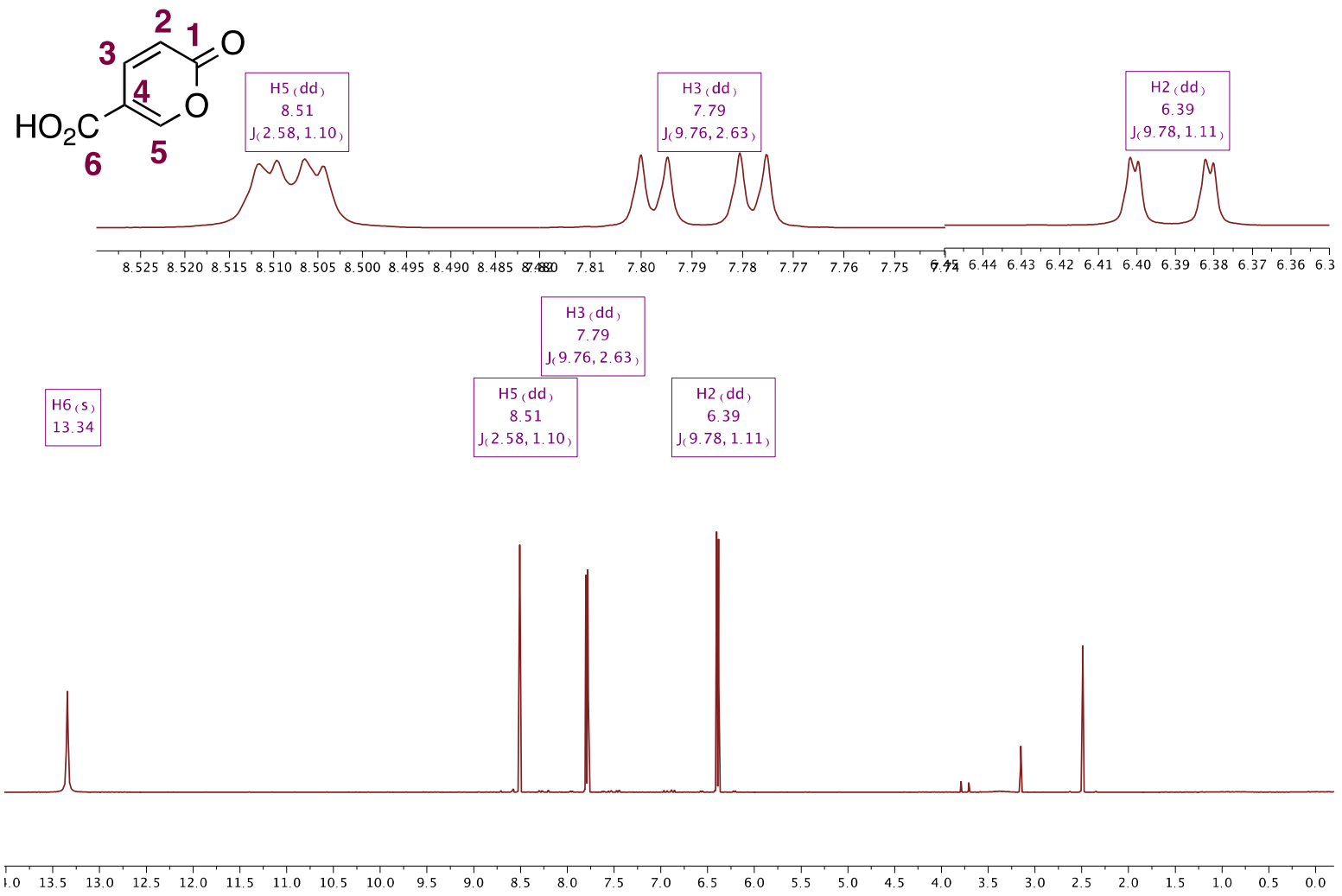


Figure 5.5. ^{1}H-NMR spectrum of coumalic acid **22**

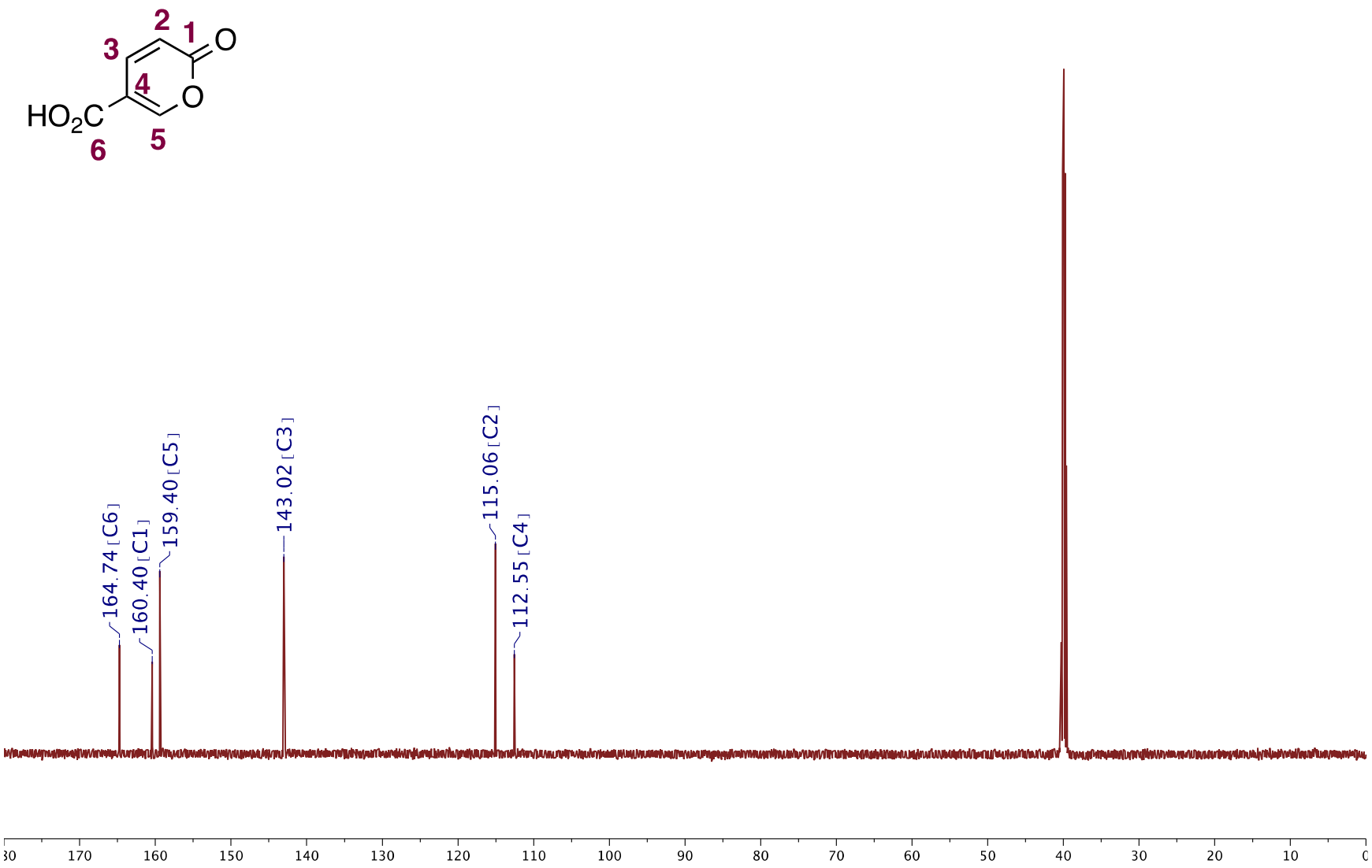


Figure 5.6. ^{13}C-NMR spectrum of coumalic acid **22**

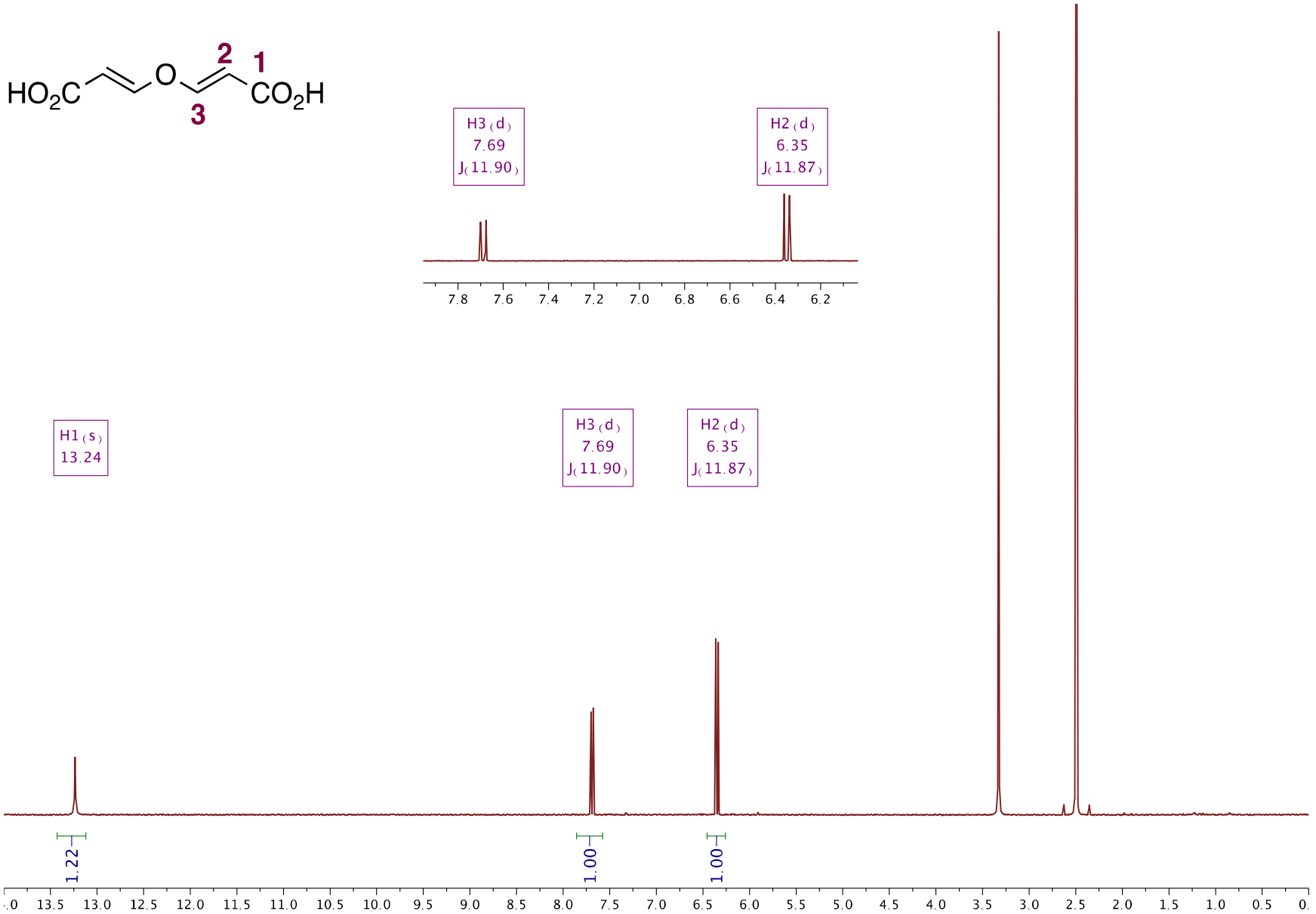


Figure 5.7. ^{1}H-NMR spectrum of *trans*-diacrylic ether 50

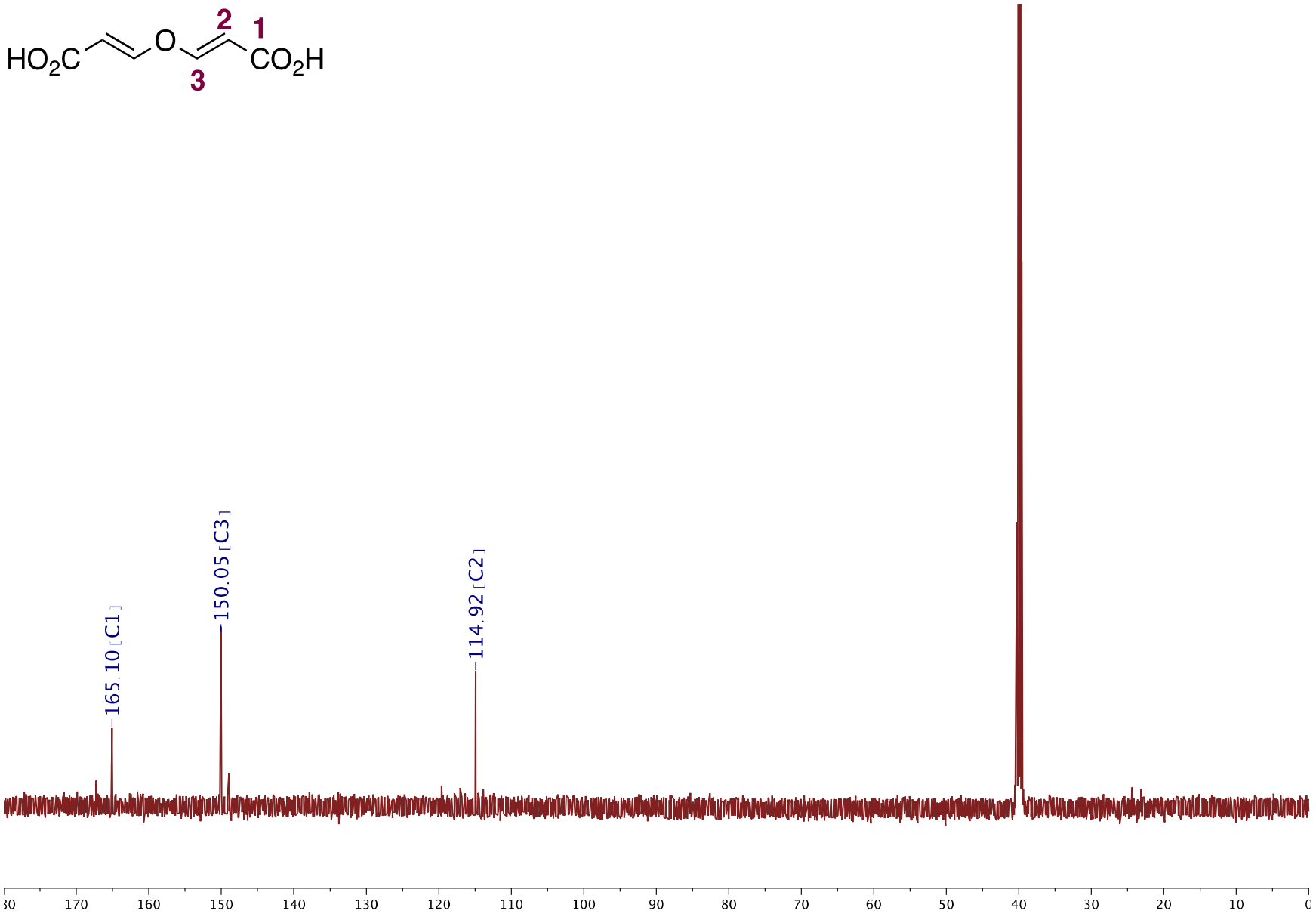


Figure 5.8. ^{13}C-NMR spectrum of *trans*-diacrylic ether **50**

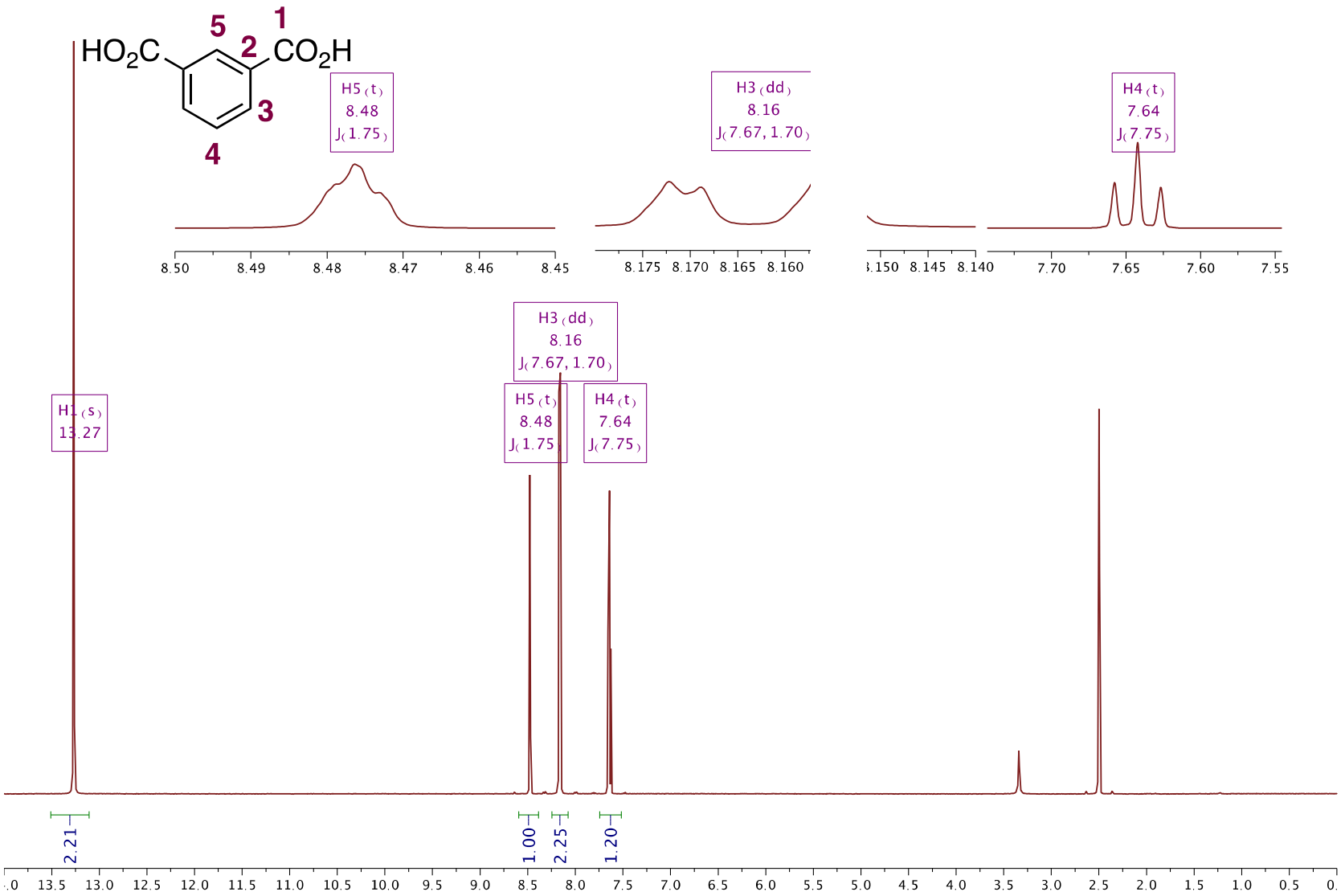


Figure 5.9. ^{1}H-NMR spectrum of isolated isophthalic acid **2**

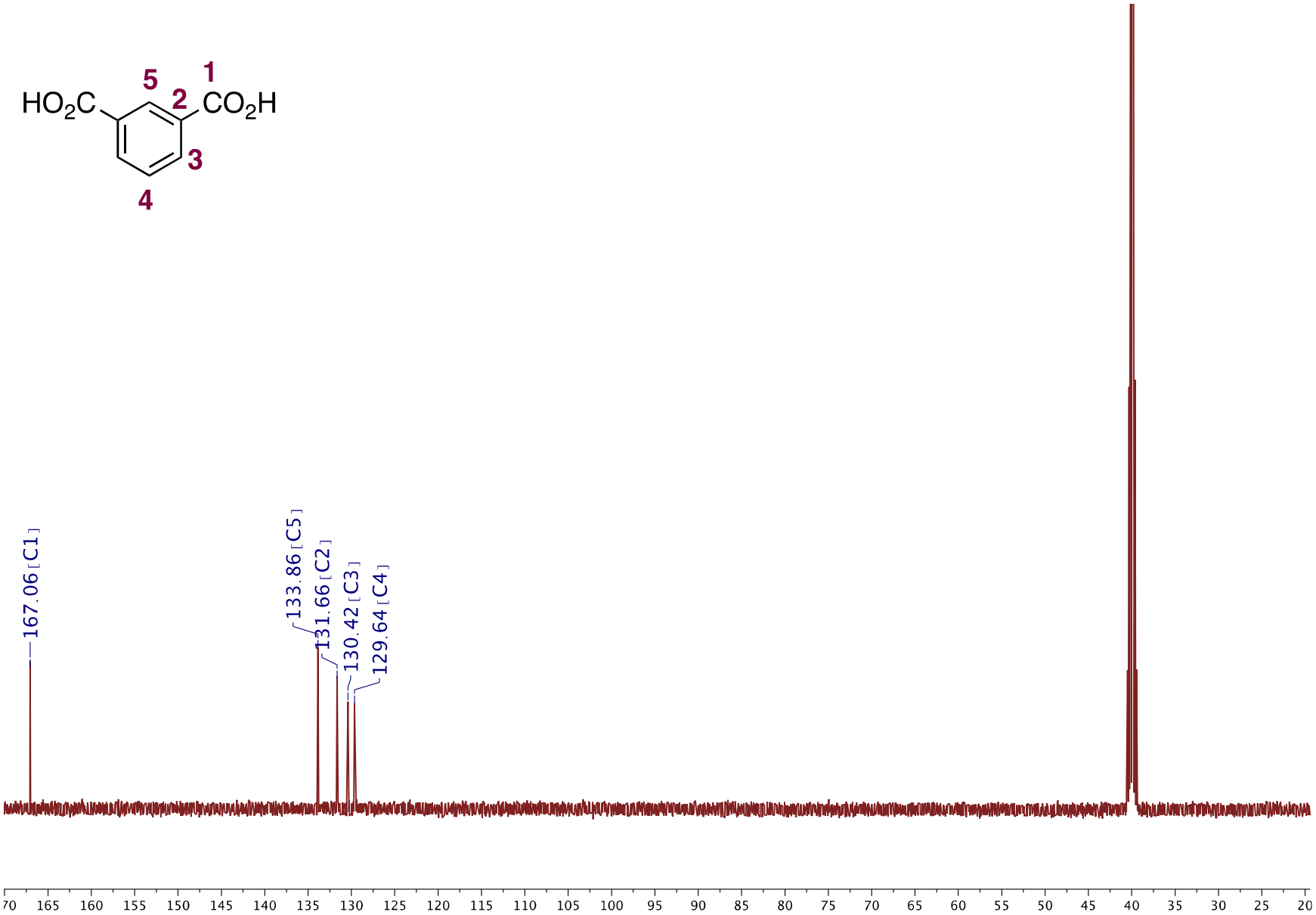


Figure 5.10. ^{13}C-NMR spectrum of isolated isophthalic acid **2**

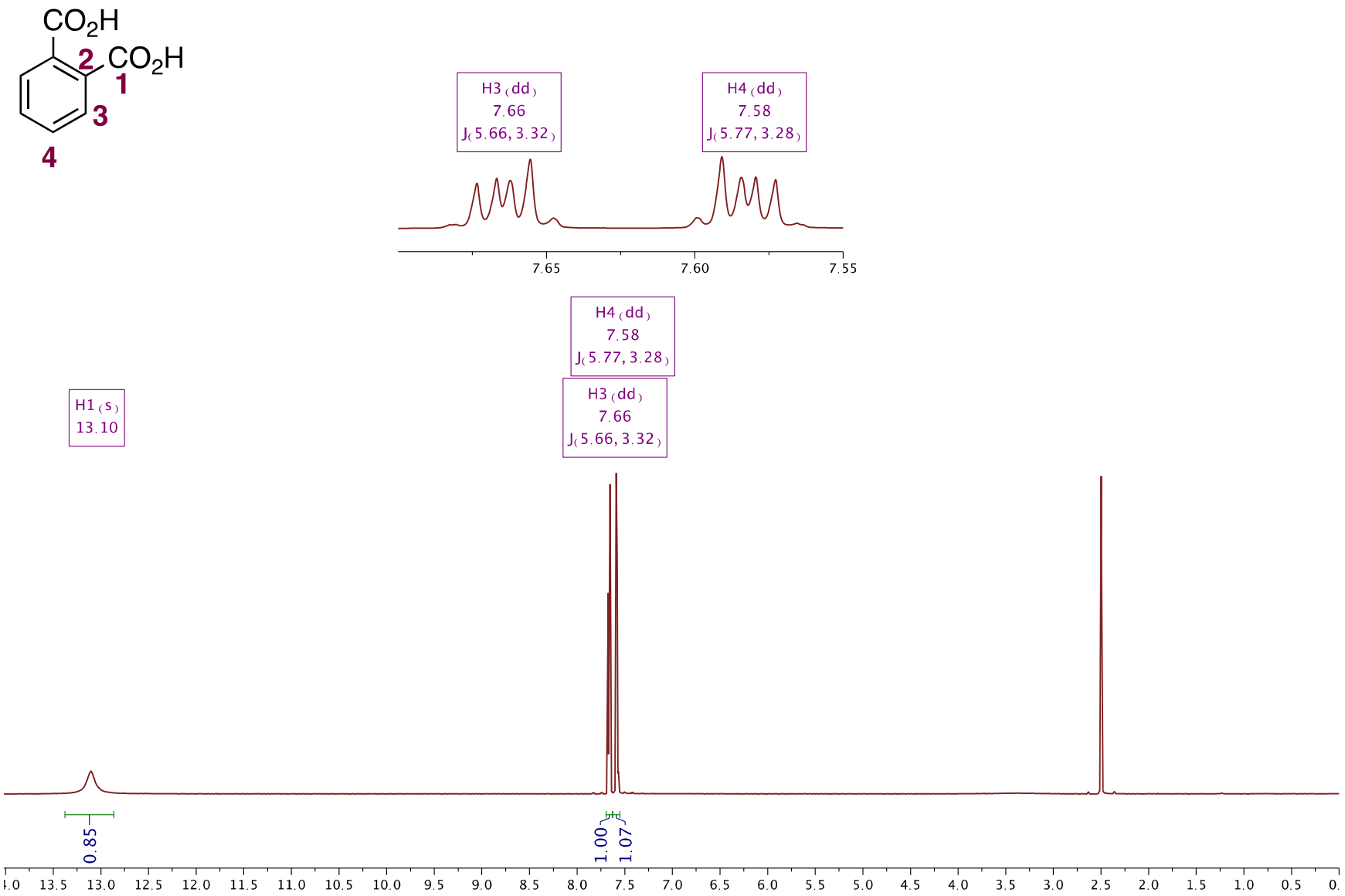


Figure 5.11. ^{1}H-NMR spectrum of isolated phthalic acid **3**

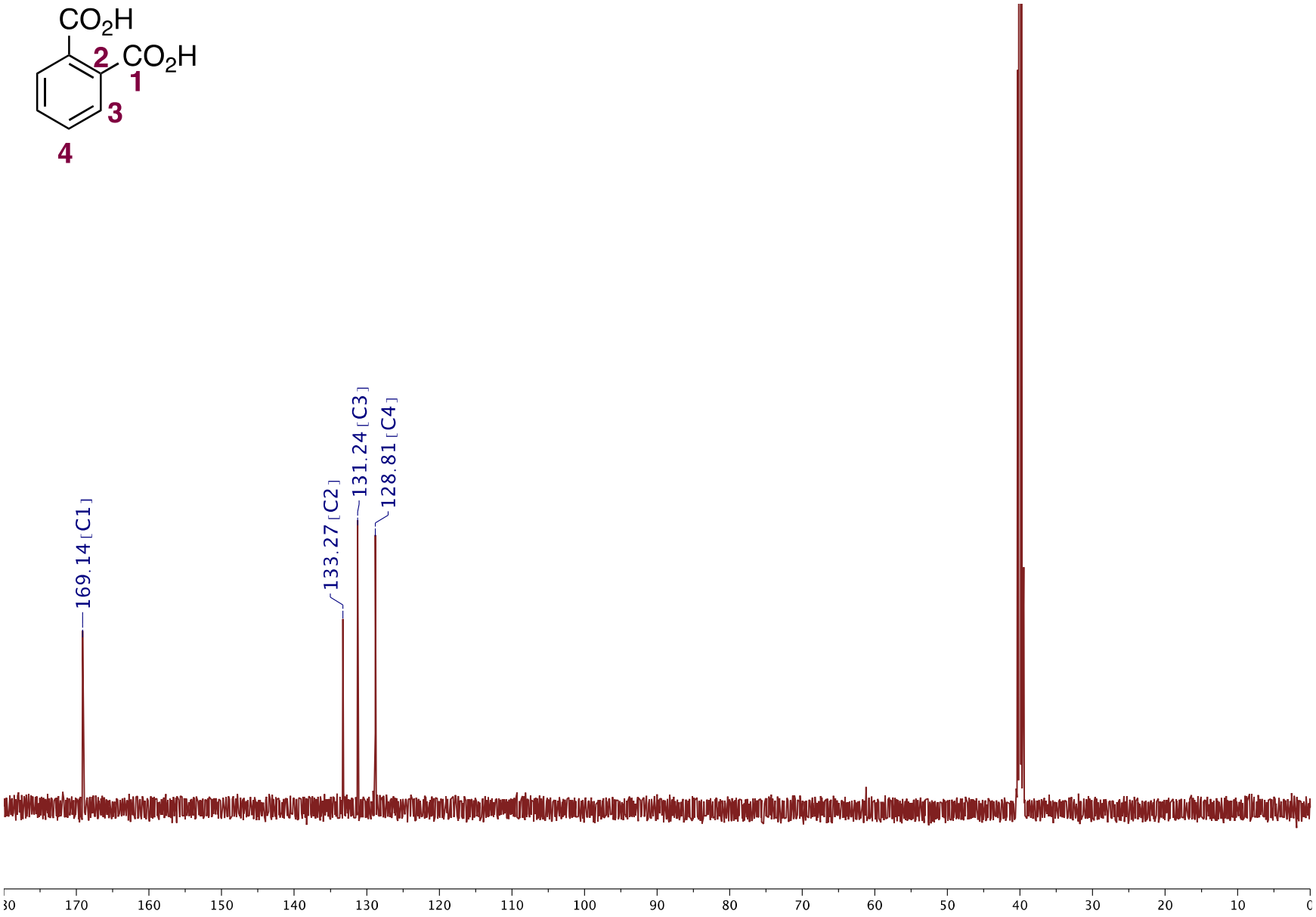


Figure 5.12. ^{13}C-NMR spectrum of isolated phthalic acid **3**

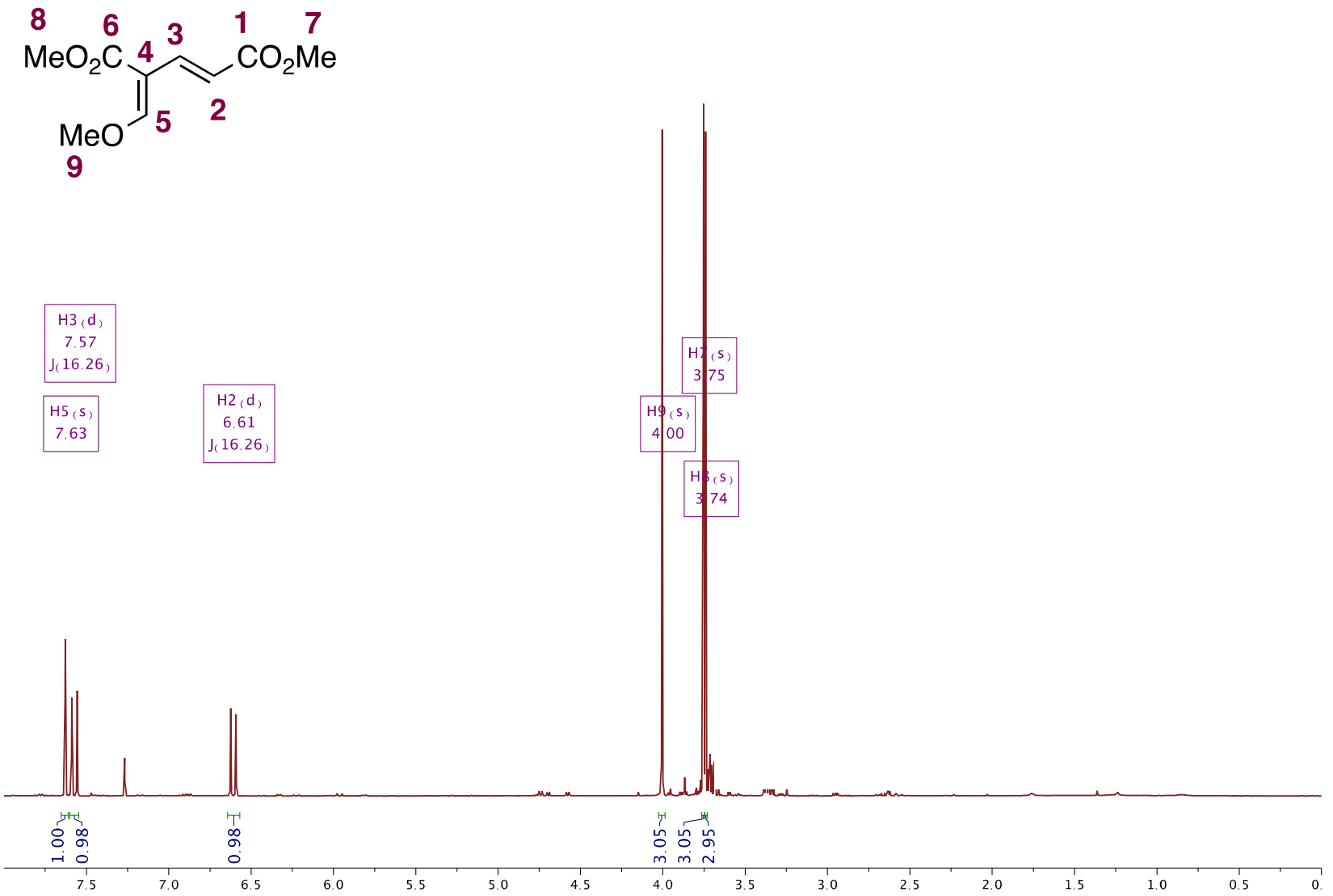


Figure 5.13. ^{1}H-NMR spectrum of methyl 4-carbomethoxy-5-methoxy-penta-2E,4Z-dienoate **45**

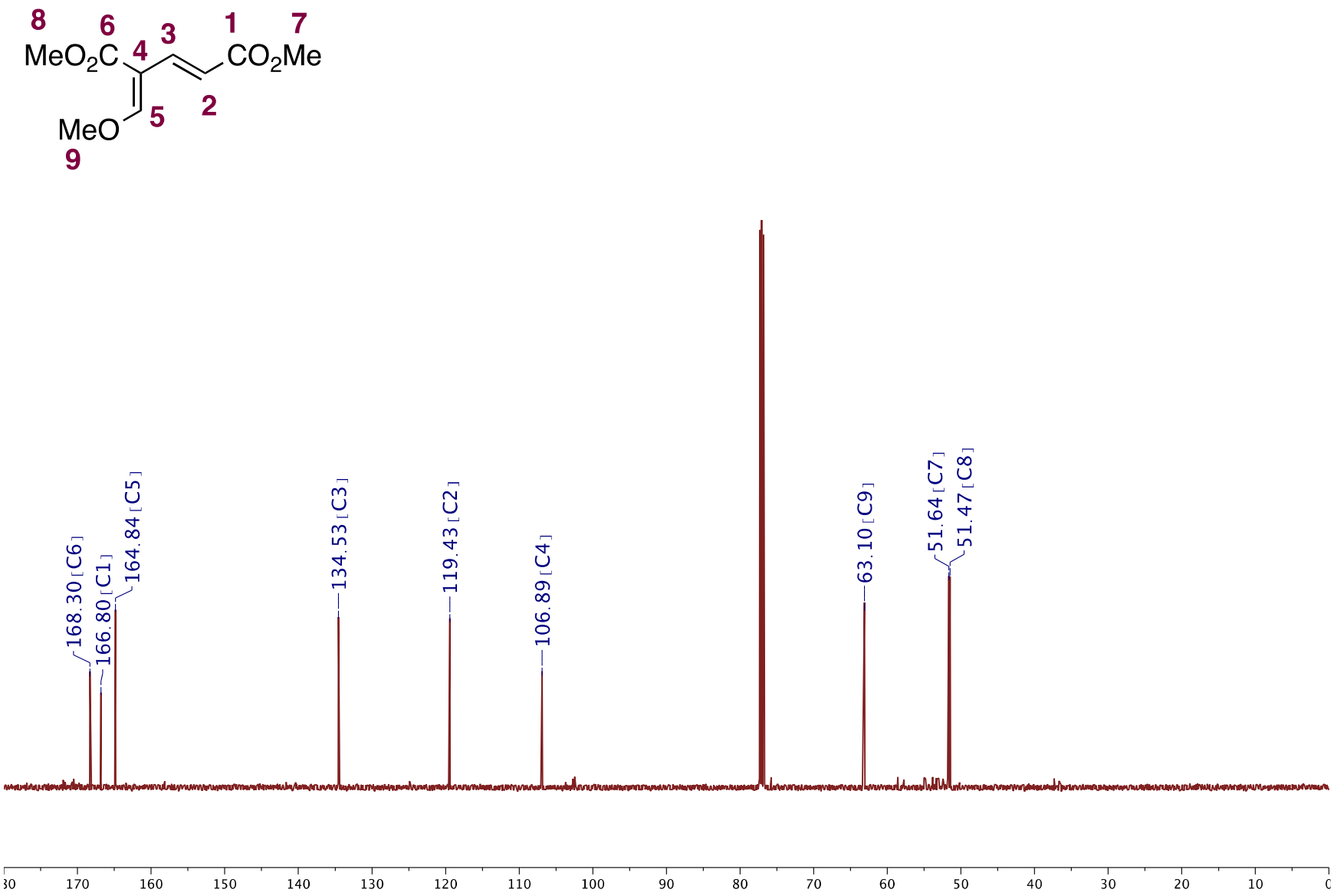


Figure 5.14. ^{13}C-NMR spectrum methyl 4-carbomethoxy-5-methoxy-penta-2E,4Z-dienoate **45**

^{1}H and ^{13}C NMR spectra of isolated isocoumalic acid **23** (Exp. 22, p. 74)[2]

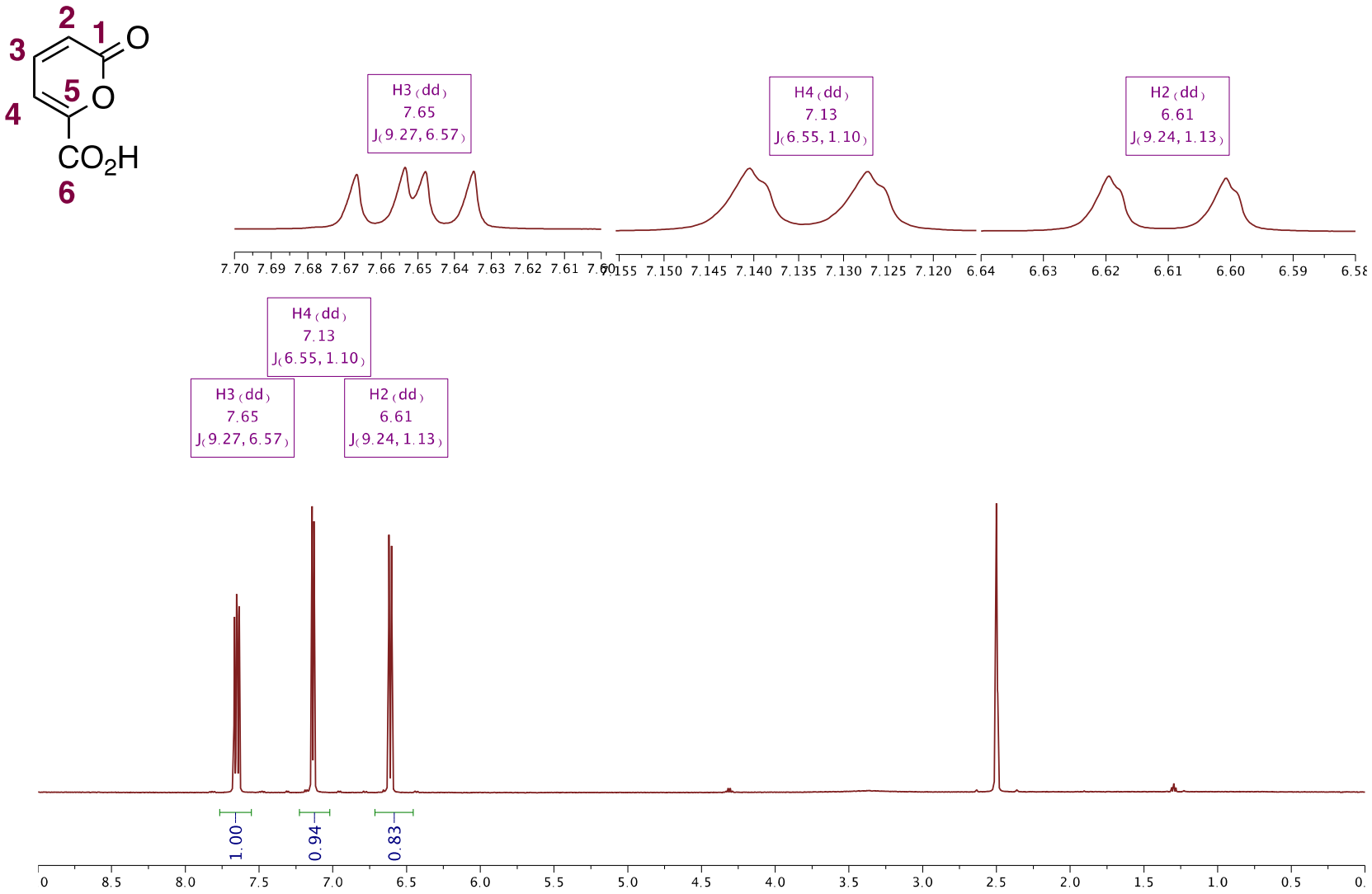


Figure 5.15. ^{1}H spectrum of isolated isocoumalic acid **23**

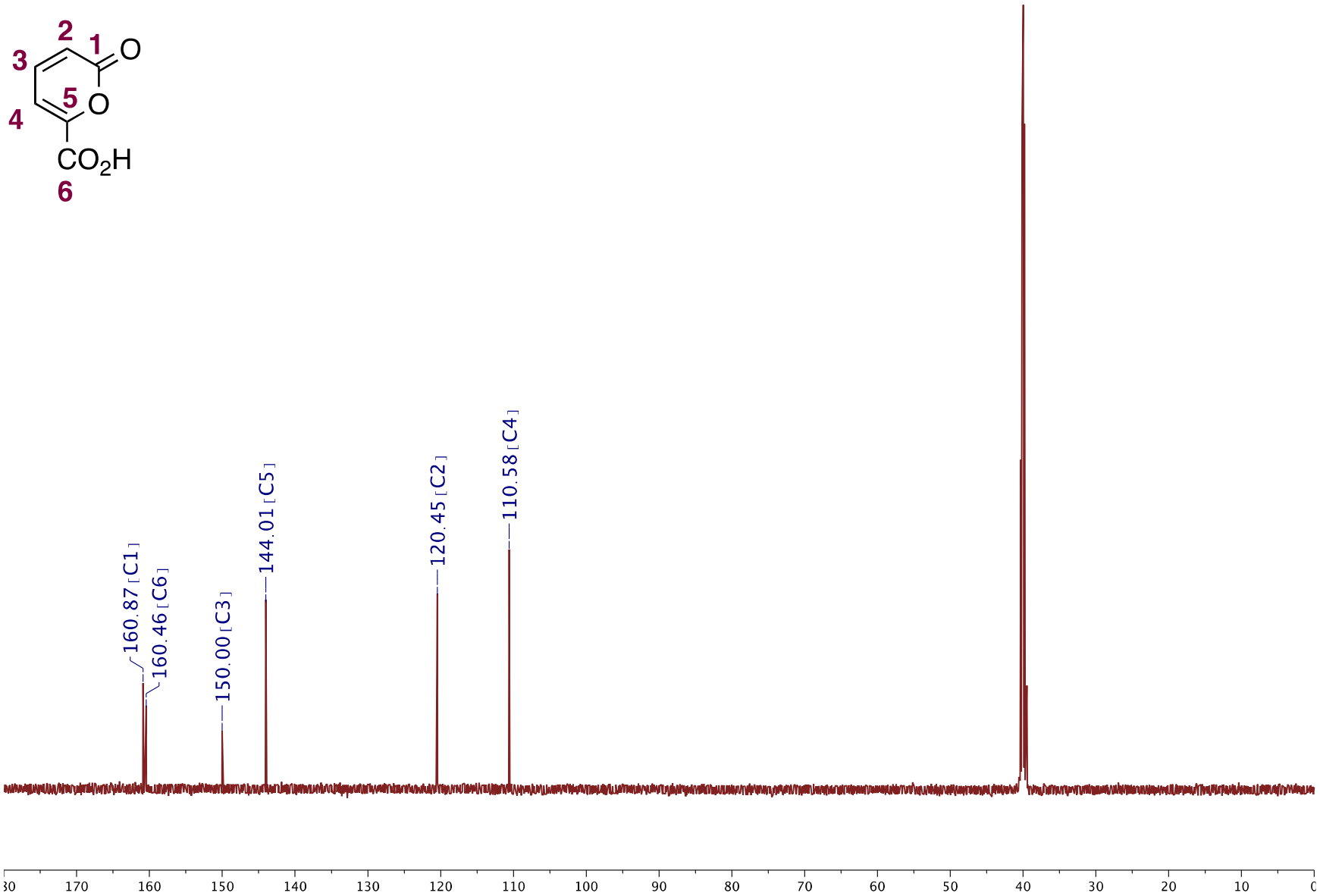


Figure 5.16. ^{13}C-NMR spectrum of isolated isocoumalic acid **23**

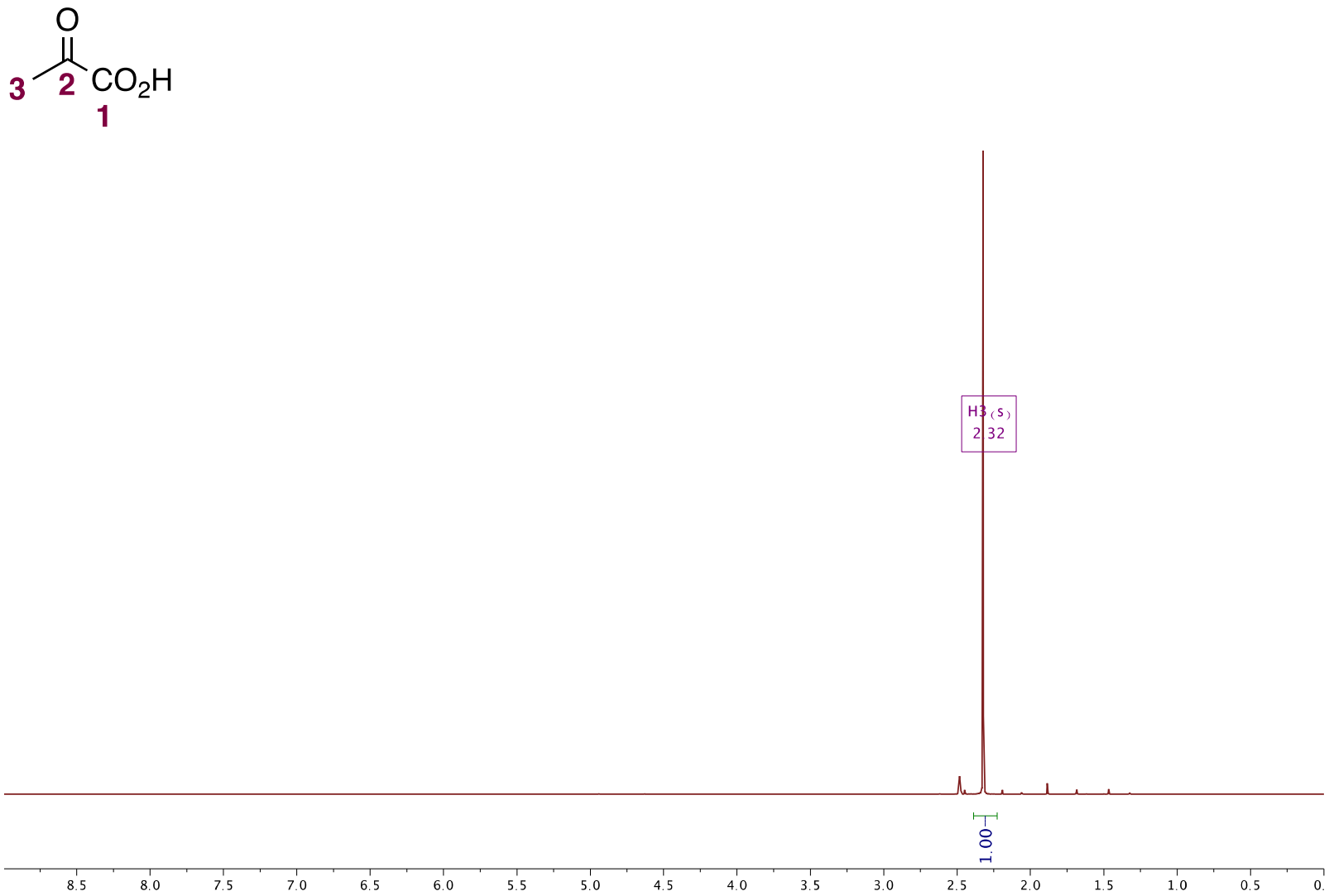


Figure 5.17. ^{1}H-NMR spectrum of pyruvic acid **59**

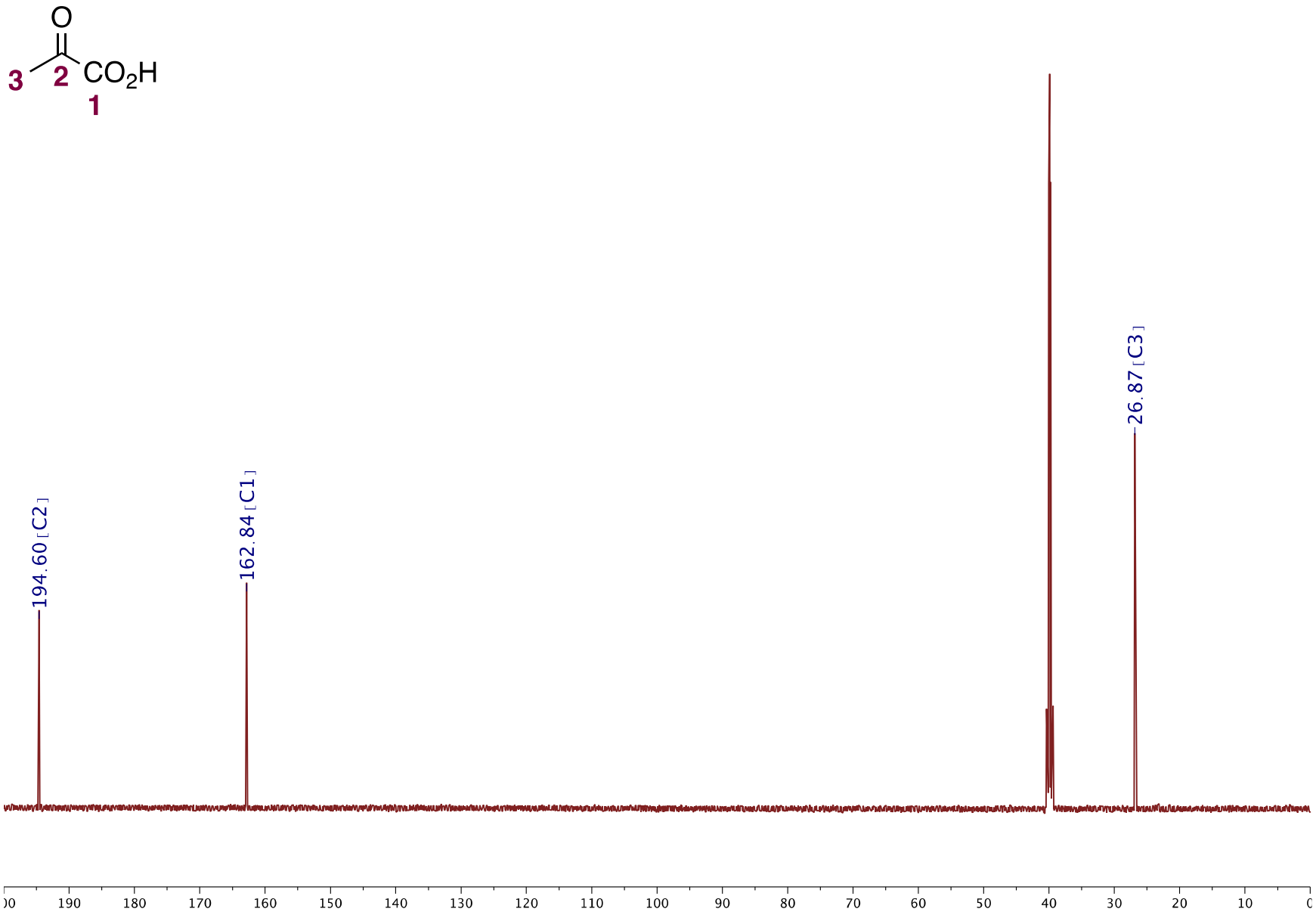


Figure 5.18. ^{13}C-NMR spectrum of pyruvic acid **59**

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