CO_2 FIXATION: CATALYTIC SYNTHESIS OF β-HYDROXYCARBOXYLIC ACIDS

by

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A thesis submitted to the Department of Chemistry

In conformity with the requirements for

the degree of Master of Science

Queen's University

Kingston, Ontario, Canada

(August, 2008)

Abstract

Although carbon dioxide as a greenhouse gas is a serious environmental concern, it remains a valuable C1 source if viable methods are available for its conversion into useful products. Herein, we present recent progress in the synthesis of aliphatic, aromatic, cyclic, and bicyclic β-ketocarboxylic acids and the promising results from subsequent asymmetric hydrogenation to give β-hydroxycarboxylic acids.

For the synthesis of the β-ketocarboxylic acids, we investigated the effects of temperature, reaction time, and amount of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), which is a promoter for carbon-carbon bond formation with CO_2. The highest-yielding conditions for this DBU-promoted carboxylation reaction were used to carboxylate a number of aliphatic and aromatic substrates.

In order to determine whether the hydrogenation reaction will effectively compete with the *in situ* decarboxylation of the β-ketocarboxylic acids, ^{1}H NMR spectroscopy was used to monitor the rate of decarboxylation. The solvent, electronic, and steric effect on the rate of decarboxylation was investigated by testing a variety of β-ketocarboxylic acids.

Using "$RuCl_2${(S)-BINAP}" catalyst precursor, we determined the effect that solvent, H_2 pressure, base, and substrate substitution had on the enantioselectivity of the asymmetric hydrogenation. CH_2Cl_2 and MeOH were determined to be the best solvents because of the high hydrogenation selectivity, high enantioselectivity, and decreased reaction times. These standard conditions were used to hydrogenate the variety of aliphatic and aromatic β-ketocarboxylic acids previously synthesized.

Additional experiments, including deuterium labelling, were performed in an attempt to elucidate the hydrogenation mechanism and the actively hydrogenated tautomer. These results lead us to believe that different reaction pathways occur in protic versus aprotic solvents.

The results discussed herein represent the first in-depth investigation of transition metal catalyzed hydrogenation of β-ketocarboxylic acids. These results are very encouraging because enantioselectivities greater than 99 % were achieved for multiple β-keto acids. This synthesis is industrially advantageous due to the limited number of reactants required, their low-cost, and the potential for recycling unused materials.

Acknowledgements

Over the past two years, I have had the opportunity to work with an outstanding group of individuals who have enriched my time at Queen's in immeasurable ways. To begin with, I would like to thank my supervisor, Dr. Philip Jessop, for his guidance, knowledge, understanding, and good-hearted nature. Thank you for never giving up on me, keeping me on target, and allowing me to pursue some of my crazier ideas.

Thank you to all Jessop members: Dominik--your constant aid, ingenious ideas, and companionship; Andrew--your endless stream of knowledge and humour; Lam--your success, personality, and attitude kept me going through the hard times; Yi--your inquisitive nature always kept me on my toes. Thanks to the newer grad students, Alaina, Chen, Darrell, Lauren, Vanessa, for your fresh points of views and for reminding me of the importance of a social life. Thanks to all Jessop members and neighbouring labs for enduring my constant singing, and for believing in "The Power of Positive Thinking!!"

I am grateful to the Crudden members, especially Judy, Kevin, Ben, Jeremy, Jonathan, Stephanie, and Chris, for your experimental guidance, for the use of your SFC, for your friendship, and for the small aliquots of chemicals that I "borrowed".

The administration and technical staff, including but not limited to Diane, Susan, and Rob, for making themselves available to me whenever needed, brightening my days consistently, and being great distractions from work. Thank you to the technical staff, including Dr. Sauriol for NMR, Jie Sui for MS, Dr. Hull for IR, and Gary and Charles for machine repair.

Thank you to R.T. Mahon for the scholarship and Robert Samuel McLaughlin for the fellowship that I was awarded during my studies.

Thank you to my family, who as per usual, was supportive, encouraging, and helpful every step of the way in any way possible. Their advice was always well-timed, and it kept any potential "earth-shattering" situation in perspective.

Saving the best for last, my fiancé, Jackie Michalchuk, continues to surprise me with her capacity for unwavering love, understanding, and support throughout all of my endeavours. Because I am a believer of "what goes around comes around," I am in debt to countless individuals, in addition to those mentioned herein; however, I look forward to repaying Jackie as we start our new life together.

Table of Contents

List of Figures

List of Schemes

List of Tables

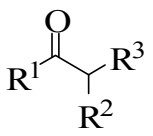
List of Abbreviations

Å	angstrom(s)
atm	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
br	broad
CO	carbon monoxide
CO_2	carbon dioxide
COSY	correlation spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIOP	*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
d	doublet
dd	doublet of doublets
DMF	dimethylformamide
ee	enantiomeric excess
EI	electron impact
eq	equivalents
GC	gas chromatography
h	hour(s)
hfc	3-(heptafluoropropylhydroxymethylene)-(+)-camphorate
HMBC	heteronuclear multiple bond correlation
HPLC	high pressure liquid chromatography

HR-MS	high resolution mass spectrometry
HSQC	heteronuclear single quantum corrletion
Hz	hertz
IR	infrared
$^{n}J_{xy}$	n bond coupling constant between atoms x and y
LDA	lithium diisopropylamide
m	multiplet
M	molarity
Me	methyl
MeOBIPHEP	2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl
min	minute(s)
MMC	magnesium methyl carbonate
mmol	millimole(s)
mol	mole(s)
m/e	mass to charge ratio
NMR	nuclear magnetic resonance
OAc	acetate
Ph	phenyl
PPC	polypropylene carbonate
ppm	parts per million
q	quartet
R	alkyl or aryl group
sec	second(s)

s	singlet
$scCO_2$	supercritical carbon dioxide
S/C	substrate/catalyst
SFC	supercritical fluid chromatography
t	triplet
tolBINAP	2,2’-bis(di-p-tolylphosphino)-1,1’-binaphthyl
THF	tetrahydrofuran
TLC	thin layer chroomatograph(y)
TMS	tetramethylsilane

List of Numbered Compounds



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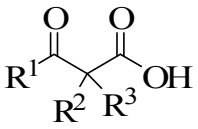

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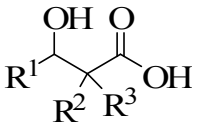

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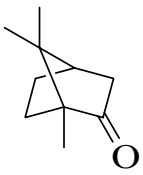
	R^1	R^2	R^3
a	Ph	H	H
b	4-ClC_6H_4	H	H
c	4-$OMeC_6H_4$	H	H
d	2-MeC_6H_4	H	H
e	naphthyl	H	H
f	Ph	Me	H
g	Ph	Me	Me
h	Me	H	H



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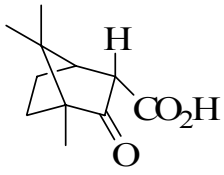

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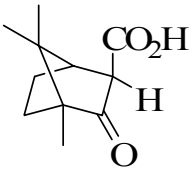

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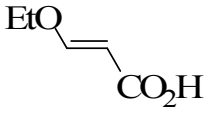

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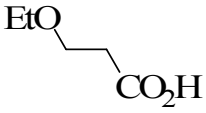


8

Chapter 1
General Introduction

1.1 Carbon Dioxide and the Environment

Carbon dioxide is the predominant greenhouse gas and, therefore, is a major environmental concern. What is not normally publicized is that carbon dioxide has the lowest global warming potential potency, based on infrared absorption, compared to the other greenhouse gases, such as water vapour, methane, nitrous oxide, and hydrofluorocarbons.[1] In fact, it is the overproduction of carbon dioxide that produces major global environmental concerns, such as changes in global climates, rain patterns, ice fields, and sea levels.[2] As an example, global warming is likely to blame for the 10 % reduction in the sea-ice thickness during the summer and autumn months of the past 3 decades.[2] There are a variety of culprits for the high concentration of atmospheric carbon dioxide; however, combustion of fossil fuels, production of ammonia and hydrogen,[3] and production of lime and cement are particularly large contributors.[4]

Although carbon dioxide is portrayed as an environmentally unfriendly substance, it is exactly this molecule which serves as the root of almost all energy for most life forms on earth. Autotrophs, such as plants, use carbon dioxide as their carbon source by fixing carbon dioxide during photosynthesis to produce glucose and oxygen (Equation (1)). Not only is glucose a plant's fuel source, but it also serves as a fuel source for higher heterotrophs that consume plants. Therefore, carbon dioxide fixation is necessary for most life forms on earth.

$$6\ CO_2 + 12\ H_2O + \text{light} \rightarrow C_6H_{12}O_6 + 6\ O_2 + 6\ H_2O \qquad (1)$$

Another natural carbon dioxide fixation process includes the spontaneous calcification by some marine organisms to produce calcite from carbon dioxide. Studying these fixation mechanisms by biomimetic chemistry allows researchers to elucidate and understand how these natural processes fix carbon dioxide so efficiently; this knowledge can then be used to alter existing technology or develop new and more efficient technology for human use. Any new technologies subsequently developed could improve economic efficiency by reducing and reusing waste products, therefore minimizing the environmental impact by reducing carbon dioxide emission.

1.2 Carbon Dioxide Utilization

Since the start of the industrial revolution, carbon dioxide concentration in the atmosphere has increased by 30 %.[5] On an industrial level, there are two methods for dealing with carbon dioxide overproduction: adaptive and mitigative. The passive adaptive approach assumes that global warming and CO_2 overproduction will continue and that life on earth will adapt in order to survive; the outcome would be very similar to that observed 2 billion years ago when the reductive, sulphur-based environment became the present-day oxidative, oxygen-based atmosphere.[6]

The more proactive, mitigative approach involves developing technologies to lower the amount of CO_2 released into the atmosphere.[7] This mitigation approach is broken down into numerous components, including improving fuel efficiency, using non-carbonaceous fuels, exploiting biomass energy, sequestering CO_2, and utilizing CO_2.[7] Within CO_2 utilization, only large-scale processes such as enhanced-oil recovery

and desalination of water hold potential in mitigating a significant portion of the vast quantities of CO_2 produced. Although industrial CO_2 fixation is classified as CO_2 utilization, its potential for CO_2 mitigation is almost none (*vide infra*).

1.3 Industry and Carbon Dioxide Utilization

It would be environmentally and economically ideal for large-scale industrial products to be synthesized from a cheap, safe, ubiquitous, and benign starting material such as carbon dioxide; however, for this to be feasible, carbon dioxide must be recaptured from industrial processes. Fossil-fuel power plants are good candidates because the exhausts contain high CO_2 concentrations.

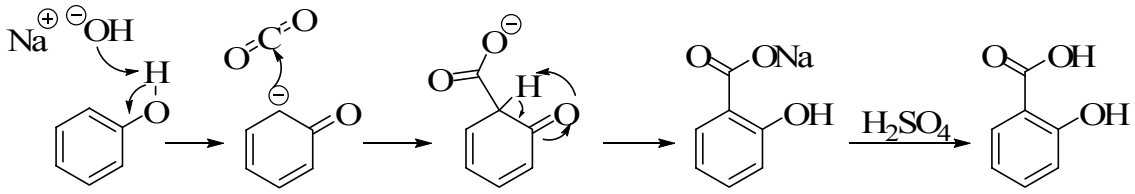
Even after CO_2 collection, modern mitigation technologies are not efficient enough to reduce or even maintain current CO_2 emissions. Based on optimistic projections, a 60 % reduction in CO_2 emissions could be observed by replacing traditional transportation fuels with synthetic carbonaceous fuels from CO_2, such as methanol, if a nonfossil energy source for synthesis is used; an additional 32 % reduction could occur by sequestering/utilizing CO_2 for enhanced oil recovery. Other chemical and commodity uses, including CO_2/oil slurry transportation and CO_2 fixation for the synthesis of plastics and fertilizer, would cause less than a 5 % reduction in CO_2 emissions.[7]

Unfortunately, most utilization techniques eventually release CO_2 to the atmosphere. Although CO_2 fixation permanently removes the CO_2 from the atmosphere, high-energy compounds are required to activate CO_2; the energy needed to produce these

high-energy compounds actually creates additional CO_2. Even though mitigation of a significant amount of anthropogenic CO_2 is ideal, CO_2 fixation products, such as such as urea, polymers, and formic acid, are not required on such a large scale. Therefore, syntheses involving CO_2 fixation do not hold potential for mitigating CO_2. However, new synthetic pathways involving CO_2 fixation can benefit the environment by reducing fossil fuels consumption and eliminating the use of very toxic reagents, such as phosgene and carbon monoxide (Section 1.5).[8]

1.4 Current Carbon Dioxide Fixation Techniques

Numerous transformations involving CO_2 and organic substrates have been studied.[9] The Kolbe-Schmitt reaction, producing salicylic acid, is one of the most well-known CO_2 fixation processes (Scheme 1.1).[10] Its use in industry is possible because of its efficiency and simplicity. Upon heating the alkali phenolate, nucleophilic attack on carbon dioxide occurs, followed by tautomerization; protonation gives the final product.[10]



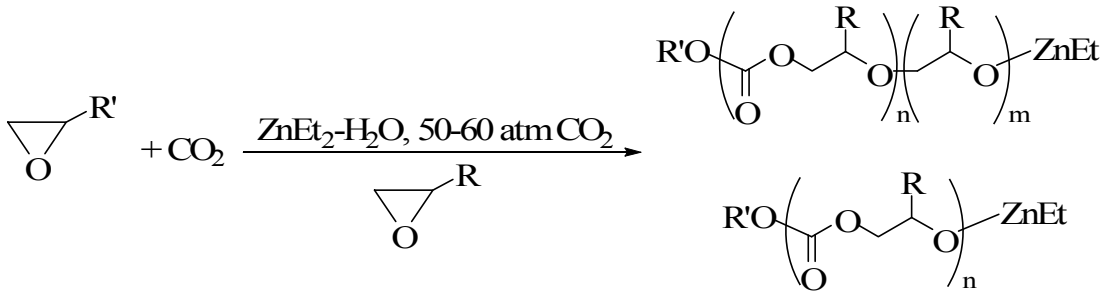
Scheme 1.1. Kolbe-Schmitt Reaction.[10]

There are, however, a number of other reactions that are interesting and useful. The largest industrial use for CO_2 is the synthesis of urea (Equation 1);[10] because of its

water-soluble nature and high nitrogen content, 90 % of urea produced is used as fertilizer.

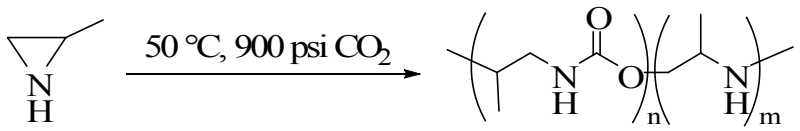
$$2NH_3 + CO_2 \rightarrow [NH_4]^+[H_2NCOO]^- \rightarrow H_2NCONH_2 + H_2O \quad (1)$$

Copolymerization of CO_2 with an epoxide has also been studied (Scheme 1.2).[11] If the active polymer terminus reacts directly with the epoxide, a block copolymer of propylene oxide and propylene carbonate is created; however, if CO_2 and the epoxide react alternately with the active polymer terminus, a polypropylenecarbonate polymer (PPC) is created. PPC is a good candidate for food packaging because of its low oxygen permeability, and it is a widely-used plastic for general use. Thermal decomposition of PPC can also produce cyclic propylene carbonate, a valuable solvent with a high boiling point, and an electrolyte for lithium ion batteries.[12] Because the isolated yield from thermal decomposition is low, propylene carbonate is synthesized directly from the propylene oxide and CO_2.



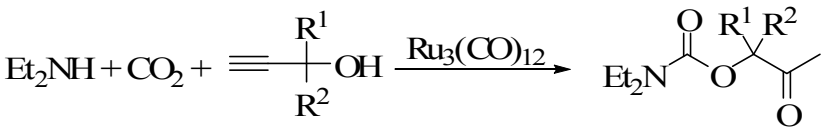
Scheme 1.2. Copolymerization of CO_2 with Epoxide.[11]

Similarly, Beckman *et al.*[13] reacted CO_2 and 2-methylaziridine at 50 °C to produce a polyurethane (Scheme 1.3). Although polyurethanes are among the most used plastics, current syntheses normally involve the use of toxic isocyanate monomers.



Scheme 1.3. Synthesis of Polyurethanes from CO_2 and 2-methylaziridine.[13]

Sasaki synthesized β-oxopropylcarbamates from secondary amine, propargyl alcohol, and CO_2 in the presence of $Ru_3(CO)_{12}$ in up to 64 % yield (Scheme 1.4).[14]



Scheme 1.4. Urethane Synthesis from Secondary Amine, Propargyl Alcohol, and CO_2.[14]

Many other syntheses of organic products from CO_2 have been discovered, including syntheses of acids, alcohols, carbamate esters, dialkylcarbonates, ureas, formamides, formate esters, lactones, and many others.[9]

1.5 Why Research CO_2 Fixation?

Because of its more reactive nature, carbon monoxide (CO) utilization is preferred over CO_2 utilization, such as the synthesis of formic acid. Even though CO may be energetically favourable for a reaction, CO raises many safety concerns: it is a colourless, flammable, odourless gas that binds more strongly than oxygen to hemoglobin, causing asphyxiation.[15] Therefore, developing new CO_2 fixation methods that can effectively compete with CO fixation methods is of industrial interest.

Carbon dioxide is kinetically and thermodynamically stable. Kinetically, it requires a large amount of energy to overcome its activation barrier before a reaction can

occur.[9] To lower the activation barrier, catalysts, such as transition metals, can be used; carbon dioxide can coordinate through various modes due to the nucleophilic oxygen atoms and electrophilic carbon atom. Although coordination through C-M and C=O-M bonding are most prevalent, a variety of binding methods have been reviewed by Aresta *et al.* and Gibson.[16-18] After the CO_2 transformation is complete, the final product is released from the metal.

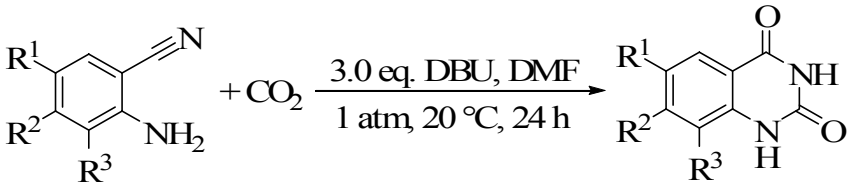
A variety of methods can be used to overcome the thermodynamic stability of CO_2: (1) choose a common base, such as alkyl lithium or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[7] for product stabilization, (2) choose high-energy starting materials, such as ring-strained compounds, or (3) choose low-energy products, such as carbonates. Furthermore, removal of the final product will shift the equilibrium to favour the CO_2 transformation; likewise, strong drying agents can remove the coproduced water.[9] Although thermodynamically stable, nucleophilic attack on the electron deficient carbonyl carbon is often the mode of reaction.

Many of these methods require a large energy input; this energy makes the synthesis more expensive, and additional CO_2 is created during the energy production. Therefore, in order to make an industrially viable CO_2 fixation method, the recycling of the activating species is financially preferable. This thesis will briefly investigate the reusability of DBU.

1.6 DBU and its Properties

DBU is a sterically hindered amidine that has demonstrated usefulness in a variety of different reactions. Jessop *et al.*[19] demonstrated that the reduction of carbon dioxide to formic acid increases by an order of magnitude when NEt_3 is replaced with DBU. With DBU as the base, the carboxylation of activated methyl and methylene groups has been studied successfully, provided the substrate's pK_a(DMSO) is within the range of 20-30.[20,21]

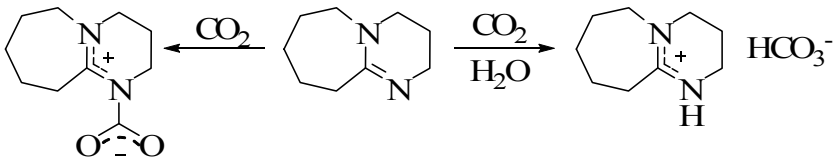
The synthesis of 1H-quinazoline-2,4-diones from 2-aminobenzonitriles and 1 atm CO_2 is possible when a catalytic amount of DBU is present.[22] Instead of the traditionally used mineral bases for Suzuki coupling, Chanthavong *et al.*[23] demonstrated that an organic base, such as DBU, in a water/ethanol solution could be used.



Scheme 1.5. Synthesis of 1H-quinazoline-2,4-diones.[22]

Yet, the CO_2 activation that DBU offers to these reactions in not fully understood. Previous literature reported that reacting DBU with CO_2 forms a detectable and even isolateable zwitterionic adduct that might be responsible for the activating effect (**A** in Scheme 1.6).[24] However, it has more recently been shown that the detectable species is in fact the DBU bicarbonate salt instead (**B** in Scheme 1.6).[25] It is therefore possible that the promoting effect of DBU, and other amidines, could be a result of the increased stability and solubility of the bicarbonate salt in organic solvents. In the case of reactions

in the absence of water, the promoting effect of DBU may simply be due to its basicity (*vide infra*).



Scheme 1.6. Zwitterionic Adduct (**A**)[24] and $DBUH^+$ Bicarbonate (**B**)[25] Salt Formation.

With the intent of making industrial processes more environmentally friendly, Jessop *et al.*[26,27] set out to develop a solvent capable of changing its polarity whenever synthetically needed; they subsequently established that DBU alkylcarbonate salts function as such switchable solvents. Addition of CO_2 to a mixture of DBU and alcohol forms an ionic liquid; upon removal of CO_2, the solution returns to the non-ionic state. Therefore, this system allows for the solvent polarity switching using only carbon dioxide as a trigger.

For this thesis, DBU was selected as the base of choice because it is more basic than amines, having a $pK_{aH}(H_2O)$ of 12[28] and $pK_{aH}(MeCN)$ of 24.1[29] as opposed to triethylamine with a $pK_{aH}(H_2O)$ of 10.8 and $pK_{aH}(MeCN)$ of 18.8[29]; pK_{aH} is defined as the pK_a of the conjugate acid. This increased basicity is due to the stabilization of DBU's conjugate acid by delocalization of the cationic charge. The bridgehead nitrogen would be expected to be more basic because it has less s orbital character; however, the sp^2 nitrogen must be protonated to allow for delocalization to occur.[30]

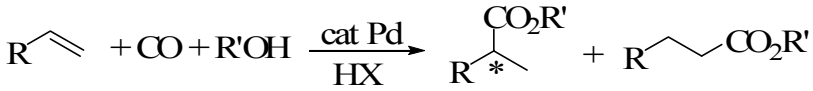
1.7 Asymmetric Hydrogenation in General

Because a mixture of enantiomers can have adverse effects, such as birth defects from the (S)-enantiomer of thalidomide,[31] the enantiomeric purity of a chiral compound is a critically important characteristic. If purification is required, chiral separation methods can be expensive and time consuming; additionally, 50 % product loss from the purification of a racemic mixture is not ideal. With industry's growing interest in "greener" processes, asymmetric catalysis is a promising solution for several reasons: (i) lower activation energy lowers associated energy costs, (ii) reusability of the catalyst lowers material costs, (iii) catalytic conditions produce more efficient atom economy, and (iv) one chiral catalyst molecule produces many chiral product molecules.[1] Conversely, biological methods remain a very effective method of synthesizing molecules with high enantioselectivity.[32]

The pioneering work by Horner *et al*.,[33] and Knowles and Sabacky[34] demonstrated that an achiral catalyst could be made chiral by including a phosphine ligand containing a chiral phosphorus atom. Although ee's of only 3-15 % were attained, this was the birth of homogeneous asymmetric hydrogenation. In 1971, Dang and Kagan[35] hydrogenated α-(acylamino)acrylic acids using *O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) with 80 % ee, proving that a chiral phosphorus atom is not required if a chiral bidentate ligand is used instead. This was advantageous because ligands containing a chiral phosphorus are difficult to enantiomerically enrich.[36]

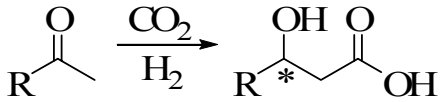
1.8 Hydrocarboxylation

The palladium-catalyzed hydrocarboxylation of alkenes using CO and water (or alcohol) produces aliphatic acids (or esters) (Scheme 1.7).[37] The regioselectivity for this reaction is more dependent on the ligand choice than the alcohol choice. The reaction involving 2-phenyl-1-butene and (R,R)-DIOP produced 95 % of the terminal carboxylation product; whereas, [(S)-2-phenylbutyl]diphenylphosphine produced 95 % of the internal carboxylation product.[38] Although CO/H_2O and CO_2/H_2 are thermodynamically equivalent and are related by the facile water gas shift reaction, CO_2 has not been used as the carboxylating species.



Scheme 1.7. 1,2-Hydrocarboxylation of Alkenes.[37]

Because the net 1,3-hydrocarboxylation of ketones is unknown (Scheme 1.8), our proposed one-pot synthesis of β-hydroxycarboxylic acids would be the first of its kind. This synthesis involves the carboxylation described in Chapter 2 followed by hydrogenation of the β-ketocarboxylate anion (Chapter 4) to produce the desired β-hydroxycarboxylic acid. This would be experimentally beneficial because the isolation of the unstable β-keto acid would not be required.



Scheme 1.8. 1,3-Hydrocarboxylation of Ketones.

1.9 Thesis Objective

The objective of this thesis project is the investigation of carbon dioxide fixation as it pertains to the synthesis of β-ketocarboxylic acids. This type of utilization offers an alternative to traditional carboxylation techniques that involve very toxic reagents. Furthermore, optimization of these reactions could result in the creation of more efficient technologies and processes for industry, thereby creating cheaper syntheses with less waste and a safer working environment.

Subsequent catalytic asymmetric hydrogenation of these β-ketocarboxylic acids results in the desired β-hydroxycarboxylic acids. This particular synthesis is of both academic and industrial interest because transition metal catalyzed hydrogenation of these substrates has not yet been studied. Therefore, the overall synthesis produces industrially and biologically valuable β-hydroxycarboxylic acids from cheap starting materials, and this synthetic route could improve upon current methods by producing less waste while still maintaining high enantioselectivity.

1.10 References

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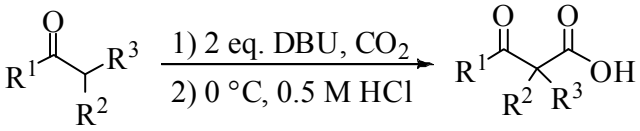
Chapter 2
Carbon Dioxide Fixation: Carboxylation of Ketones

2.1 Introduction

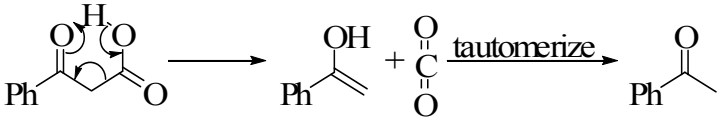
The objective of this project is to utilize CO_2 as a feedstock for the synthesis of industrially useful products. In this case, β-ketocarboxylic acids were synthesized by carboxylating a variety of ketones in the α-position (Scheme 2.1). These acids are then converted into value added products through a subsequent hydrogenation step (Chapter 4).



Scheme 2.1. General Carboxylation Reaction of Ketones.

2.1.1 Characteristics of β-Ketocarboxylic Acids

The interest in β-ketocarboxylic acids has so far been primarily academic rather than for practical applications. The major reason for this lack in practical application is the facile decarboxylation of the β-keto acid, reforming the original ketone (Scheme 2.2).



Scheme 2.2. Decarboxylation of β-Ketocarboxylic Acids.

Similar to diketone compounds, β-keto acids display the expected tautomerization between the keto and enol tautomers. Studies by Rosenfeld *et al.*[1,2] determined that the

percentage of keto tautomer present in solution increases with solvent polarity; this result is not surprising because the keto form is more polar due to its greater dipole moment. Rosenfeld also determined that the keto:enol ratio decreased with increasing β-keto acid concentration. This finding was surprising because the solvent polarity would increase due to the increased concentration of polar substrate, thereby favouring more keto tautomer.

As shown in Figure 2.1, there are a number of expected tautomeric forms for acetoacetic acid. ^{1}H NMR spectroscopy studies have been performed to determine the intramolecular bonding and structure of these β-keto acid tautomers.[1] The NMR spectra from these studies show no changes in the keto methylene chemical shifts. If internal H-bonding were present in the ketonic form, structure **A** (Figure 2.1**)**, a change in the methylene chemical shift would be observed in strongly H-bonding solvents. This shift would be caused by the disruption of intramolecular interactions; however, because this shift is not observed, structure **A** was determined to be the best representation for the keto tautomer. There is, however, internal H-bonding observed for the enol tautomer, structure **B** (Figure 2.1**)**, based on the downfield chemical shift compared to non H-bonded enol molecules.[3] The trans enol, structure **C** (Figure 2.1**)**, is assumed to be unstable due to the lack of H-bonding.[4] The ^{1}H NMR chemical shifts for the enol hydroxy proton in structure **D** (Figure 2.1**)** would be shifted upfield, while the carboxy proton would be shifted downfield; since this is not observed, these two conformers are not present in large percentages.

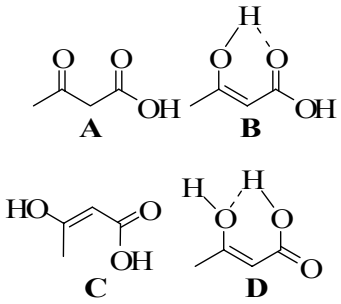
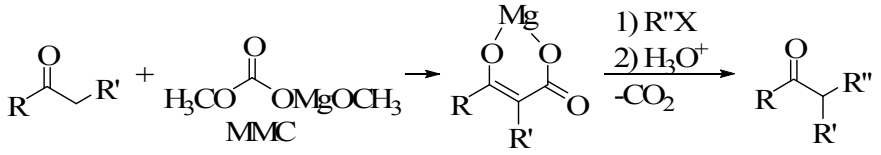


Figure 2.1. Expected Tautomeric Forms of Acetoacetic Acid.

2.1.2 Applications of β-Ketocarboxylic Acids

One β-keto acid, acetoacetic acid, in addition to acetone and β-hydroxybutanoic acid, is categorized as a ketone body. Ketone bodies are produced in the liver from acetyl-CoA and can be used as energy sources for both the heart and brain during exertion. Although the heart can utilize fatty acids for energy production, the brain relies on glucose. However, if low blood sugar occurs, the brain can derive its energy from these ketone bodies.[5]

Stiles *et al.*[6] determined that metal chelated β-ketocarboxylate anions could be used to alkylate ketones *in situ*, thereby producing a variety of substituted ketones (Scheme 2.3). This system takes advantage of the normally undesirable decarboxylation reaction to produce the nucleophilic enol anion for alkylation. Numerous substituted hydantoin derivatives[7] and biological antagonists[8] have been synthesized using this method; however, considering the simplicity this MMC synthesis, this method is not extensively utilized.

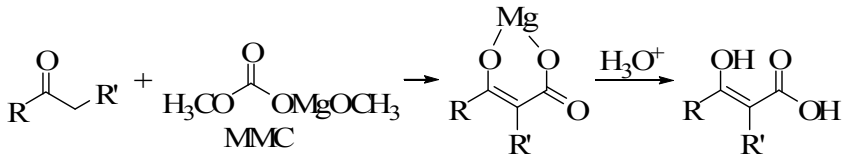


Scheme 2.3. Alkylation of Ketones via Metal Chelation Followed by Decarboxylation.[6]

2.1.3 Synthesis of β-Ketocarboxylic Acids

One prevalent method for synthesizing β-ketocarboxylic acids is via the hydrolysis of the corresponding esters. Hydrolysis can be performed under either basic[9] or acidic conditions,[10] both resulting in reasonable yields. However, the extent to which these methods can be used is limited because: (i) long reaction times are required, (ii) *in situ* decarboxylation occurs during the long reaction time, and (iii) substrate scope may be limited due to harsh reaction conditions.

One of the earliest reports on carboxylation involving the isolation of a β-keto acid was published in 1959 by Stiles (Scheme 2.4).[6] As noted by Stiles in the title of his article, chelation was the driving force in his synthesis. Magnesium methyl carbonate (MMC), used as a Lewis acid additive and carboxylating agent, generates a β-ketocarboxylate salt which is stabilized by a postulated six-membered chelate ring. This stability affects the thermodynamic equilibrium between the substrate enolate and carboxylate anions, favouring the product.[11]



Scheme 2.4. Magnesium Chelate Synthesis of β-Ketocarboxylic Acid.[6]

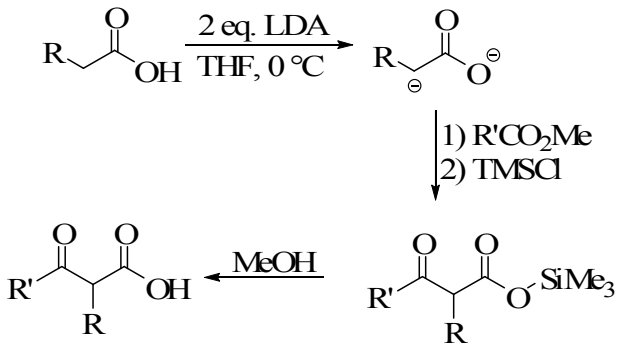
The above synthetic method is popular due to its broad substrate scope; however, this method proves to be ineffective under two conditions: (i) if only one α-hydrogen is present, or (ii) if large steric factors prevent the formation of the chelate.[2] From these necessary conditions, the logical conclusion would be that the enol form would be the chelated species.

Despite the broad scope of useful substrates, the synthesis outlined by Stiles is not ideal for current practices for several reasons: (i) 5-20 equivalents of MMC are required, which is not only wasteful but also expensive, (ii) higher temperatures are needed, which is destructive for the β-keto acid, (iii) large volumes of dimethylformamide (DMF) are required for extraction, and (iv) large amount of metal-containing waste is produced.

As an alternative to MMC, Matsumura *et al.*[12] showed that magnesium chloride in the presence of triethylamine effectively promoted the formation of β-keto acids; however, from studies performed by Rathke *et al.*,[13] magnesium iodide was found to be a better Lewis acid for the reaction. Unfortunately, both of these systems still require a large excess of both the magnesium halide and triethylamine.

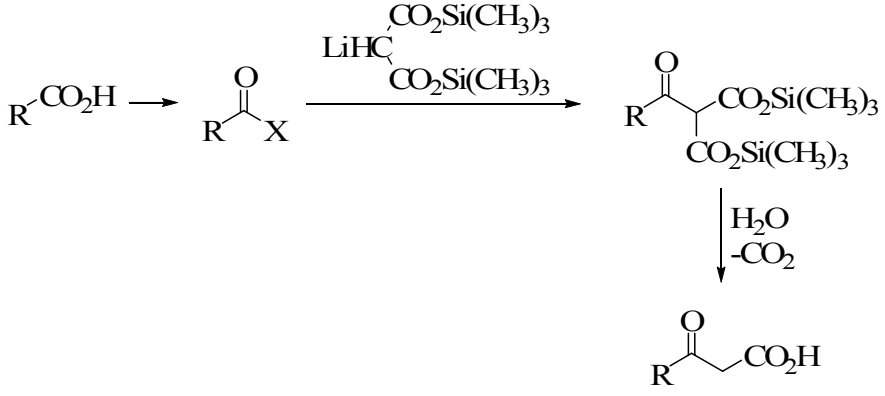
Kuo *et al.*[14] demonstrated another synthetic approach that is simple, performed under moderate conditions, and offers a broad substrate scope, especially for highly substituted ketones (Scheme 2.5). This synthesis involves a dianion of a carboxylate acid reacting with a methyl ester, forming the β-ketocarboxylate anion; addition of trimethylsilylchloride (Me_3SiCl) traps the carboxylate anion as the trimethylsilyl ester.

Solvolysis in neutral methanol at room temperature yields the β-keto acid. One drawback to this system is the use of lithium diisopropylamide (LDA) to produce the dianion.



Scheme 2.5. Synthesis of β-Ketocarboxylic Acids via Trimethylsilyl Ester.[14]

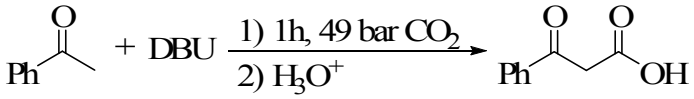
Most of the methods discussed contain strongly basic or acidic conditions, which is undesirable. With this in mind, Van der baan *et al.*[15] developed a synthesis of β-keto acids for substrates containing acid- or base-sensitive groups (Scheme 2.6). To activate the carbonyl, aliphatic or aromatic carboxylic acids were converted to their corresponding acyl chloride, ester, or triazole derivatives. Nucleophilic attack by lithium bis(trimethylsilyl)malonate was completed, and the Me_3Si group was removed via hydrolysis. Finally, loss of one equivalent of CO_2 produced the desired β-keto acids.



Scheme 2.6. Synthesis of β-Keto Acids via Activated Carbonyl Group.[15]

A number of other syntheses of β-ketocarboxylic acids have also been developed. In an attempt to mimic the enzymatic carboxylation involving biotin, Haruki used dicyclohexylcarbodiimide-tetraalkylammonium hydroxide-CO_2 and lithium salts of urea derivatives,[16] while Matsumura used lithium 1,8-diazabicyclo[5.4.0]undec-7-en-6-ide[17] to carboxylate activated methylene groups.

Relating to this project, DBU has been used to promote the carboxylation of ketones;[18] advantageously, this synthetic route does not involve a metal. Haruki *et al*.[18] have shown that optimal carboxylation conditions (including temperature, reaction time, equivalents of base, and CO_2 pressure) are substrate specific; however, a number of general rules were determined: (i) higher carbon dioxide pressures result in higher yields by Le Chatelier's Principle, (ii) polar aprotic solvents give highest yields by stabilizing the resulting ionic charges, and (iii) longer reaction times give better yields, even if only slightly. Optimal reaction temperatures range from -40 °C to 30 °C, and the optimal number of equivalents of DBU varies between substrates. This reaction has been successfully applied to a number of ketones, including cyclohexanone, 1-indanone, 5-tert-butyl-2-methyl-cyclohexanone, 2-hydroxyacetophenone, α-tetralone, and 4-phenyl-3-buten-2-one.[18]



Scheme 2.7. DBU-Promoted Carboxylation of Acetophenone.[18]

Mori *et al.*[19] studied the mechanism of cyclohexanone carboxylation using 1 atm of carbon dioxide and DBU, and they determined that the cyclohexanone enolate was carboxylated by the CO_2 dissolved in DMSO.

Other carboxylation reactions involve the use of 1,3-diphenylurea, diphenylcarbodiimide, potassium carbonate, and CO_2.[20-23]

In this chapter, the ideal operating conditions for the DBU carboxylation reaction and the synthesis of numerous β-ketocarboxylic acids, including aliphatic, aromatic, and bicyclic substrates will be discussed. Also discussed is the variety of workup methods attempted in order to increase reaction yields for certain substrates and to produce a more environmentally friendly synthesis.

2.2 Results and Discussion

2.2.1 Carboxylation of Acetophenone

Acetophenone was used to determine the highest-yielding conditions for the carboxylation reaction (Scheme 2.7). Work by the Jessop group has determined that the reaction is best performed without solvent (provided that the starting material is a liquid), and with two equivalents of DBU.[24] Therefore, these conditions are used as the standard conditions in future carboxylation reactions.

To reduce the formation of the [DBUH][HCO_3] salt,[25] it was determined that using dry reagents provided good yields (Table 2.1). Reducing the amount of the [DBUH][HCO_3] salt produced increases the efficiency of the reaction for two reasons: (i)

less DBU is wasted, increasing economic efficiency, and (ii) a lower viscosity reaction mixture is maintained, increasing the mass transfer of CO_2 into solution and the overall efficacy. Therefore, as part of the standard conditions, dried solvents and reagents were used in subsequent carboxylations. It was also determined that lower temperatures produce higher yields, in agreement with results by Haruki.[18]

Table 2.1. Carboxylation of Acetophenone (**1a**).[a]

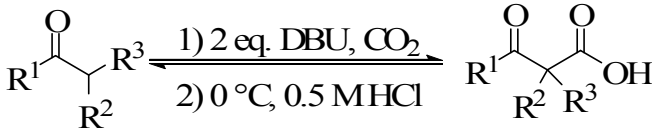
DBU[b]	T (˚C)	P_{CO2} (bar)	Solvent	Yield (%)
2[c]	0	60	none	91
2[c]	23	60	none	83
2	23	22	THF (5 mL)	trace
1	40	25	none	54
1	23	20	none	51
0.5	23	25	MeOH (1.5 mL)	0

[a]Reactions conducted in a neat DBU/acetophenone mixture with 10 mmol acetophenone for 21-29 h in a 160 mL stainless steel autoclave unless otherwise noted. [b]Equivalents of DBU relative to acetophenone. [c]Dry conditions.

2.2.2 Carboxylation of Other Ketones

A variety of ketones (Scheme 2.8) were tested for the carboxylation (Table 2.2) using the standard conditions. As Haruki *et al.*[18] noted, the optimal reaction temperature is substrate dependent. Because no further optimization was done for the carboxylation of these ketones, the yields are lower than those obtained with acetophenone. Three ketones gave particularly low yields (Table 2.2, entries 11, 12, 14); two of these ketones (**1f**, **1g**) produce 1,3-allylic strain in the enol tautomer that would presumably be less reactive towards carboxylation due to increased steric repulsion. However, the facile carboxylation of cyclohexanone (Table 2.2, entry 19) shows that high yields are not

limited to methyl ketones. Haruki[18] determined that 35 °C was optimal for the carboxylation of cyclohexanone.



1				**2**
	R^1	R^2	R^3	
a	Ph	H	H	
b	4-ClC_6H_4	H	H	
c	4-$OMeC_6H_4$	H	H	
d	2-MeC_6H_4	H	H	
e	naphthyl	H	H	
f	Ph	Me	H	
g	Ph	Me	Me	
h	Me	H	H	

Scheme 2.8. Carboxylation of Ketones.

Extending the carboxylation reaction time for **1f** beyond 9 h did not affect the isolated yield of **2f** (Table 2.2, entries 6-9), confirming that this carboxylation system exists as an equilibrium.[26] Although the optimal reaction time was shown by Haruki *et al.*[18] to be substrate dependent, future reactions were run for ~24 h to ensure the highest possible yields.

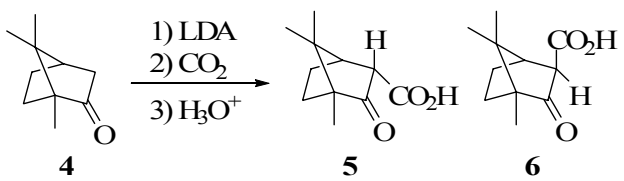
For (1*R*)-camphor and isobutyrophenone (**1g**), the DBU/CO_2 method was ineffective (Table 2.2, entry 21). Camphoric acid was instead synthesized using LDA in toluene followed by addition of dry ice (Scheme 2.9).[27] In accordance with previous literature,[27] only the keto tautomer is observed by ^{13}C NMR spectroscopy. It is clear from the ^{1}H NMR spectra that the product mixture is always present as a 7:3

diastereomeric mixture of **5** and **6**. This suggests that a thermodynamic equilibrium exists between the diastereomers, providing evidence of a transient enol intermediate.

Table 2.2. Carboxylation of Various Ketones with DBU and CO_2.[a]

Entry	Ketone	CH pK_a (DMSO)	Temp (°C)	Time (h)	Yield[b] (%)
1	**1a**	24.7	0	27	91
2	**1b**	23.8	23	25	28
3	**1c**[c]	25.7	23	72	71
4	**1d**	na[e]	0	26	68
5	**1e**[c]	na[e]	0	25	64
6	**1f**	24.4	0	9	26
7	**1f**	24.4	0	14	25
8	**1f**	24.4	0	30	58[d]
9	**1f**	24.4	0	72	24
10	**1f**	24.4	23	24	24
11	**1f**	24.4	40	20	16
12	**1g**	na[e]	0	29	0
13	**1g**	na[e]	23	29	0
14	**1h**	26.5	0	24	11
15	**1h**	26.5	0	24	26[d]
16	**1h**	26.5	23	16	12
17	**1h**	26.5	40	24	16
18	Cyclohexanone	26.4	23	24	17
19	Cyclohexanone	26.4	40	18	78
20	2-acetylfuran	na[e]	23	24	35[f]
21	(1*R*)-camphor	na[e]	23	25	0

[a]Conditions: 160 mL autoclave vessel, 60 bar CO_2, 2 eq. DBU used, neat conditions unless otherwise noted. [b]Isolated yield, except as specified. [c]3 mL MeCN. [d]$CaCl_2$ used during extraction. [e]na = not available. [f]^{1}H NMR yield.



4 **5** **6**

Scheme 2.9. Carboxylation of (1*R*)-Camphor.

In order to investigate a ketone with only one α proton, the carboxylation of **1g** was attempted. Unfortunately, the aforementioned LDA/dry ice synthesis proved ineffective, possibly due to steric hindrance. Instead, Tirpak's[13] MgI_2/NEt_3 promoted carboxylation of **1g** with 1 atm CO_2 proved effective. This β-keto acid proved very valuable for elucidating the hydrogenation mechanism in Chapter 4.

2.2.3 Other Workup Procedures for β-Ketocarboxylic Acid Isolation

Due to the low yields attained for the carboxylation of acetone, workup methods other than the traditional aqueous acid and extraction were attempted. To determine if the decarboxylation of the free acid is the primary problem, the acidification was performed under CO_2 pressure, thereby maintaining the equilibrium for acid formation (Figure 2.2, vessels 1 and 2). To perform this experiment, vessel 1, containing the carboxylation reaction mixture, is connected to vessel 2, containing an HCl solution, via a diptube; vessel 2 also contains a higher pressure of CO_2 than vessel 1. When the carboxylation is complete, the valve is opened, causing the HCl solution to enter vessel 1, and acidify the reaction mixture. Unfortunately, performing the extraction in the open atmosphere provided only the original ketone. Although HCl addition was performed at 0 °C to reduce decarboxylation, the rapid addition is assumed to be problematic due to the rapid generation of heat. In order to increase stability of the formed β-keto acids, extraction with EtOAc under CO_2 pressures was also attempted using the same procedure (Figure 2.2, vessels 3 and 4); unfortunately, this method also yielded no β-keto acid.

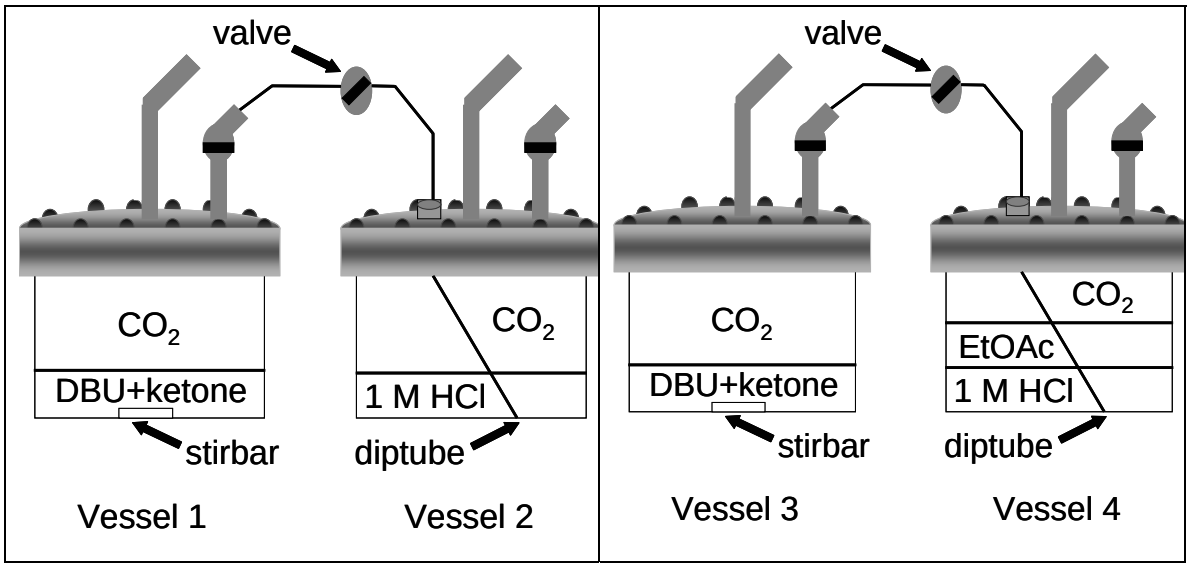


Figure 2.2. Carboxylation Reaction using CO_2 Pressure Work-Up Procedure.

Supercritical CO_2 extraction was also attempted, offering a "greener" solution because less solvent waste is produced during product workup (Figure 2.3). Although acids are generally not very soluble in supercritical CO_2, the low molecular weight and lack of aromaticity of 3-oxobutanoic acid make it a good candidate.

In this $scCO_2$ extraction system, carbonic acid is produced when CO_2 dissolves in water, which in turn can protonate the β-ketocarboxylate anion; the free β-keto acid could then be extracted by supercritical CO_2 into a collection flask placed in an ice bath. Unfortunately, this method proved to be ineffective for the extraction of both acetophenone and acetone. These negative results could be due to the lack of protonation by carbonic acid, the acid's insolubility in $scCO_2$, or the increased decarboxylation due to the elevated temperature needed for $scCO_2$.

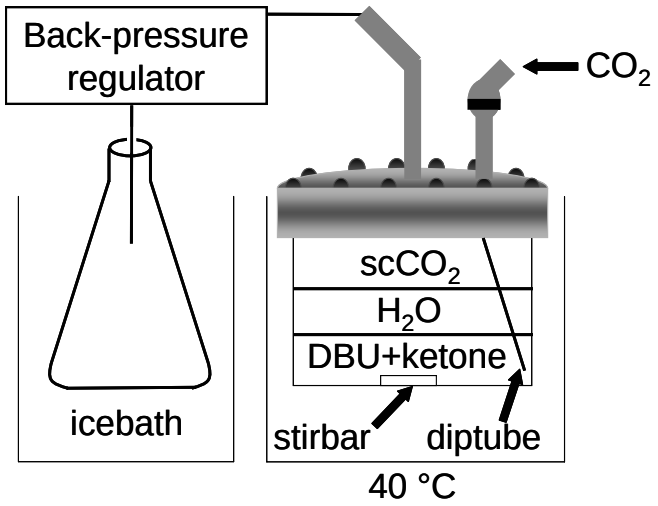


Figure 2.3. Supercritical Carbon Dioxide Extraction Apparatus.

To ensure that protonation by carbonic acid is occurring in solution, benzoic acid was implemented as a representative acid. Advantageously, benzoic acid does not suffer from decarboxylation, which simplifies the reaction scheme. After subjecting the aqueous mixture of benzoic acid and DBU to 60 bar CO_2, the pressure was released, and a traditional aqueous/organic extraction recovered the original benzoic acid. Therefore, carbonic acid is a strong enough acid for protonation to occur. Hence, the problem with the $scCO_2$ extraction is the insolubility of the β-ketocarboxylic acids in $scCO_2$.

Logic would hold that if benzoic acid is protonated, extracted, and recovered, the $[DBUH][HCO_3]$ salt must remain in the aqueous phase. This salt could then be heated in order to recover the DBU,[28] increasing the overall carboxylation reaction efficiency. To test this logic, benzoic acid and DBU were reacted in an aqueous solution, diethyl ether was added, and the reaction mixture was bubbled with 1 atm CO_2 for 1 h. From the ^1H NMR spectra, a 1:1 ratio of benzoic acid and DBU is present in both the organic and

aqueous layers, meaning the reaction did not go to completion. Therefore, for this reaction to succeed, higher pressures or longer reaction times are required to ensure full protonation of benzoic acid. Furthermore, the addition of the organic extraction solvent should be delayed to ensure any excess DBU has already been protonated.

A simple method to significantly increase the reaction yield is to use a saturated $CaCl_2$ solution during acid workup and extraction. $CaCl_2$ serves two functions: it increases the ionic strength of the solution, and acts as a Lewis acid. Increasing the ionic strength ensures that the β-keto acid is more soluble in the organic water. Chelation of the β-keto carboxylate anion to calcium stabilizes the acid against decarboxylation. To determine what role the $CaCl_2$ is performing, a non-chelating salt, such as NaCl, solution should be tested.

Using this $CaCl_2$ method, yields for both **2f** and **2h** were more than doubled to 58 % and 26 %, respectively (Table 2.2, entries 8, 15). These were the only β-keto acids tested, so the yields listed in Table 2.2 could be increased by using this method.

2.2.4 Potential Side Reactions

A number of possible side products could potentially be formed. To be industrially viable, only mono-carboxylation products should be synthesized, and, as previously mentioned, any unreacted ketone must be easily recoverable and reusable. However, formation of dicarboxylic acids and other side products would require additional separation steps.

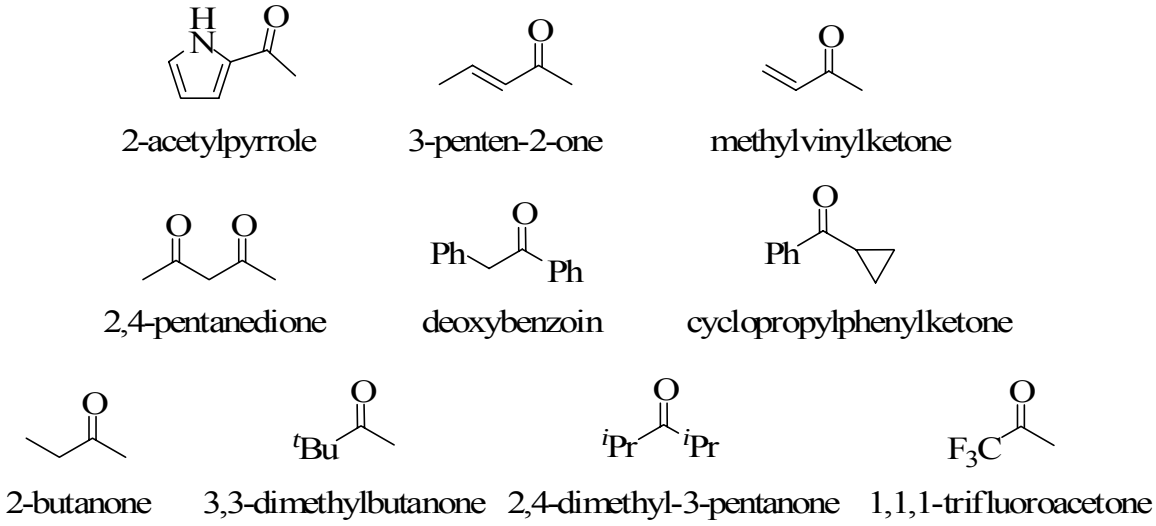
Firstly, carboxylation can occur twice. After the first carboxylation, the α-proton is more acidic than the original ketone α-proton; therefore, deprotonation followed by carboxylation is feasible, producing a α,α-dicarboxylic acid. This product is not observed for any of the ketones probably because decarboxylation of the diacid would be rapid; the decarboxylation of 1,3-dicarboxylic malonic acid has been studied in literature.[29] Likewise, no symmetrical dicarboxylic acid is observed for ketones with α-protons on both sides of the carbonyl (ie. cyclohexanone, and **1h**).

Secondly, aldol chemistry could occur. Neither of the expected aldol products, the alcohol or olefin from dehydration, are observed in any reactions. Ketones that produce primary enolate anions and conjugation are most likely to participate in aldol chemistry; however, no side products are observed for any of the acetophenone derivatives.

Lastly, because of the α,β-unsaturation present in the enol tautomer, conjugate, 1,4-, and Michael-type addition chemistry can also occur. Fortunately, no such products are observed.

2.2.5 Other Attempted Carboxylation Reactions

In an attempt to expand the substrate scope for the DBU-promoted carboxylation method and elucidate details of the hydrogenation mechanism, numerous other ketones were attempted (Scheme 2.10).



Scheme 2.10. Ketones that were Unsuccessfully Carboxylated.

These particular ketones were tested because the proposed β-ketocarboxylic acids would provide valuable information during the study of the β-keto acid hydrogenation: (a) 2-acetylpyrrole, 3-penten-2-one, and methylvinylketone would provide information regarding the chemoselectivity of "$RuCl_2$(BINAP)" because of their γ,δ-unsaturation; (b) 2,4-pentanedione would offer another heteroatom that would compete for catalyst coordination; (c) The enol tautomer of deoxybenzoin was postulated to be favoured because of the electron withdrawing substituents and the resulting conjugation; (d) cyclopropylphenyl ketone is incapable of an enol tautomer so would fix the β-keto acid in its keto tautomer; (e) 2-butanone, 2,4-dimethyl-3-pentanone and 3,3-dimethylbutanone were tested to broaden the aliphatic substrate scope; and (f) after the success of **1h**, 1,1,1-trifluoroacetone was tested for interest sake.

None of these ketones was successfully carboxylated with the DBU method (Table A1.1). In some cases, the original ketone was recovered in non-quantitative

amounts. This suggests that carboxylation occurred, but the decarboxylation of these acids was too rapid to allow for isolation on the small scale tested. No trend was observed with regards to carboxylation and pK_a. Unfortunately, the $CaCl_2$ effect on the reaction yields was not determined before performing these experiments. Therefore, any produced β-ketocarboxylic acid may have been more soluble in the aqueous phase and, therefore, not recovered.

2.3 Conclusions and Future Work

2.3.1 Conclusions

Although standard conditions were determined with acetophenone, carboxylation using two equivalents of DBU, no solvent, and 60 bar CO_2 was determined to be effective for a variety of other aliphatic and aromatic ketones. The optimization of reaction conditions for each ketone was not investigated; however, higher yields might be attained with small modification to the method. Fortunately for potential applications, any unconverted ketone from the carboxylation process can be separated from the products and re-used. However, because higher pressures are not preferred in industry, it should be noted that lower CO_2 pressures may suffice for this reaction. Although this DBU/CO_2 carboxylation method is versatile, it proved unsuccessful with isobutyrophenone and (1*R*)-camphor, possibly due to steric repulsion. Furthermore, the carboxylation of numerous other ketones was attempted unsuccessfully.

Multiple procedures, including acidification and extraction under CO_2 pressure, and supercritical CO_2 extraction, proved to be ineffective for the isolation of

β-ketocarboxylic acids. However, these experiments demonstrated the concept of DBU recovery. Carbonic acid can act as a proton source in the protonation of phenyl carboxylate for the recovery of benzoic acid and the [DBUH][HCO_3] salt. Theoretically, this salt could then be heated to recover DBU, making the process more environmentally and industrially friendly.

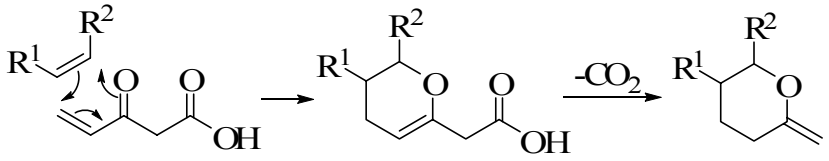
Of the numerous work-up procedures attempted, utilizing a saturated $CaCl_2$ solution during acidification and extraction proved to be most effective. This result may be due to the stabilizing chelate effect and/or the decreased β-keto acid solubility in water.

2.3.2 Future Work

Even though a number of different ketones were successfully carboxylated, the substrate scope could be larger. Repeating some of the unsuccessful carboxylation reactions using a saturated $CaCl_2$ solution during acidification and extraction could prove successful; of particular interest are those with α,β-unsaturation, such as 3-penten-2-one and methylvinylketone. Inclusion of other heteroatoms elsewhere in the substrate could be a possibility; this would not only expand the method applicability but could also be used to determine the selectivity of the hydrogenation reaction.

Based on the successful recovery of amidine by heating the bicarbonate salt,[28] the recovery of DBU from the [DBUH][HCO_3] salt still needs to be determined. Knowing that carbonic acid is a capable acid, attempts to protonate a β-ketocarboxylic acid should be attempted.

Because of the facile decarboxylation, resulting in enolate formation, an investigation of the literature for carbanion chemistry could yield valuable syntheses needing simplification. Instead of using the decarboxylation of β-keto acids, the facile decarboxylation of β,γ-unsaturated acids could be utilized instead. If a transformation similar to Diels-Alder existed involving a carbonyl instead, the resulting product would be a β,γ-unsaturated acid, which would then decarboxylate to a vinyl ether (Scheme 2.11).



Scheme 2.11. Proposed Vinyl Ether Synthesis via β-Ketocarboxylic Acid.

2.4 Experimental

2.4.1 Materials

Solvents were typically used as received; however, if dried solvents were required, diethyl ether was dried by passage through activated alumina using a Solvent Purification System; acetonitrile, ethyl acetate, chloroform, and methylene chloride were dried over calcium hydride for 48 h, distilled onto 4 Å activated molecular sieves, and stored under N_2. MeOH was dried with activated molecular sieves (4 Å) (Aldrich), followed by distillation onto additional activated molecular sieves.

DBU (TCI America) was dried over calcium hydride overnight and distilled *in vacuo*. CO_2 was then bubbled through this "semi-dried" DBU to remove any remaining

water as the insoluble DBU bicarbonate salt, which was filtered off. Liquid ketones, including acetophenone (Aldrich), 4-chloroacetophenone (Aldrich), 2-methylacetophenone (Aldrich), cyclohexanone (Aldrich), propiophenone (Alfa Aesar), and isobutyrophenone (Alfa Aesar), were dried over calcium hydride, distilled onto molecular sieves, and stored in a Schlenk flask under nitrogen. Acetone (99.5 % assay from Fisher) was dried over calcium sulphate (6 mesh), distilled onto molecular sieves, and stored in a Schlenk flask under nitrogen. Deuterated solvents, including $(CD_3)_2CO$, CD_2Cl_2, $CDCl_3$, D_2O, MeOH-d_4, $(CD_3)_2SO$, were obtained from Cambridge Isotope Laboratories, Inc. and used as received. If dry solvents were required, $CDCl_3$ and CD_2Cl_2 were dried using CaH_2 (Aldrich), distilled onto molecular sieves, and stored under N_2. (1*R*)-Camphor, 2-acetonaphthone, deoxybenzoin, 2-acetylpyrrole, 3-penten-2-one, methylvinylketone, 2,4-pentanedione, cyclopropylphenylketone, 2-butanone, 3,3-dimethylbutanone, 2,4-dimethyl-3-pentanone, diisopropylamine, *n*-butyl lithium (2.33 in hexanes), and 1,1,1-trifluroacetone were all obtained from Aldrich and used as received; Celite 545 (Fisher) was used as received.

2.4.2 Equipment and Techniques

Equipment used included an OL32 Karl Fisher Coulometer (Mettler Toledo), Thomas Hoover Capillary Melting Point Apparatus, 31 mL (serial numbers 833, 866, 897, and 898) and 160 mL (serial numbers 7163, 7572, 21935, and 32064) high pressure vessels (Parr Instrument Co.) with fittings from Swagelok, 200 bar pressure gauges with

1.6 % of span (per DIN 16 005) for accuracy (OMEGA Engineering Inc.), and a Nexus One glove box (Vacuum Atmospheres Co.).

2.4.3 Spectroscopy and Chromatography

The NMR spectra were acquired at 25 ˚C using a 300 MHz, 400 MHz, 500 MHz, or 600 MHz AVANCE spectrometer. The automatic AVANCE 400 MHz NMR spectrometer contains an automatic sample changer and automatic tuning and matching. ^{1}H and ^{13}C NMR spectra were acquired with tetramethylsilane (TMS) or solvent as the internal reference, and are reported relative to TMS at 0 ppm. For NMR predictive software, both ACDLabs and ChemDraw Ultra were used.

The high-resolution mass spectra were recorded using a Micromass GCT from Waters using an EI method in positive mode with Masslynx software. All the spectra were performed using ethyl acetate as the solvent.

Infrared spectra were obtained using an Avatar 360 FT-IR from Nicolet Instruments with EZ OMNIC E.S.P. 5.1 software. Sodium chloride plates were used to run neat liquid samples.

Thin layer chromatographs were obtained using alumina-backed TLC plates and Ultra Pure Silica Gel from Silicycle Chemical Division.

2.4.4 General Procedures for the Carboxylation of Ketones

Except where noted, all carboxylation-related manipulations were conducted in open atmosphere with undried solvents; inert atmosphere Schlenk techniques were used

if required, transferring solvents and liquid reagents with syringes and cannulae. Glassware was oven-dried (130 ºC) and evacuated while hot, or flame-dried under vacuum. Stainless steel autoclaves were oven-dried (130 ºC) and allowed to cool before use.

Method A: Using DBU. A 160 mL steel vessel, and any syringes and vials were dried in an oven at 130 °C overnight. The stir bar, ketone, 2 equivalents of dried DBU, and solvent (if needed) were added to the dried and cooled vessel. The vessel was then sealed and flushed with CO_2 three times to remove air. If temperatures higher than room temperature were used, then the vessel was placed in a controlled-temperature oil bath and allowed to equilibrate at the desired temperature for 10 min before pressurization. For reactions at 0 ˚C, the vessel was placed in a 0 °C ice bath. The vessel was then pressurized to 60 bar CO_2. After the allowed reaction time, the vessel was placed in an ice water bath for approximately 30 min, allowed to vent slowly, and disassembled. 50 mL of ice cold water was added to the crude reaction mixture and unreacted ketone and DBU were extracted with diethyl ether (2×25mL). With the reaction flask still in the ice bath, the aqueous phase was acidified to pH 2 by dropwise addition of 0.5 M ice cold HCl. The precipitated product was then extracted using 2×30 mL diethyl ether washes. The organic extracts were combined, dried with magnesium sulphate and filtered into a tared round-bottom flask. The solvent was removed by rotary evaporation. After the ^{1}H NMR spectrum of this crude material was acquired, the product was washed with hexane, filtered, and stored in the freezer.

Method B: Using LDA.[27] At -78 °C, *n*-BuLi (2 equivalents) in hexanes were added dropwise to a 25 mL toluene solution of diisopropylamine (2 equivalents). The mixture was stirred for 20 min at -78 °C and an additional hour upon warming to room temperature. The resulting solution was added dropwise to a -78 °C solution of ketone (1 equivalent) in 25 mL toluene. After an additional 20 min of stirring at -78 °C, the reaction mixture was warmed to room temperature, stirred for an additional 30 min, and added slowly to a 250 mL round bottom flask containing excess dry ice. The contents of the flask were stirred for 30 min at room temperature, washed with diethyl ether to remove unreacted materials and byproducts, and acidified to pH 2 using 1 M ice cold HCl. The product was then extracted with diethyl ether (2×30mL), the organics were then dried with $MgSO_4$, and filtered into a tared round-bottom flask. The solvent was removed by rotary evaporation.

Synthesis of Benzoylacetic Acid (2a).

Using Dry Reagents: Prepared from dried acetophenone (1.16 mL, 9.94 mmol) and dried DBU (2.79 mL, 18.7 mmol) by Method A for 21 h at room temperature. The vessel was vented in an ice bath over 1.5 h, and upon opening the vessel, a reddish solid was found (91 % isolated yield).

Using Wet Reagents: Prepared from undried acetophenone (1.16 mL, 9.94 mmol) and undried DBU (2.79 mL, 18.7 mmol) by Method A for 26 h at room temperature. The vessel was vented in an ice bath over 4 h, and upon opening the vessel, a reddish-orange paste was found (83 % isolated yield).

Using 1 atm CO_2 in MeCN. In the glovebox, acetophenone (1.60 mL, 9.94 mmol) was added to a round bottom flask containing dried DBU (2.79 mL, 18.66 mmol) and dried MeCN (8 mL). Outside the glovebox, CO_2 was bubbled through solution for 19 h at room temperature; formation of white precipitate was observed. The crude mixture was worked up using the procedure described in Method A (15 % isolated yield). The ^{1}H NMR and ^{13}C NMR spectra match those reported in the literature.[13]

The observed keto:enol ratio in $(CD_3)_2CO$ was 1:0.33. Keto acid: ^{1}H NMR ($(CD_3)_2CO$): δ 8.04 (d, $^3J_{HH}$ = 7.2 Hz, 2H, 2′-C*H*), 7.64 (t, $^3J_{HH}$ = 7.4 Hz, 1H, 4′-C*H*), 7.46-7.56 (m, 2H, 3′-C*H*), 4.10 (s, 2H, CH_2); ^{13}C{^{1}H} NMR ($(CD_3)_2CO$): δ 193.9 (keto C=O), 169.2 (*C*O_2H), 136.7 (1′-*C*), 133.8 (4′-*C*), 128.7-129.0 (2C), 45.5 (*C*H_2).

Enol acid: ^{1}H NMR ($(CD_3)_2CO$): δ 7.81 (d, $^3J_{HH}$ = 6 Hz, 2H, 2′-C*H*), 7.46-7.56 (m, 3H), 5.85 (s, 1H, C*H*); ^{13}C{^{1}H} NMR ($(CD_3)_2CO$): δ 175.1 (*C*O_2H), 172.7 (*C*OH), 131.7 (4′-*C*), 126.6 (2′-*C*), 128.7-129.0 (1C), 87.25 (enol *C*H). The 1′-C was not detectable.

3-(4′-Chlorophenyl)-3-oxopropanoic acid (2b).

Prepared from 4′-chloroacetophenone (2.60 mL, 20.0 mmol) and DBU (6.0 mL, 40.0 mmol) by Method A for 25 h at room temperature. The vessel was vented in an ice bath, and upon opening the vessel, a yellow solid was found. Workup as described in Method A yielded the desired product (28 % isolated yield).

The observed keto:enol ratio in $(CD_3)_2CO$ was 1:0.22. Keto acid: ^{1}H NMR ($(CD_3)_2CO$): δ 8.05 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2′-C*H*), 7.59 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 3′-C*H*), 4.10 (s, 2H,

C*H*$_2$); ^{13}C{^{1}H} NMR ((CD$_3$)$_2$CO): δ 192.0 (C=O), 168.2 (*C*O$_2$H), 130.0 (2′-C), 128.6 (3′-C), 139.3 (1′-C), 46.0 (*C*H$_2$). The 4′-C was not detectable.

Enol acid: ^{1}H NMR ((CD$_3$)$_2$CO): 7.90 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2′-C*H*), 7.53 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 3′-C*H*), 5.87 (s, 1H, C*H*); ^{13}C{^{1}H} NMR ((CD$_3$)$_2$CO): δ 127.5 (2′-C), 128.6 (3′-C), 132.2 (1′-C), 86.8 (*C*H). 4′-C and 3-COH carbons were not detected.

HR-MS, observed: *m/e* 198.0085 (M^+). Calculated for $C_9H_7ClO_3$: *m/e* 198.0084 (M^+).

EI-MS, observed: *m/e* 154.0 (M^+-CO_2), 139.8 ((M^+-CH_2CO_2), 111.0 (M^+-C(O)CH_2CO_2), 75.0 (M^+-C(O)CH_2CO_2-Cl).

3-(4′-Methoxyphenyl)-3-oxopropanoic acid (2c).

Using Method A at room temperature: Prepared from 4′-methoxyacetophenone (1.50 g, 10.0 mmol) and DBU (3.0 mL, 20.0 mol) and MeCN (3 mL) by Method A for 72 h at room temperature. The vessel was vented in an ice bath, and upon opening the vessel, a yellow solid was found. Workup as described in Method A yielded the desired product (71 % isolated yield).

The observed keto:enol ratio in (CD$_3$)$_2$CO was 1:0.09. Keto acid: ^{1}H NMR (CD$_3$)$_2$CO): δ 11.14 (1H, CO$_2$*H*), 8.01 (d, $^3J_{HH}$ = 8.9 Hz, 2H, 2′-C*H*), 7.06 (d, $^3J_{HH}$ = 8.9 Hz, 2H, 3′-C*H*), 4.02 (s, 2H, C*H*$_2$), 3.91 (s, 3H, OC*H*$_3$); ^{13}C{^{1}H} NMR ((CD$_3$)$_2$CO): δ 191.7 (*C*=O), 168.7 (*C*O$_2$H), 164.3 (4′-*C*), 131.1 (2′-*C*), 128.1 (1′-*C*), 114.2 (3′-*C*), 55.4 (O*C*H$_3$), 45.1 (*C*H$_2$).

Enol acid: ^{1}H NMR $(CD_3)_2CO$): δ 7.84 (d, $^{3}J_{HH}$ = 8.9 Hz, 2H, 2′-C*H*), 7.0-7.1 (m, 2H, 3′-C*H*), 5.74 (s, 1H, C*H*), 3.87 (s, 3H, OC*H*$_3$), 2.94 (1H, OH). Enol tautomer was not detectable by ^{13}C NMR due to low keto:enol ratio.

HR-MS, observed: *m/e* 194.0580 (M^+), 150.0594 (M^+-CO_2), 135.0319 (M^+-CH_2CO_2), 107.0470 (M^+-C(O)CH_2CO_2), 92.0244 (M^+-C(O)CH_2CO_2-CH_3), 77.0370 (M^+-C(O)CH_2CO_2-OCH_3). Calculated for $C_{10}H_{10}O_4$: *m/e* 194.0579 (M^+).

3-(2′-Methylphenyl)-3-oxopropanoic acid (2d).

Using Method A at 0 °C: Prepared from 2′-methylacetophenone (1.32 mL, 10.0 mmol) and DBU (3.0 mL, 20.0 mmol) by Method A for 26 h at 0 °C. The vessel was vented in an ice bath, and upon opening the vessel, a yellow solid was found with no liquid remaining. Workup as described from Method A yielded the desired product (68 % isolated yield).

The observed keto:enol ratio in $(CD_3)_2CO$ was 1:0.20. Keto acid: ^{1}H NMR ($(CD_3)_2CO$): δ 7.85 (d, $^{3}J_{HH}$ = 7.7 Hz, 1H, 5′-C*H*), 7.45 (m, 1H, aryl C*H*), 7.25-7.39 (m, 2H, aryl C*H*), 4.03 (s, 3H, C*H*$_2$), 2.49 (s, 3H, 2′-C*H*$_3$); ^{13}C{^{1}H} NMR ($(CD_3)_2CO$): δ 196.5 (*C*=O), 168.6 (*C*O_2H), 138.8 (1′-*C*), 126.1-137.2 (5 aryl C), 47.8 (*C*H_2), 20.8 (CH_3).

Enol acid: ^{1}H NMR ($(CD_3)_2CO$): δ 7.45 (m, 1H, aryl C*H*), 7.25-7.39 (m, 3H, aryl C*H*), 5.36 (s, 1H, C*H*), 2.45 (s, 3H, 2′-C*H*$_3$); ^{13}C{^{1}H} NMR ($(CD_3)_2CO$): δ 126.1-137.2 (6 aryl C), 90.9 (*C*H), 20.0 (CH_3). The acid carbonyl was not detectable by ^{13}C NMR spectroscopy due to low concentration.

HR-MS, observed: *m/e* 178.0631 (M^+). Calculated for $C_{10}H_{10}O_3$: *m/e* 178.0630 (M^+).

EI-MS, observed: *m/e* 134.0 (M^+-CO_2), 120.0 (M^+-CH_2CO_2), 91.0 (M^+-$C(O)CH_2CO_2$), 77.0 (M^+-$C(O)CH_2CO_2$-CH_3).

3-(Naphthalen-2′-yl)-3-oxopropanoic acid (2e).

Using Method A at 0 °C: Prepared from 2′-acetylnaphthone (0.86 g, 5.0 mmol) and DBU (1.5 mL, 10.0 mmol) by Method A for 25 h at 0 °C. The vessel was vented in an ice bath, and upon opening the vessel, an off-white solid remained. Workup as described in Method A yielded the desired product (64 % isolated yield).

The observed keto:enol ratio in $(CD_3)_2CO$ was 1:0.19. Keto acid: ^{1}H NMR ($(CD_3)_2CO$): δ 8.70 (s, 1H, 1′-C*H*), 8.12 (d, $^3J_{HH}$ = 8.0 Hz, 1 aryl C*H*), 7.58-7.70 (m, 5 aryl C*H*), 4.23 (s, 2H, keto CH_2).

Enol acid: ^{1}H NMR ($(CD_3)_2CO$): δ 8.50 (s, 1H, 1′-C*H*), 7.58-7.70 (m, 3 aryl C*H*), 7.82-8.14 (m, 3 aryl C*H*), 6.00 (s, 1H, α-C*H*).

HR-MS, observed: *m/e* 214.0625 (M^+). Calculated for $C_{13}H_{10}O_3$: *m/e* 214.0630 (M^+).

EI-MS, observed: *m/e* 170.0 (M^+-CO_2), 155.0 (M^+-CH_2CO_2), 127.0 (M^+-$C(O)CH_2CO_2$).

2-Methyl-3-oxo-3-phenylpropanoic acid (2f).

Using Method A at 0 °C (with $CaCl_2$ during extraction): Prepared from propiophenone (2.6 mL, 19.5 mmol) and DBU (6.00 mL, 40.1 mmol) by Method A at 0 °C for 30 h. The vessel was vented in an ice bath, and upon opening the vessel, a yellow paste had formed. For product extraction in Method A, a saturated $CaCl_2$ aqueous solution and ethyl acetate were used (58 % isolated yield).

Using Method A at 0 °C: Prepared from propiophenone (1.30 mL, 9.77 mmol) and DBU (3.00 mL, 21.0 mmol) by Method A at 0 °C for 9 h. The vessel was vented in an ice bath, and upon opening the vessel, a yellow paste had formed. During aqueous acid workup, a white precipitate formed at pH=9, which was determined to be propiophenone by ^{1}H NMR spectroscopy using $CDCl_3$; the precipitate was removed by filtration. Further workup as described in Method A yielded the desired product (26 % isolated yield).

Using Method A at room temperature: Prepared from propiophenone (1.30 mL, 9.77 mmol) and DBU (3.00 mL, 21.0 mmol) by Method A for 24 h at room temperature. The vessel was vented in an ice bath, and upon opening the vessel, a yellow paste had formed. Workup as described in Method A yielded the desired product (24 % isolated yield).

Using Method A at 40 °C: Prepared from propiophenone (1.00 mL, 7.51 mmol) and DBU (2.25 mL, 15.0 mmol) by Method A for 21 h at 40 °C. The vessel was vented in an ice bath, and upon opening the vessel, a yellow paste had formed. Workup as described in Method A yielded the desired product (16 % isolated yield).

The ^{1}H NMR and ^{13}C NMR spectra match those reported in the literature.[30]

The enol acid is not observable by ^{1}H NMR or ^{13}C NMR spectroscopy. ^{1}H NMR ($CDCl_3$): δ 7.97 (d, $^{3}J_{HH}$ = 7.8 Hz, 2H, 2′-C*H*), 7.56 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, 4′-C*H*), 7.47 (t, $^{3}J_{HH}$ = 7.8 Hz, 2H, 3′-C*H*), 4.47 (q, $^{3}J_{HH}$ = 7.2 Hz, 1H, C*H*), 1.54 (d, $^{3}J_{HH}$ = 7.2 Hz, 3H,

C*H*$_3$); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 196.0 (*C*O), 176.2 (*C*O_2H), 135.4 (1′-C), 133.9 (2′-C), 128.9 (aryl C), 128.7 (aryl C), 47.6 (*C*H), 14.2 (*C*H_3).

2,2-Dimethyl-3-oxo-3-phenylpropanoic acid (2g).

Using $MgCl_2$, NaI, and NEt_3: Under nitrogen, anhydrous magnesium chloride (1.90 g, 20 mmol) and dried sodium iodide (6.00 g, 40 mmol) were added to a 250 mL round bottom flask containing dry acetonitrile (30 mL) and stirred for 30 min. Dried NEt_3 (5.6 mL, 40.4 mmol) was added and the flask was flushed with CO_2 for 10 min. Isobutyrophenone (1.48 mL, 10 mmol) was added and the bubbling of CO_2 was continued for an additional 2.5 h at room temperature. Additional acetonitrile (30 mL) was added due to solvent loss. The flask contents were mixed with 50 mL ice cold water and then washed with 20 mL ether to remove unreacted material. With vigorous stirring, the aqueous layer was acidified aqueous to pH=3-4 using 0.7 M ice cold HCl. The solution was extracted with ether (2x30 mL), the organic extracts were dried with MgSO4, and the solvent was removed under vacuum (44 % isolated yield).

Using Method A at 0 °C: Prepared from isobutyrophenone (1.50 mL, 10.0 mmol) and dried DBU (3.00 mL, 20.1 mmol) by Method A at 0 °C for 29 h. The vessel was vented in an ice bath, and upon opening the vessel, a small amount of solid and excess yellow liquid was found. Workup as described in Method A yielded only isobutyrophenone.

Using Method A at room temperature: Prepared from isobutyrophenone (1.50 mL, 10.0 mmol) and dried DBU (3.00 mL, 20.1 mmol) by Method A at room temperature for

29 h. The vessel was vented in an ice bath, and upon opening the vessel, a small amount of orange solid and excess orange liquid was found. MeCN (15 mL) was added to the vessel, the precipitate was filtered off, and characterization was attempted by ^{1}H NMR spectroscopy. ^{1}H NMR spectroscopy using D_2O is inconclusive because of peak overlap from the $DBUH^{+}$ and the expected ketocarboxylate product. Workup as described in Method A yielded only isobutyrophenone.

Using Method B: Prepared from isobutyrophenone (0.97 g, 6.56 mmol), n-BuLi (5.64 mL, 13.2 mmol), and diisopropylamine (1.85 mL, 13.2 mmol) by Method B. ^{1}H NMR spectroscopy of the crude sample shows a small amount of the desired product, but also 67 % 2-methyl-3-phenylpropan-3-ol, and butanol. To purify this sample, NaOH was added and CH_2Cl_2 was used to extract the unwanted organics. The aqueous layer was acidified to pH=2, producing a white precipitate. The solution was extracted with ether, the organic layer was dried with $MgSO_4$, and the solvent was removed under vacuum to isolate the desired product (1 % isolated yield).

The ^{1}H NMR and ^{13}C NMR spectra match those reported in the literature.[13]

^{1}H NMR ($CDCl_3$): 7.87 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H, 2′-C*H*), 7.52 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, 4′-C*H*), 7.41 (t, $^{3}J_{HH}$ = 8 Hz, 2H, 3′-C*H*), 1.54 (s, 6H, CH_3); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 132.8 (4′-*C*), 128.5 (2′-*C*), 128.37 (3′-*C*), 53.17 (*C*$(CH_3)_2$), 23.75 (CH_3). The 1′-C was not observable.

3-Oxo-butanoic acid (2h).

Using Method A at 0 °C (using $CaCl_2$ during workup): Prepared from acetone (0.91 mL, 12.4 mmol) and DBU (3.70 mL, 24.7 mmol) by Method A for 24 h at 0 °C and 30 bar CO_2. The vessel was vented in an ice bath, and upon opening the vessel, a yellow paste had formed that filled the volume of the vessel. For the product extraction as described in Method A, a saturated $CaCl_2$ aqueous solution and ethyl acetate were used, yielding the desired product (26 % isolated yield).

Using Method A at 0 °C: Prepared from acetone (0.91 mL, 12.4 mmol) and DBU (3.70 mL, 24.7 mmol) by Method A for 22 h at 0 °C and 40 bar CO_2. The vessel was vented in an ice bath, and upon opening the vessel, a yellow paste had formed that filled the volume of the vessel. Workup as described in Method A yielded the desired product (14 % isolated yield).

Using Method A at room temperature: Prepared from acetone (1.00 mL, 13.5 mmol) and DBU (4.04 mL, 27.0 mmol) by Method A for 17 h at room temperature. The vessel was vented in an ice bath, and upon opening the vessel, a yellow paste had formed that filled the volume of the vessel. The paste was washed with EtOAc, and the precipitate was filtered off. The ^1H NMR spectrum using D_2O contains a peak at 5.3 ppm, potentially assigned to the enol CH of the carboxylate/$DBUH^+$ salt Workup as described in Method A yielded the desired product (12 % isolated crude yield).

The ^1H NMR and ^{13}C NMR spectra match those reported in the literature.[1]

The observed keto:enol ratio in $CDCl_3$ was 1:0.22. Keto acid: ^1H NMR ($CDCl_3$): 3.54 (s, 2H, C*H*$_2$), 2.36 (s, 3H, C*H*$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 201.63 (keto *C*O), 171.49 (*C*O_2H), 48.85 (*C*H_2), 30.31 (*C*H_3),

Enol acid: ^1H NMR ($CDCl_3$): 5.04 (s, 1H, C*H*), 2.00 (s, 3H, C*H*$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 178.56 (*C*O_2H), 176.5 (3-*C*OH), 89.01 (*C*H), 21.53 (*C*H_3).

D-3-Camphoric acid (5/6).

Using Method A: Prepared from (1*R*)-camphor (1.09 g, 6.56 mmol) and DBU (1.97 mL, 13.2 mmol) by Method A for 25 h at room temperature. The vessel was vented in an ice bath, and upon opening the vessel, both a liquid and solid were present. Workup as described in Method A yielded no desired acid product.

Using Method B: Prepared from (1*R*)-camphor (1.085 g, 6.56 mmol), n-BuLi (5.64 mL, 13.2 mmol), and diisopropylamine (1.85 mL, 13.2 mmol) by Method B (85 % isolated yield).

No enol tautomer is observed by ^1H or ^{13}C NMR spectroscopy. The ^1H NMR and ^{13}C NMR spectra match those reported in the literature.[31,32]

exo-CO_2H acid: ^1H NMR ($CDCl_3$): δ 2.89 (s, 1H, 3-C*H*), 2.68 (m, 1H, 4-C*H*), 1.85-1.95 (m, 1H, 5-C*H*$_2$), 1.75-1.85 (m, 1H, 6-C*H*$_2$), 1.60-1.65 (1H, 5-C*H*$_2$), 1.38-1.48 (m, 2H, 5-C*H*$_2$), 1.03 (C*H*$_3$), 0.96 (1-C*H*$_3$), 0.90 (C*H*$_3$).

endo-CO_2H acid: ^1H NMR ($CDCl_3$): δ 3.38 (d, 1H, 3-C*H*), 2.48 (m, 1H, 4-C*H*), 2.05-2.15 (m, 1H, 5-CH_2), 1.75-1.85 (m, 2H, 6-CH_2), 1.52-1.60 (1H, 5-CH_2), 1.38-1.48 (m, 2H, 6-CH_2), 1.00 (CH_3), 0.95 (1-CH_3), 0.75 (CH_3).

2-Oxo-cyclohexanoic acid.

Using Method A at room temperature: Prepared from cyclohexanone (1.00 mL, 9.65 mmol) and DBU (3.00 mL, 20.1 mmol) by Method A at room temperature for 24 h. The vessel was vented in an ice bath, and upon opening the vessel, a yellow solid had formed. Workup as described in Method A yielded the desired product. The ^1H NMR spectrum shows the presence of both β-keto acid and the original ketone; however, both are soluble in hexane, so a new purification method is needed (17 % crude isolated yield).

Using Method A at 40 °C: Prepared from (1.00 mL, 9.65 mmol) and DBU (3.00 mL, 20.1 mmol) by Method A for 18 h at 40 °C. The vessel was vented in an ice bath, and upon opening the vessel, a yellow solid had formed. Workup described in Method A yielded the desired product (78 % crude isolated yield). Attempts at further purification of the product were unsuccessful.

mp=70-71 °C (literature value = 78-80 °C)[33]

The ^1H NMR and ^{13}C NMR spectra match those reported in the literature.[13]

^1H NMR ($CDCl_3$): δ 1.6-2.1 (m, 4H), 2.2-2.6 (m, 4H), 3.39 (dd, $^3J_{HH}$ = 11.2 Hz, 5.6 Hz, 1H, 1-C*H*).

2-Acetylfuran carboxylic acid.

Prepared from 2-acetylfuran (1.00 mL, 10.0 mmol) and DBU (3.00 mL, 20.0 mmol) by Method A for 25 h at room temperature. The vessel was vented in an ice bath, and upon opening the vessel, a brown solution remained. Using ethyl acetate for extraction, workup as described in Method A yielded the desired product (35 % NMR yield).

The ^{1}H NMR spectrum agrees with expected shifts; however, attempts at further purification were unsuccessful. ^{1}H NMR ($CDCl_3$): δ 7.66 (m, 1H, 5-C*H*), 7.33 (m, 1H, 4-C*H*), 6.60 (m, 1H, 3-C*H*), 5.66 (s, 1H, enol C*H*), 3.92 (s, 2H, keto CH_2).

The calculated NMR is as follows: δ 7.79 (5-C*H*), 7.05 (4-C*H*), 6.78 (3-C*H*), 5.54 (enol C*H*), 4.13 (keto CH_2).

2.4.5 Alternate Workup Methods

Using CO_2 pressure during acidification and/or extraction.

Prepared by reacting acetone (0.74 mL, 10.03 mmol) and DBU (3.00 mL, 20.07 mmol) in a 160 mL vessel for 22 h at room temperature and 60 bar CO_2. The vessel then was cooled for 1 h in an ice bath. A 0.5 M HCl (50 mL) solution was added to another 160 mL vessel containing a dip tube; this vessel was cooled to 0 °C, pressurized to 80 bar CO_2, and connected to the reaction vessel. The adjoining valve was opened in order to acidify the reaction mixture. Upon opening the vessel, a yellow solution with pH=1 resulted. (1) For extraction in open air: The solution was extracted using ethyl acetate, the organic layer was dried by $MgSO_4$, and the solvent was removed

under vacuum, yielding no product. (2) For extraction under CO_2 pressure: the vessel containing 50 mL of 0.5 M HCl also contained 30 mL ethyl acetate. After opening the vessel, a yellow aqueous layer was found. The organic layer was dried with $MgSO_4$, and removed under vacuum, yielding no acid product.

Using scCO_2 workup.

Prepared by reacting acetone (0.91 mL, 12.4 mmol) and DBU (3.70 mL, 24.7 mmol) for 24 h at 0 °C and 60 bar CO_2. The vessel then was cooled for 30 min in an ice bath. The vessel was vented slowly, and upon opening the vessel, a yellow paste remained; ice cold water (50 mL) was then added. For scCO_2 conditions, the vessel was placed in a 40 °C water bath and the vessel was pressurized to 100 bar CO_2. A CO_2 pump was used to maintain a constant flow of CO_2 through the vessel, and an attached back-pressure regulator vented excess pressure into a Schlenk flask cooled to 0 °C. After performing this extraction for 1 h, no product was recovered.

Benzoic Acid Recovery at 60 bar CO_2.

Reacted benzoic acid (0.5 g, 4.10 mmol) with DBU (0.5 mL, 4.1 mmol) in H_2O (10 mL) at room temperature. The reaction mixture and diethyl ether (10 mL) were added to a 160 mL vessel. The vessel was pressurized to 60 bar CO_2 and allowed to stir for 24 h. Upon opening the vessel, the organic layer was separated, dried with $MgSO_4$, and removed under vacuum. The ^1H NMR spectrum using $CDCl_3$ shows the successful recovery of benzoic acid.

Benzoic Acid Recovery at 1 atm CO_2.

Reacted benzoic acid (0.1 g, 0.82 mmol) with DBU (0.12 mL, 0.82 mmol) in H_2O (2 mL) at room temperature. The solution was bubbled with 1 atm CO_2 for 20 min at room temperature then diethyl ether (4 mL) was added to extract the product. The bubbling of CO_2 was continued for an additional 20 min; however, additional diethyl ether (4 mL) needed to be added due to solvent loss. The layers were separated, and both the organic layer and aqueous layer were removed under vacuum. The oil contained in the organic layer was confirmed by ^1H NMR spectroscopy ($CDCl_3$) to be a mixture of benzoic acid and DBU. The aqueous layer ^1H NMR spectrum also shows benzoic acid and DBU, presumably in the carboxylate $DBUH^+$ salt form.

2.5 References

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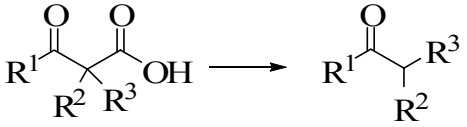
Chapter 3
Decarboxylation of β-Ketocarboxylic Acids

3.1 Introduction

The objective of this portion of the project is to determine the relative rates of decarboxylation of the previously synthesized β-ketocarboxylic acids (Scheme 2.8). The solvent, electronic, and steric effects on the rate of decarboxylation will be determined in order to ensure that the asymmetric hydrogenation, the primary goal of this thesis, will effectively compete.



2 **1**

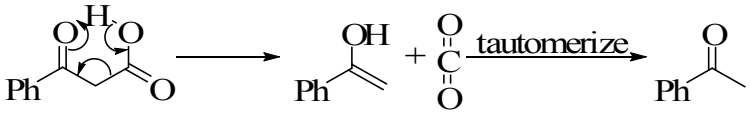
	R^1	R^2	R^3
a	Ph	H	H
b	4-ClC_6H_4	H	H
c	4-$OMeC_6H_4$	H	H
d	2-MeC_6H_4	H	H
e	naphthyl	H	H
f	Ph	Me	H
g	Ph	Me	Me
h	Me	H	H

Scheme 3.1. Decarboxylation of Various β-Keto Acids.

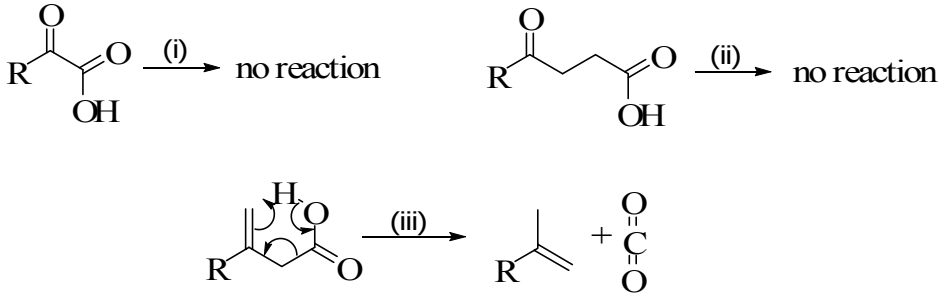
3.1.1 General Background

Decarboxylation occurs easily at ambient temperature and is accelerated in solution; therefore, samples must be stored at low temperatures to slow the reaction. Numerous factors contribute to the reaction (Scheme 3.2): (i) the formation of a six membered transition state, (ii) the loss of CO_2 as a stable leaving group, (iii) the increase

in entropy, and (iv) the high rate of the subsequent tautomerization. Because a six-membered transition state is not possible for other ketocarboxylic acids, such as α- and γ-keto acids, decarboxylation does not occur (Scheme 3.3). Yet, experiments have shown that β,γ-unsaturated carboxylic acids also undergo a similar concerted decarboxylation transition state, involving a twisted chair conformation.[1,2]



Scheme 3.2. Decarboxylation of β-Ketocarboxylic Acids.



Scheme 3.3. Decarboxylation of (i) α-Keto Acid, (ii) γ-Keto acid, and (iii) β,γ-Unsaturated Acid.

Since the first experimentally-observed decarboxylation of β-keto acids by Pollak in 1907,[3] there has been a great deal of research into the reaction mechanism.[4-6] The decarboxylation of the carboxylate anion is a simple carbon-carbon bond breakage, forming carbon dioxide and an enolate anion.[7] However, although it is well-known that the free acid decomposes to produce carbon dioxide and an enol, the exact nature of the hydrogen transfer is still under debate.[8,9] Figure 3.1 shows three proposed transition states for decarboxylation. Structure **A** was first postulated by Pedersen, involving a charge-separated species.[10] Structure **B** is also well-regarded and involves a concerted

reaction mechanism.[11-13] This non-polar structure most closely resembles the established transition state for the decarboxylation of β,γ-unsaturated carboxylic acids.[13] Structure **C** is proposed for the decarboxylation of bicyclic β-keto acids with the carboxylic acid located on the bridgehead carbon; the enol formation in the other transition states would violate Bredt's rule, stating that a bridgehead carbon of a strained bridged ring molecule cannot be sp^2 hybridized.[14,15]

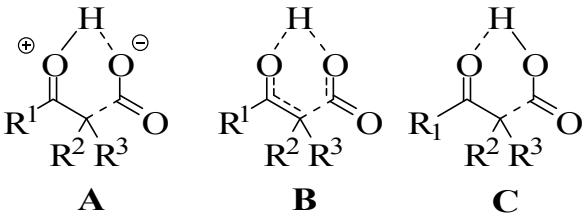


Figure 3.1. Proposed Decarboxylation Transition States.[9]

3.1.2 Decarboxylation Studies

Because of the prevalence of decarboxylation, numerous rate studies have been performed to determine solvent,[8,16] substituent,[7] and pH effects.[17] *Ab initio* calculations by Lien *et al.*[6] confirmed experimental data that solvent polarity has only a small effect on the decarboxylation energy barriers. Bender *et al.*[9] studied substituent effects on substituted benzoylacetic acids and found the decarboxylation rate of the free acid is independent of substituent; however, the rate for the carboxylate anion is increased by electron-withdrawing substituents. Hay and Tate speculate that the anionic decarboxylation was significantly influenced by substituent choice because of electronic effects.[7] In this case, electron-withdrawing substituents stabilize the enolate that is formed from anion decarboxylation. Unfortunately, the majority of research investigated

para substituted β-keto acid decarboxylation; other factors, such as entropy and steric repulsion, may also play a role in the mechanism.

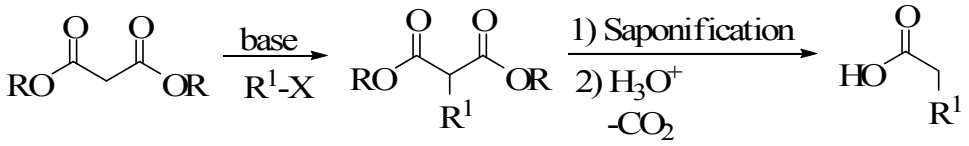
3.1.3 Decreasing the Rate of Decarboxylation

Hydrolysis of β-keto methyl esters by Mitz[18] produced the corresponding straight chain β-keto acids ranging from fourteen to twenty carbons in length. Impressively, these long-chain β-keto acids can be recrystallized and show higher stability at room temperature in comparison to shorter chain β-keto acids. Therefore, increasing the hydrophobicity increases stability.

Haruki found that water at 0 °C stabilized the carboxylate anion from decarboxylation through hydration and H-bonding.[19] Normally, decarboxylation occurs easily *in situ*, but even after the β-ketocarboxylate salt was dissolved in water for 3 h followed by protonation, good yields of free acid were still obtained.

3.1.4 Importance of Decarboxylation

Decarboxylation can also be of importance, depending on the desired reaction. As mentioned previously, decarboxylation of a β-keto acid can be utilized in the alkylation of ketones.[20] In addition, using the malonic ester synthesis, the carbonyl and α carbon from malonic ester are added primary or secondary alkyl halides. The loss of CO_2 is a key step during this synthesis.[21]



Scheme 3.4. Two Carbon Extension by Malonic Ester Synthesis.[21]

3.2 Results and Discussion

3.2.1 Solvent Effect on Decarboxylation Rate

To determine if the decarboxylation rate is solvent dependent, the decarboxylation of **2a** in various deuterated solvents was monitored automatically by ^{1}H NMR spectroscopy at 10 min intervals (Figure 3.2).

Due to the need for sample shimming, tuning, and matching, a short time delay occurred between the β-keto acid addition and the first acquisition. Also, the NMR sample was kept in the NMR spectrometer for the first 200 min to ensure a constant environment; however, upon removing the sample for the NMR spectrometer, changes in the external environment caused the data points to deviate from the expected linear log plot. Therefore, for the purpose of analysis reproducibility, only these first 200 min are displayed.

The percent decarboxylation after each 10 min interval was calculated from the integrations of the CH enol and CH_2 keto peaks of the acid starting material, and the CH_3 peak of the ketone product. Plotting ln(100-conversion) versus time produced a straight line (linear for over 2 half lives in DMSO-d_6 and MeOH-d_4 and for the duration of the experiment in the other solvents), and the rate was calculated from the slope of this line. Over the tested time span, the decarboxylation follows first order kinetics for all solvents.

The rate of decarboxylation was significantly lower in the low polarity solvents chloroform-d_3 and dichloromethane-d_2, and the medium polarity solvent acetone-d_6 than in the high polarity solvents dimethylsulfoxide-d_6 and MeOH-d_4. Therefore, the first conclusion is that highly polar solvents should be avoided unless the asymmetric hydrogenation is correspondingly faster in these solvents.

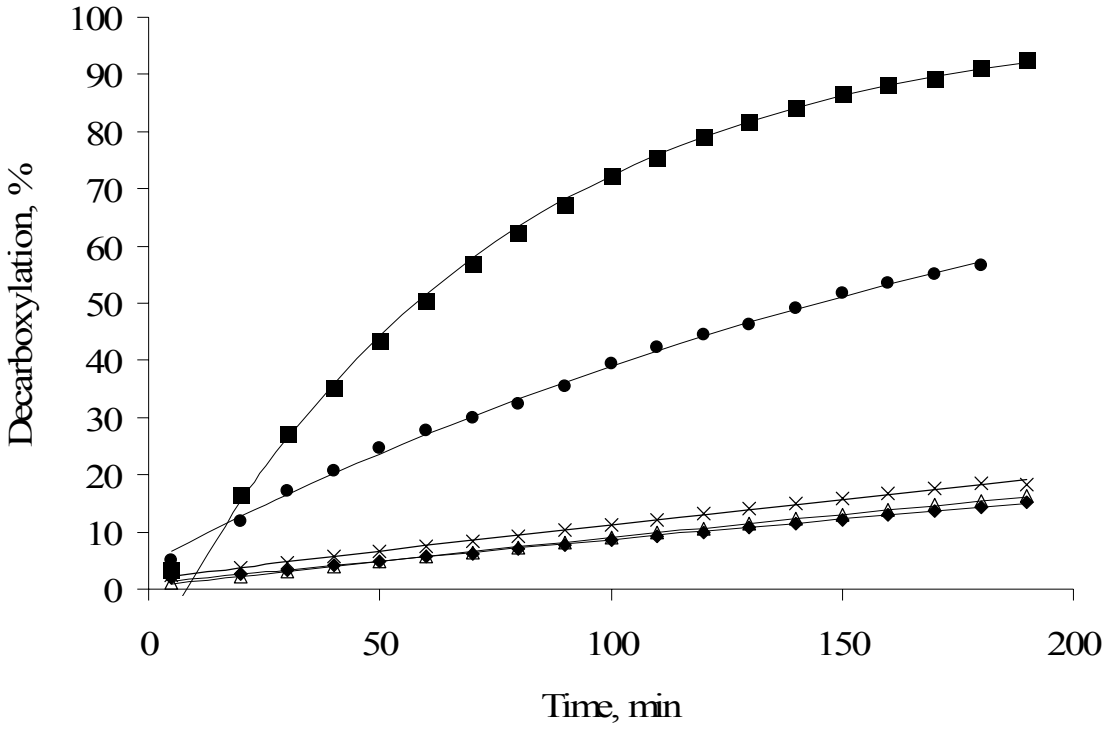


Figure 3.2. Observed Decarboxylation of Benzoylacetic Acid (**2a**, 0.08 M) at 25 ˚C in DMSO-d_6 (■), MeOH (•), CD_2Cl_2 (Δ), $CDCl_3$ (×) and acetone-d_6 (♦). The data points represent the average of duplicate decarboxylation experiments. The curves are those predicted for first order reactions listed in Table 3.1.

The solvent effect on the rate of decarboxylation roughly correlates with the solvent effect on the keto/enol ratio. This is not surprising as decarboxylation is reported to occur from the keto tautomer[8] and, according to Rosenfeld,[22] the keto/enol ratio is

higher in more polar solvents. At a concentration of 0.08 M at 25 °C, it was found that decarboxylation of **2a** is generally faster in solvents that favour a larger keto:enol ratio (Table 3.1).

Table 3.1. Decarboxylation Rate Constants of **2a** Compared to the Keto:Enol Ratio.[a]

Solvent	keto:enol ratio	Rate Constant (sec^{-1})	$t_{1/2}$ (min)
$(CD_3)_2SO$	5.5	2.0×10^{-4}	70
CD_3OD	3.8	6.9×10^{-5} [d]	170
$CDCl_3$ [b]	2.9	1.7×10^{-5}	670
CD_2Cl_2	3.6	1.5×10^{-5}	770
PhMe-d_8 [c]	0.79	1.3×10^{-5}	900
$(CD_3)_2CO$	1.9	1.3×10^{-5}	900

[a]Average values from duplicate experiments, assuming first order reaction. [b]Lower concentration due to solubility. [c]Due to poor solubility, 0.014 M solution was tested. [d]Rate measured in undeuterated CH_3OH.

Compound **2a** did not completely dissolve in chloroform-d_3, and therefore, a lower sample concentration was used, accounting for the lower than expected keto:enol ratio. During the initial decarboxylation measurements, moving the sample after the initial 200 min caused some previously insoluble substrate to dissolve, producing an unexpected decrease in the conversion curve. Although a lower concentration of **2a** was used with PhMe-d_8, a low keto:enol ratio was still observed, following the expected solvent polarity trend.

Based on solvent polarity (Table 3.1), acetone-d_6 gave a larger $t_{1/2}$ than expected. A Lewis basic solvent, such as acetone, can participate in hydrogen-bonding with the β-keto acid hydroxy proton, increasing its electron density and disrupting the

decarboxylation transition state. Because the hydroxy proton is made less electrophilic, carbonyl oxygen reactivity towards the proton becomes lower, slowing decarboxylation. Along these lines, solvent tests with EtOAc and THF for the carboxylation (Chapter 2) and hydrogenation reactions (Chapter 4) have shown increased stability of **2a**; this trend with diethyl ether and THF has been noted in the literature.[23]

The rate constant in MeOH was determined in MeOH-d_0 by ^{1}H NMR spectroscopy for two reasons: (i) rapid deuterium exchange in MeOH-d_4 causes the disappearance of the α-proton peaks of **2a**, and (ii) the aromatic region of the keto tautomer overlaps with the original ketone in the ^{1}H NMR spectrum. Therefore, MeOH-d_4 was used as an external reference instead.

At a lower concentration of 0.01 M at 25 °C in CD_2Cl_2, the keto:enol ratio for **2a** was 6.5, but the $t_{1/2}$ was 900 min. This means that the half life of decarboxylation is concentration independent (as one would expect for a first-order reaction) even though the keto:enol ratio is not. This same trend is found in each decarboxylation experiment; as decarboxylation occurs, the keto:enol ratio slowly increases due to decreased concentration of β-keto acid,[24] but the log plot of decarboxylation remains linear. This reinforces the Curtin-Hammett Principle.

Methylene chloride was selected as the optimal solvent for determining the decarboxylation rate of other substrates for three reasons: (i) moderate rates of decarboxylation are observed in this solvent, (ii) the solvent is chemically inert towards the substrate, and (iii) the substrates are fully soluble.

3.2.2 Electronic Effect on the Rate of Decarboxylation

The electronic effect on the rate of decarboxylation was also determined (Table 3.2 and Figure 3.3), and the expected correlation between the keto:enol ratio and the decarboxylation rate was not observed. Furthermore, no trend between the ketone α-proton pK_a and decarboxylation rate is observed.

Upon comparing the decarboxylation rate with the electron-withdrawing ability of the substituent, a general increase in rate is observed proceeding from **2h** to **2a** to **2b**. In this series, the increasingly electron-withdrawing nature of the aromatic ring may make the carbonyl oxygen more reactive, and therefore, more prone to protonation.[8] However, comparing **2a**, **2b**, and **2c** illustrates that *para* substituents on the aromatic ring do not affect the rate of decarboxylation to any large extent, in agreement with literature findings.[9] Substitution in the *ortho* location does lower the rate of decarboxylation, potentially caused by the increased steric repulsion from the *o*-Me.

Table 3.2. Decarboxylation Rate Constants of Keto Acids of the Formula $RC(O)CH_2CO_2H$.

R[a]	pK_a of $RC(O)CH_3$ (DMSO)	keto:enol ratio[b]	Rate Constant[c] (sec^{-1})	$t_{1/2}$ (min)
4-ClC_6H_4 (**2b**)	23.8	2.9	2.8×10^{-5}	410
Ph (**2a**)	24.7	3.6	1.5×10^{-5}	770
2-MeC_6H_4 (**2d**)	na	3.2	5.1×10^{-6}	2200
4-$MeOC_6H_4$ (**2c**)	25.7	11.6	2.4×10^{-5}	470
Me (**2h**)	26.5	7.4	4.6×10^{-6}	2500

[a]Acids are listed in order of increasing electron donation, as measured by the pK_a of the corresponding compound **1**. [b]In CD_2Cl_2 solvent at 0.08 M and 25 °C. [c]Average values from duplicate experiments, assuming first order reaction.

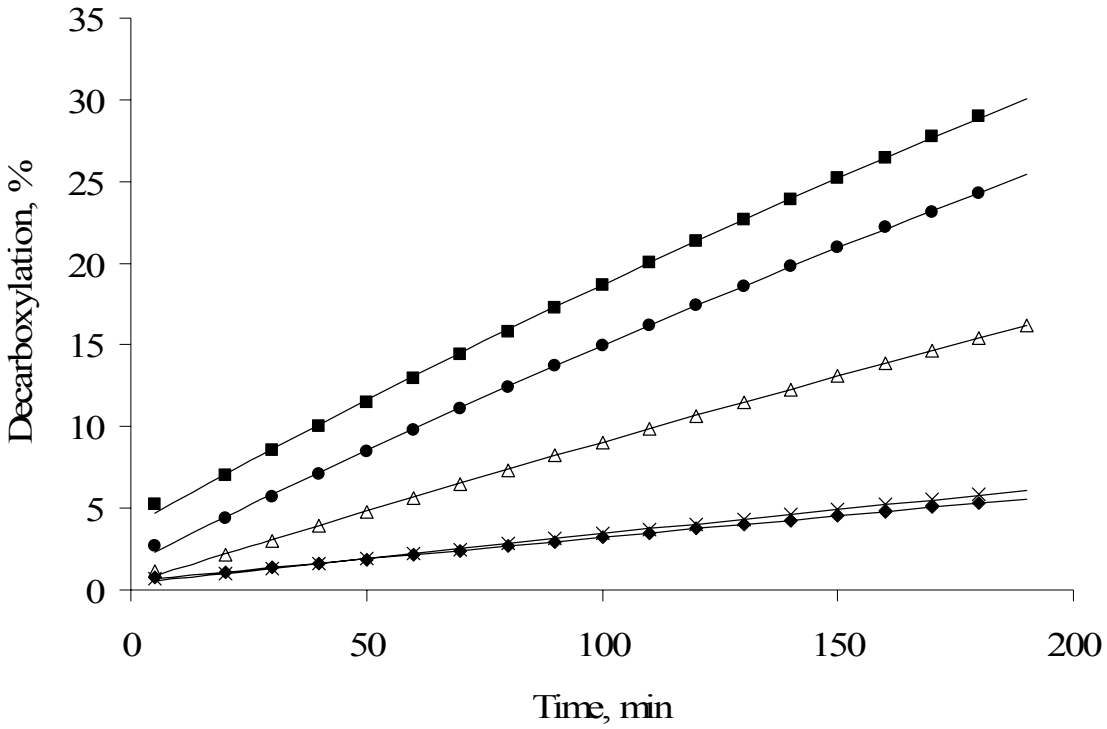


Figure 3.3. Observed Decarboxylation of **2a** (Δ), **2b** (■), **2c** (•), **2d** (×), and **2h** (♦) at 0.08 M and 25 ˚C in CD_2Cl_2. The data points represent the average of duplicate decarboxylation experiments. The curves are those predicted for first order reactions listed in Table 3.2.

3.2.3 Steric Effect on Decarboxylation Rate

The steric effect on the rate of decarboxylation was tested as well (Figure 3.4). Because decarboxylation is reported to occur from the keto tautomer,[8] fixing the substrate in the keto tautomer could increase the rate of decarboxylation. However, as evidenced by the very slow decarboxylation of **2g**, this assumption is not correct. The decarboxylation mechanism for this substrate must be structure **C** in Figure 3.1 or else Bredt's Rule would be violated.

In order to investigate the steric effect with substrates that are not fixed in the keto form, the decarboxylations of **2f** and **5**/**6** were investigated. Although the keto tautomer is possible, it has been shown, in the literature and our work, that **2f**[25] and **5/6**[26] do not contain detectable amounts of the enol tautomer. Decarboxylation of **2f** and especially **5**/**6** is slower than **2a**. The electron-donating ability of the methyl group(s) may account for the increased stability, but steric hindrance may also be a contributing factor.

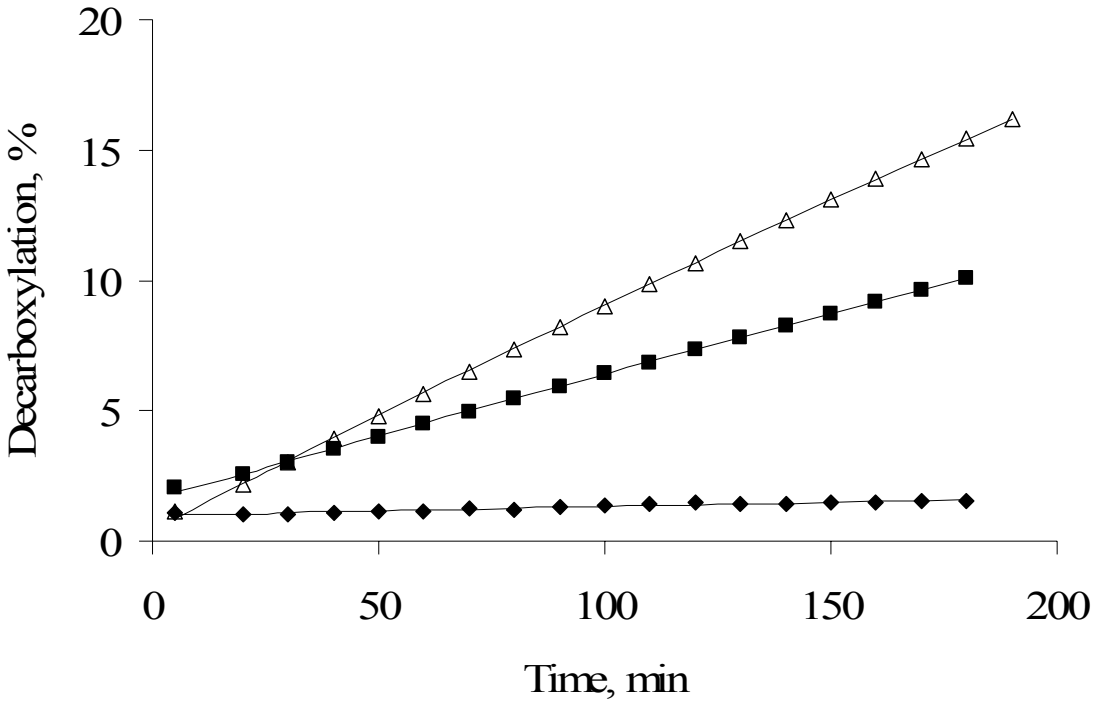
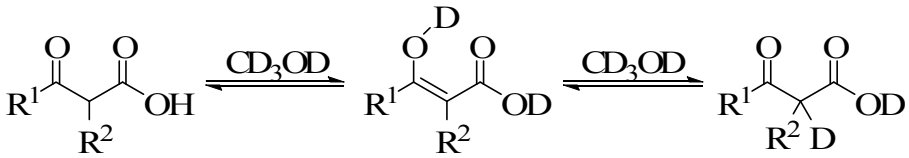


Figure 3.4. Observed Decarboxylation of **2a** (Δ), **2f** (■), and **2g** (♦) at 0.08 M and 25 ˚C in CD_2Cl_2. The data points represent the average of duplicate decarboxylation experiments. The curves are those predicted for first order reactions with rate constants 1.5 x 10^{-5}, 8.3 x 10^{-6}, 5.5 x 10^{-7} sec^{-1}, respectively.

3.2.4 Isotopic Labelling Experiments for Enol Detection

Although the enol tautomers of **2f** and **5/6** may be undetectable on the NMR timescale, tautomerization may still be taking place. If such tautomerization is occurring, deuterium exchange with MeOH-d_4 and subsequent deuterium incorporation would be observed by ^{1}H NMR spectroscopy (Scheme 3.5). Through tautomerization, deuteration at the α-position should be observed.



Scheme 3.5. Deuterium Incorporation into β-Keto Acid via Tautomerization.

A low rate of deuteration was observed for **2f**, producing 50 % deuteration within 780 min. In contrast, full deuteration of camphoric acid at the α position occurred within 20 min. The 2-endo-H from **6** deuterated within 8 min, and the 2-exo-H from **5** deuterated within 20 min, meaning that the 2-endo-H is more accessible for deprotonation or enolization. No deuteration was observed at any other location in camphoric acid, eliminating the possibility of non-classical ion formation. It was concluded that the keto-enol tautomerization readily occurs for **5/6** and slowly for **2f**, but in neither case is the enol tautomer present in sufficient quantities to be detected by NMR spectroscopy because of its quaternary nature.

As a result of tautomerization, **5** and **6** are in thermodynamic equilibrium, which is observable from the consistent 7:3 ratio observed by ^{1}H NMR spectroscopy.

3.2.5 Enol Structure versus Decarboxylation Transition State

The enol tautomer of β-ketocarboxylic acids can exist as two isomers: the (Z)-enol and (E)-enol isomers. The (Z)-enol isomer has been shown to be favoured over the (E)-enol isomer due to internal hydrogen bonding.[27] Because the resulting six-membered ring is similar to the proposed decarboxylation intermediate, the rate of enolization and decarboxylation may be comparable. However, as previously mentioned, enolization of camphoric acid occurs quickly, yet no decarboxylation was observed during the 17 h ^{1}H NMR spectroscopy decarboxylation experiment. For camphoric acid, poor orbital overlap between the carbonyl and acid hydroxy moieties could account for the significantly lower decarboxylation rate.

3.2.6 Decarboxylation of β-Ketocarboxylate Anion

Lastly, the decarboxylation rate of **2a** in the presence of DBU was also tested to determine the feasibility of a one-pot hydrocarboxylation method. With no CO_2 present, 1 equivalent of dry DBU, and CH_2Cl_2 as the solvent, full decarboxylation of **2a** occurred within 30 min. This rapid decarboxylation signifies that CO_2 must be present to suppress decarboxylation for the one-pot method to succeed. To definitively determine the feasibility of the one-pot hydrocarboxylation method, a ^{1}H NMR spectroscopy decarboxylation experiment under CO_2 atmosphere should be performed.

3.3 Conclusions

It was observed that the rate of decarboxylation for benzoylacetic acid is solvent dependent, with higher rates corresponding in more polar solvents. Methylene chloride

was selected as the optimal solvent because of its chemical inertness, its dissolution ability, and the decreased rate of β-keto acid decarboxylation. Lewis basicity of the solvent also plays a role in increasing the substrate stability by disrupting the H-bonding necessary for proton transfer.

Findings herein agree with the literature that *para* substituents have little effect on the rate of decarboxylation; however, the less studied *ortho* substituents do show promise in slowing decarboxylation. Because of the small electronic effect from a methyl moiety, it is likely that steric hindrance plays a role in reducing decarboxylation. 3-Oxobutanoic acid displayed impressive stability in solution, which is advantageous due to its involvement in the metabolic cycle. In addition to electronic effects, increasing the methyl substituents at the α position of benzoylacetic acid produced a marked decrease in decarboxylation rate. Throughout these experiments, no trend between pK_a of the original ketone and decarboxylation of the β-keto acid is observed.

Although the enol tautomer is undetectable by ^{13}C NMR spectroscopy, evidence of a transient enol species for both **2f** and **5**/**6** was established via deuterium labelling experiments.

Having determined the stability of these substrates, the *in situ* asymmetric hydrogenation can now be attempted.

3.4 Future Work

Although the effect of *para* aromatic substitution has been well studied, further investigation of the effect of *ortho* aromatic substitution should be performed. To begin

with, *in situ* decarboxylation using ^{1}H NMR spectroscopy could be used; in the future, thermodynamic and theoretical calculations could be performed to validate the experimentally determined effects.

The decarboxylation of benzoylacetic acid should be attempted under CO_2 pressure. This would not only provide information about the rate of decarboxylation under CO_2 pressure but also the carboxylation equilibrium. Because standard NMR spectroscopy procedure could be used, high pressure NMR spectroscopy is a simple option. An alternative spectroscopic method to monitor the decarboxylation other than ^{1}H NMR spectroscopy could be reactive infrared spectroscopy. In this case, a CO_2 atmosphere baseline would need to be acquired prior to the experiment.

A simple method for detecting the presence of the enol forms of **2f** and **5/6** would be to trap the enol using Me_3SiCl. This would conclusively demonstrate the enol tautomer and it would negate the possibility of deuterium incorporation via simple deprotonation.

3.5 Experimental

See Section 2.4 for a description of general experimental materials, equipment and techniques, and spectroscopy and chromatography. Any changes or additions to those procedures are described herein.

3.5.1 General Considerations for Decarboxylation of β-Keto Acids Monitored by ^{1}H NMR Spectroscopy

The standard procedure is as follows: (1) the solvent (0.55 mL) was added to the β-keto acid (0.04 mmol), (2) the first NMR spectrum was acquired within 5 min at 25 °C, and (3) the decarboxylation rate was calculated by monitoring the disappearance of the keto-CH_2 and enol-CH peaks, and the appearance of the ketone CH_3 peak.

3.5.2 Decarboxylation of Benzoylacetic Acid (2a)

The decarboxylation was monitored by the standard method (Table 3.3). **2a** was fully soluble in solvents, except PhMe-d_8 and $CDCl_3$; in the case of PhMe-d_8, undissolved **2a** was removed via a small Celite 545 pipette column and isopropanol (0.01 mmol) was added as an internal standard. For MeOH and MeOH-d_4, an additional time delay (~1 min) was required to ensure that all of **2a** dissolved.

Table 3.3. Chemical Shifts of Key Signals Monitored by ^{1}H NMR Spectroscopy During the Decarboxylation of **2a** in Various Solvents.

Solvent	δ C*H* (ppm)	δ CH_2 (ppm)	δ CH_3 (ppm)
DMSO-d_6	5.82	4.05	2.58
MeOH-d_4	5.72	4.02	2.60
MeOH	5.66	3.97	2.54
CD_2Cl_2	5.73	4.10	2.61
CD_2Cl_2[a]	5.73	4.10	2.61
$CDCl_3$[b]	5.73	4.09	2.61
PhMe-d_8[a]	5.54	3.22	7.70[c]
acetone-d_6	5.84	4.00	2.58

[a]0.007 mmol used. [b]Unknown concentration due to insolubility.
[c]The ketone *ortho*-CH was monitored, rather than the CH_3.

3.5.3 Decarboxylation of Benzoylacetic Acid (2a) in the Presence of Base

Benzoylacetic acid (0.04 mmol) was added to CD_2Cl_2 (0.55 mL) containing DBU (0.05 mmol) and the standard procedure was used.

3.5.4 Decarboxylation of Other β-Keto Acids

The standard procedure was used for the decarboxylation of other β-ketocarboxylic acids (0.04 mmol) in CD_2Cl_2 (0.55 mL) by monitoring the following peaks (Table 3.4):

Table 3.4. Chemical Shifts of Key Signals Monitored by ^{1}H NMR Spectroscopy During the Decarboxylation of Other β-Keto Acids in CD_2Cl_2.

Substrate	δ enol (ppm)	δ keto (ppm)	δ ketone (ppm)
2b	5.72	4.06	2.56
2c	2.65	4.03	2.52
2d	5.36	4.05	2.49
2f	--	4.48	3.00
2g	--	1.55	1.18
2h	5.05	3.54	2.16
5/6	--	2-exo-H (3.38) 2-endo-H (3.00)	0.83

3.5.5 Deuterium Incorporation Experiments

2-Methyl-3-oxo-phenylpropanoic acid (**2f**) (0.04 mmol) and CD_3OD (0.55 mL) were placed in an NMR tube. Immediately thereafter, the first of a series of ^{1}H NMR spectra was acquired. The % deuteration at the α (2-) position was calculated from the integration ratio between the methyl peak and the α proton peak. Decarboxylation of the substrate was also monitored.

D-3-camphoric acid (**5**/**6**) (0.05 mmol) and CD_3OD (0.55 mL) were placed in an NMR tube. Immediately thereafter, the first of a series of ^1H NMR spectra was acquired. The % deuteration was calculated using the integration ratio between the 4-C*H* and α (ie. 3-C*H*) proton peak. Decarboxylation of the substrate was also monitored.

3.6 References

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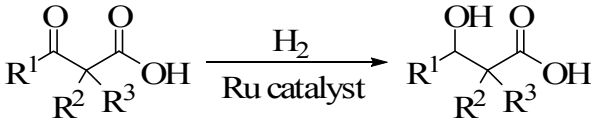
Chapter 4
Asymmetric Hydrogenation to β-Hydroxycarboxylic Acids

4.1 Introduction

The objective of this project is to asymmetrically hydrogenate the β-ketocarboxylic acids, previously synthesized (Chapter 2) using CO_2 fixation and cheap ketones, in order to convert them into biologically important and industrially valuable chiral β-hydroxycarboxylic acids (Scheme 4.1).



2			**3**
	R^1	R^2	R^3
a	Ph	H	H
b	4-ClC_6H_4	H	H
c	4-$OMeC_6H_4$	H	H
d	2-MeC_6H_4	H	H
e	naphthyl	H	H
f	Ph	Me	H
g	Ph	Me	Me
h	Me	H	H

Scheme 4.1. Asymmetric Hydrogenation of β-Ketocarboxylic Acids.

4.1.1 Uses for β-Hydroxycarboxylic Acid

Due to the presence of two functional groups, β-hydroxycarboxylic acids are good candidates in a number of research areas, ranging from natural products to anaesthetics.[1] To illustrate the biological importance, (R)-3-hydroxydecanoic acid is found in the secretion of the leaf cutting ant,[2] and (S)-3-hydroxyhexadecanoic acid, known as

pahutoxin, is poisonous to fish.[3] β-Hydroxy acids are also valuable building blocks in total syntheses; (R)-3-hydroxyoctadecanoic acid is used in a convergent synthesis to produce (R,R)-corynomycolic acid, a cord factor.[4,5] Compactin, which displays high hypocholesterolemic activity,[6] has been synthesized using a β-hydroxycarboxylate intermediate.[7] As mentioned earlier, 3-hydroxybutanoic acid, a ketone body, is used by skeletal and cardiac muscles as an energy source in times of exertion. However, this β-hydroxy acid can also be used as an anaesthetic because it enhances GABAa (γ-amino butyric acid type A) receptor function.[1] Industrially, a number of acids, including 3-hydroxypropanoic acid, are listed by the U.S. Department of Energy as the top twelve building block chemicals for high-value bio-based materials and chemicals.[8]

Two other examples of β-hydroxycarboxylic acids very important to human life are: L-carnitine and L-threonine (Figure 4.1). L-carnitine is produced within the liver and kidneys and is responsible for transporting fatty acids from the cell cytosol into the mitochondria and transporting toxic compounds out of the cell. Because of its involvement with energy production, L-carnitine is found in high concentration in skeletal and cardiac muscles.[9] L-Threonine is one of the 20 essential amino acids, and because the body does not produce L-threonine, it must be acquired from foods, such as poultry, fish, and lentils.[10]

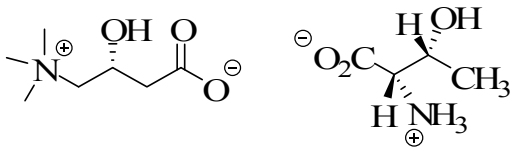


Figure 4.1. Structures of L-Carnitine and L-Threonine.

4.1.2 Synthesis of β-Hydroxycarboxylic Acids

A review of the literature reveals that β-hydroxycarboxylic acids can be synthesized using a variety of starting materials and techniques, such as enzymes,[11] chiral ligands, [12-14] or metal complexes.[15]

Baker's yeast, *Saccharomyces cerevisiae*, has been shown to effectively reduce small chain 3-oxo-carboxylate potassium salts to the corresponding (R)-3-hydroxy-carboxylate salt in >99 % ee and upwards of 60 % yield.[11] Utaka *et al.*[16] also used baker's yeast to reduce β-keto acids, ranging from C4 to C15, to the (R)-3-hydroxy enantiomer with 98 % ee. Unfortunately, although the enantioselectivity is very high, the yields are low.

Ramachandran *et al.*[12,13] have shown that DIP-Cl (β-chlorodiisopinocampheylborane) and the parent diisopinocampheylborane effectively reduce α-, β-, and γ-ketocarboxylic acids with ee's normally above 90 %. Fortunak *et al*. speculated that these high ee's were observed because of a rigid bicyclic transition state (Figure 4.2). The favoured state involves the keto carbonyl in better proximity to the boron, and less steric repulsion between the R-group and methyl of the isopinocampheyl; whereas, the equatorial R-group would be disfavoured.[17]

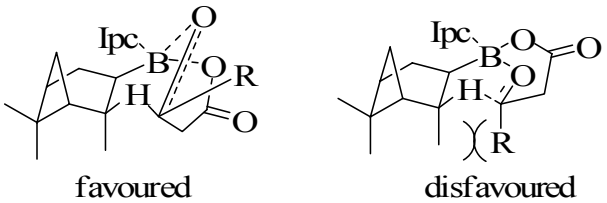
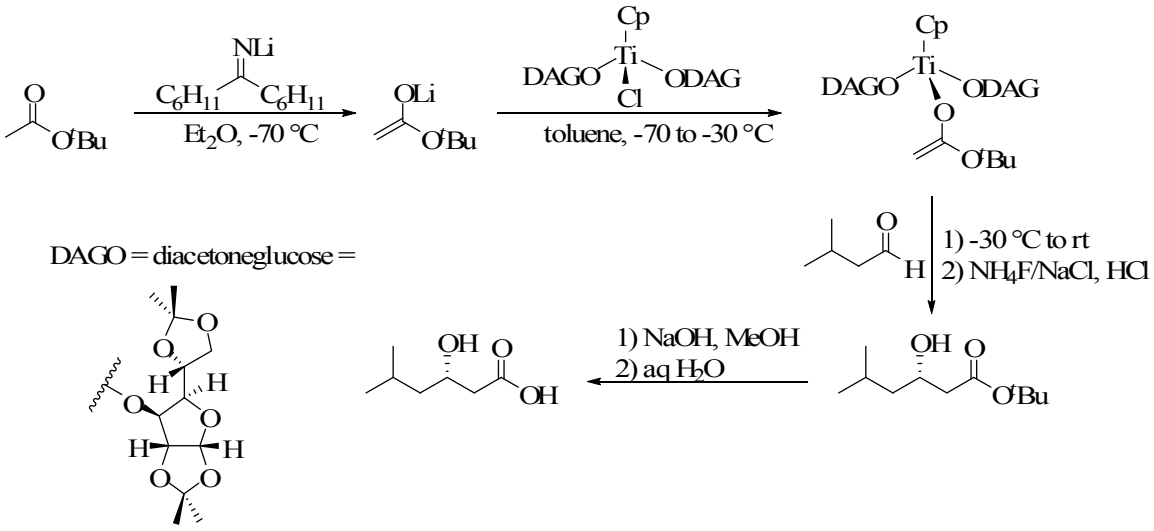


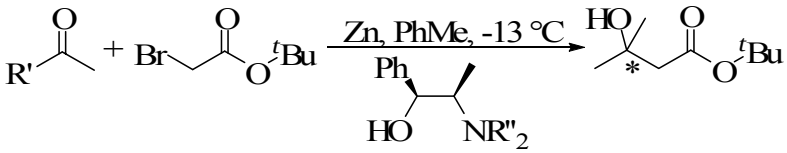
Figure 4.2. Proposed Transition States for DIP-Cl Reduction of β-Keto Acids.[17]

In aldol condensations, the use of chiral complexes for enolate stabilization, such as titanium-carbohydrate complexes,[14] induce chirality into the product (Scheme 4.2); the resulting β-hydroxy ester was hydrolyzed to produce the β-hydroxy acid in >99 % ee.[18] Although the titanium complex is non-toxic, and easily reformed and reused, these aldol reactions involve low temperatures, numerous steps, and are more energy intensive, and are, therefore, not ideal for industry.



Scheme 4.2. β-Hydroxycarboxylic Acid Synthesis via Chiral Titanium-Carboxylate Aldol Condensation.[18]

Another alternative synthesis involves the Reformatsky reaction. By using *N*,*N*-dialkylnorephedine as a chiral ligand, Soai *et al.*[15] produced β-hydroxy esters in 74 % ee from prochiral ketones (Scheme 4.3). This value was improved upon by using zinc bromide and aldehydes, thereby attaining 93 % ee.[19]



Scheme 4.3. Enantioselective Reformasky Reaction.

In the literature, the preferred method of synthesizing β-hydroxy acids is via the hydrolysis of the corresponding β-hydroxy ester or the involvement of biological media, thereby requiring additional workup steps. On the other hand, transition metal catalyzed asymmetric hydrogenation avoids this problem, providing an industrial interest; this reaction is also of academic interest due to a lack of published research in this area.

4.1.3 Ruthenium Hydrogenation in General

Homogeneous ruthenium catalysts have been known and studied for almost 40 years[20] and have been shown to display higher selectivity, and wider functional group tolerance than other popular transition metals, such as rhodium. For example, ruthenium catalysts are preferred over cationic rhodium catalysts for the hydrogenation Z-α-(acylamino)acrylic acids and esters.[21] The hydrogenations of imines[22] and unfunctionalized ketones[23] have also been studied using ruthenium catalysts. In terms of selectivity, chiral ruthenium catalysts show excellent enantioselectivity, and a number of catalysts have shown chemoselectivity for carbonyl groups over olefin groups.[24]

Although hydrogen is added across an unsaturated bond in all cases of substrates, the operating hydrogenation mechanism can be very different.[25] Mechanisms involving hydrogen gas as the hydride or proton source are considered hydrogenation mechanisms; however, if the source is a protic solvent, such as 2-propanol or formic acid, the

mechanism occurs via a transfer mechanism. In order to further categorize these reactions, the species participating in the electrophilic activation of the substrate is analyzed (Figure 4.3). The inner sphere mechanism involves a metal that contains a vacant site to which the substrate binds. This mechanism can actually be less chemoselective between C=C and C=O because of the competitive binding that occurs. The outer sphere mechanism involves substrate activation by an external electrophile or a catalyst ligand; this type of mechanism was extensively studied by Noyori, and he coined the term "metal-ligand bifunctional catalysis" to describe this occurance.[26]

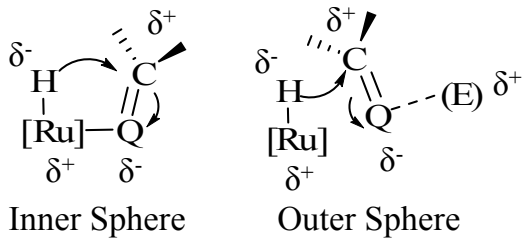


Figure 4.3. Inner Sphere and Outer Sphere Ruthenium Hydrogenation Mechanisms.[25]

4.1.4 Hydride Formation

In a hydrogenation mechanism, the metal hydride complex can be formed by a variety of routes, as shown in Figure 4.4. Coordination of H_2 to the metal, followed by heterolytic cleavage will result in the metal hydride and a protonated base (pathway i), or protonated ligand (pathway ii); the dihydride Ru(II) or Ru(IV) species resulting from oxidative addition of H_2 (pathway iii) can also be formed reversibly.

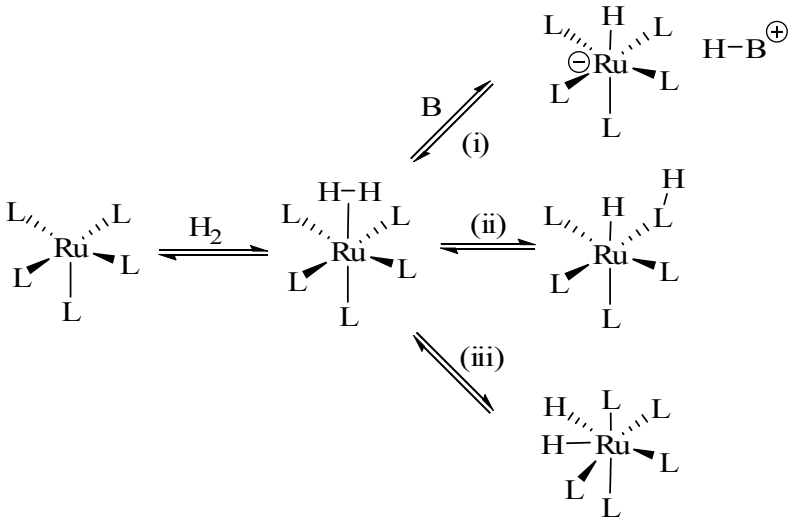


Figure 4.4. Pathways for Metal Hydride Formation.[25]

4.1.5 Chiral Ligands for Hydrogenation Reactions

Noyori first used 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (Figure 4.5) to asymmetrically hydrogenate α-(acylamino)acrylic acid using a rhodium catalyst.[27] Industrially, (S)-BINAP-Rh is used in the isomerization of diethylgeranylamine to (R)-citronellal enamine, used for the production of 1-menthol.[28] However, BINAP quickly became associated with ruthenium catalysis because of the versatile nature of ruthenium.[29-32]

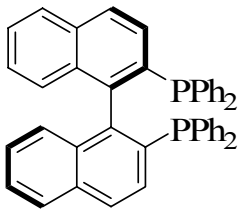


Figure 4.5. Structure of (R)-BINAP.

Analysis of BINAP's structure reveals why this is such an efficient asymmetric ligand. The atropisomeric nature of BINAP is produced by steric repulsion between the

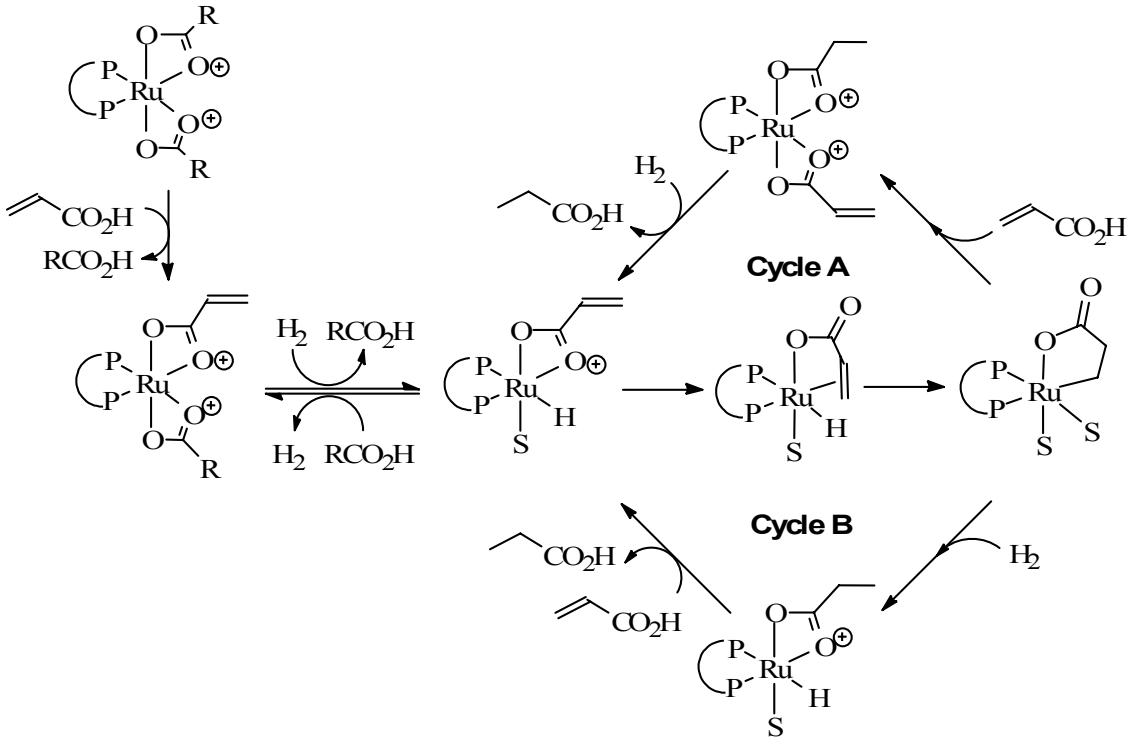
protons located at the C(10) positions, generating axial chirality. However, the BINAP backbone is still regarded as flexible because rotation of the C(1)-C(1') and C(2 or 2')-P bonds is possible. This flexibility allows for a variety of metals to be incorporated into the seven-membered chelate ring, such as rhodium, ruthenium, and iridium, without a significant increase in strain energy.[30]

Although it is the binaphthyl moiety that is chiral, this chirality is transmitted to the phosphorus-bound phenyl rings. Two phenyl rings are situated axially while the other two protrude equatorially into the metal equatorial coordination sites. This creates a great deal of steric influence for the coordinating substrate by blocking the two diagonally-related quadrant sites.[30] As a result of this steric repulsion, the diastereomeric complexes that form after substrate coordination have different energies. The more reactive diastereomeric complex, which is higher in energy, often produces the major product.[33]

4.1.6 Hydrogenation of α,β-Unsaturated Carboxylic Acids

Takaya *et al.*[31] first discovered that $Ru(OAc)_2$(BINAP) catalysts were able to hydrogenate α,β-unsaturated acids without the α-acylamino group, which was previously thought to be required based on work with rhodium. Naproxen, a non-steroidal anti-inflammatory drug, has been synthesized using this method.[34] The proposed hydrogenation mechanism for these unsaturated acids is shown below in Scheme 4.4. The two proposed methods for hydrogen incorporation are pressure-dependent, with the hydrogenation mechanism dominating at lower pressures (Cycle A), and hydrogenolysis (Cycle B) dominating at higher pressures.[35]

Takaya *et al.*[35] also showed that hydrogenation of α,β-unsaturated carboxylic acids occurred with *cis* stereochemistry. Gaseous hydrogen atoms were incorporated into the α position, and the solvent hydrogen atoms were incorporated into the β position (with an increasing incorporation of gaseous protons at higher pressures). From these results, it was concluded that the mechanism followed a monohydride Ru complex catalytic cycle, lending evidence to the mechanism depicted in Scheme 4.4. β,γ-Unsaturated carboxylic acids were shown to hydrogenate via a similar mechanism with a gaseous hydrogen atom incorporated into the γ position and a solvent hydrogen atom into the β position.[35]



Scheme 4.4. Asymmetric Hydrogenation of α,β-unsaturated Carboxylic Acids Catalyzed by [Ru(OAc)$_2${(R)-tolBINAP}].[35]

Interestingly, a literature review for the hydrogenation of α,β-unsaturated carboxylic acids seems to exclusively describe the use of $Ru(OC(O)R)_2(BINAP)$ and does not include similar hydrogenations using "$RuX_2(BINAP)$," existing in dimeric form.[36,37] For $Ru(OC(O)R)_2(BINAP)$, the facile ligand exchange between the unsaturated carboxylic acid and the carboxylate is expected to be the reason for its effectiveness.[30] Furthermore, the $Ru(OC(O)R)_2(BINAP)$ complexes would allow for more rigid and unambiguous binding of the substrate than the "$RuX_2(BINAP)$" complex. The substrate scope for hydrogenation with this dicarboxylate catalyst has been extensively studied.[30-32]

A common feature for many of the substrates studied is the inclusion of a heteroatom peripheral to the unsaturated moiety.[30] As depicted in Figure 4.6, this heteroatom coordination provides an "anchoring" site, thereby, providing more rigidity to the substrate and better selectivity. It is due to the lack of a peripheral heteroatom that causes the aforementioned catalysts to be ineffective catalysts for ketone hydrogenation. For these substrates, $RuCl_2(phosphine)_2(diamine)_2$ catalysts produce excellent enantioselectivity.[24]

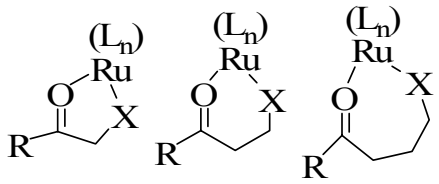
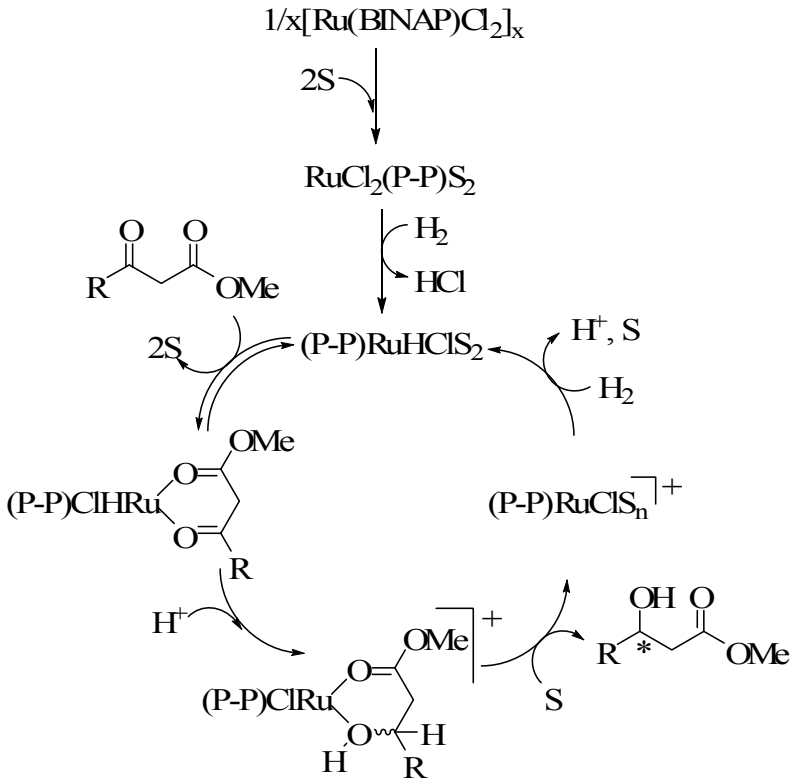


Figure 4.6. Potential Heteroatom Coordination to Metal Catalyst.

4.1.7 Hydrogenation of β-Keto Esters

Although $Ru(OAc)_2(BINAP)$ is an efficient catalyst for a number of substrates, it gives very poor results for the hydrogenation of β-keto esters unless a strong acid is present.[38] Instead, the $RuX_2(BINAP)$ (X=Cl, Br, or I) catalysts produce the desired β-hydroxy ester with up to 99 % ee, 99 % yield, and substrate/catalyst (S/C) ratio of 2000.[37] From mechanistic studies, the hydrogenation is believed to proceed through the monohydride ruthenium species (Scheme 4.5).[30] Upon hydrogen addition, loss of chloride from the precursor $[RuX_2(BINAP)]_n$ occurs, thereby forming HCl and the active



Scheme 4.5. The Mechanism of Asymmetric Hydrogenation of β-Keto Esters.[33]

catalyst. Coordination of the β-keto ester to the metal occurs, followed by hydride insertion at the electrophilic carbonyl carbon. The final β-hydroxy ester product is released upon protonation by the coordinated protic solvent; addition of dihydrogen to the metal complex completes the catalytic cycle.

4.1.8 Determination of Enantiomeric Excess

Supercritical Fluid Chromatography (SFC) is one method used for determining enantiomeric excess (ee) in this thesis. This type of chromatography uses the same technology as more standard chromatography techniques, such as Gas Chromatography (GC), and High Performance Liquid Chromatography (HPLC). The analytes have different interactions with the stationary phase of the column, resulting in different retention times. The primary difference with SFC is that supercritical fluid, usually carbon dioxide, is used as the mobile phase. The advantages of this mobile phase are two-fold: (1) shorter retention times are achieved than in liquid phase, and (ii) lower temperatures are needed than in gas phase, allowing for more thermally unstable molecules to be analyzed. However, solubility of the analyte can be problematic, so an organic modifier is often added.[39]

The use of ^{1}H NMR spectroscopy with a chiral derivatizing agent, and diastereomeric salt formation is also used for the ee determination of selected substrates. With a lanthanide chiral shift agent such as europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] ($Eu(hfc)_3$), one enantiomer interacts more strongly than the other. Ideally, this causes enough of a change in the

chemical shift that peak separation occurs, allowing the integration of the two enantiomers to be determined. An alternative method, following the same principle, is the addition of a chiral base to the acid in order to form a diastereomeric salt; again ^{1}H NMR spectroscopy can determine the ratio.

4.2 Results and Discussion

4.2.1 Asymmetric Hydrogenation of Benzoylacetic Acid

Table 4.1 outlines the solvent effect for the hydrogenation of benzoylacetic acid (**2a**) and the relative rates of hydrogenation and decarboxylation. Based on the observed reduction in the rate of decarboxylation in non-polar solvents (Section 3.2.1), it is no surprise that toluene provides the greatest selectivity for hydrogenation. EtOAc (Table 4.1, entries 3-5) and THF (entries 6-8) show low rates of hydrogenation and decarboxylation, requiring extended reaction times and/or elevated temperatures. At higher temperatures, good yields of the hydroxy acid are obtained, but not without some parallel decarboxylation to the ketone. The low decarboxylation rate of the β-keto acid is due to the solvent's Lewis basic nature, as discussed in Section 3.2.1, and the low rate of hydrogenation could be a result of the solvent's ability to coordinate to the metal. CH_2Cl_2 and MeOH show the most promising results with short reaction times and good selectivity for hydrogenation. The high selectivity for hydrogenation in MeOH (entries 11, 12) was unexpected because the decarboxylation in MeOH is rapid (Figure 3.2); the hydrogenation must therefore be even faster. In the most polar solvents MeCN (entry 14)

and DMF (entry 13), but not MeOH, decarboxylation predominates without any significant hydrogenation.

The enantioselectivity of hydrogenation also showed a large solvent dependency. Although excellent hydroxy acid yields were attained in toluene, the enantioselectivity was very low. However, the enantioselectivity is far superior in solvents that are somewhat more polar, including EtOAc, THF, CH_2Cl_2, and MeOH. Overall, in addition to shorter reaction times and good selectivity, the hydrogenation in CH_2Cl_2 (Table 4.1, entries 9, 10) and MeOH (Table 4.1, entries 11, 12) also gave high enantioselectivity. Therefore, these solvents were used for the hydrogenation of other β-keto acids (Section 4.2.3). Unfortunately, the one drawback to MeOH is the formation of the β-hydroxy methyl ester in variable yields; esterification conditions will be discussed in Section 4.2.7.

In order to determine the most effective reaction times in Table 4.1, a number of other experiments were performed (Table 4.2). These reactions show the necessity of longer reaction times for EtOAc and THF (Table 4.2, entries 1-4). For CH_2Cl_2, almost complete conversion at 70 bar H_2 is achieved after 30 h (entry 7); whereas, 72 h is required at 5 bar H_2 (entries 5, 6). In the case of MeOH, the longer reaction times used initially (entries 8, 9) were effectively reduced to ~24 h.

Table 4.1. Solvent Effect on Hydrogenation of Benzoylacetic Acid (**2a**).[a] Entries are in order of increasing solvent polarity as determined by dielectric constants.

Entry	Solvent	P_{H2} (bar)	Time (h)	**1a** (%)	**2a**[b] (%)	**3a** (%)	1-phenylethanol (%)	ee of **3a** (%R)[c]
1	PhMe	5	84	96	4	0	0	-
2	PhMe	80	60	2	0	97	1	30
3	EtOAc	5	24	28	64	18	0	98
4	EtOAc	80	72	4	37	59	0	75
5	EtOAc[d]	80	72	22	5	70	3	nd[e]
6	THF	8	24	18	82	0	0	-
7	THF	80	70	5	50	45	0	nd[e]
8	THF[d]	80	72	25	19	55	1	>99
9	CH_2Cl_2	5	72	58	8	28	6	76
10	CH_2Cl_2	80	72	4	0	93	3	99
11	MeOH	5	27	37	0	63	0	>99
12	MeOH	70	25	14	0	85	1	>99
13	DMF	80	48	87	0	13	0	nd[e]
14	MeCN	80	72	100	0	0	0	-

[a]Structures outlined in Section 4.1 (page 73). Reaction Conditions: 3 mL solvent, "$RuCl_2${(S)-BINAP}":**1a** = 1:100. [b]Including both keto and enol tautomers. [c]Determined by SFC. [d]At 40 °C. [e]nd = not determined.

Table 4.2. Determining Optimal Reaction Time.[a]

Entry	Solvent	P_{H2} (bar)	Time (h)	**1a** (%)	**2a**[b] (%)	**3a** (%)	1-phenylethanol (%)
1	EtOAc	70	24	42	51	7	0
2	THF	70	24	19	76	5	0
3	THF[c]	70	72	56	30	13	0
4	THF	70	168	31	44	25	0
5	CH_2Cl_2	5	48	59	21	17	3
6	CH_2Cl_2	5	72	72	6	19	3
7	CH_2Cl_2	70	30	54	5	40	1
8	MeOH	5	72	35	0	65	0
9	MeOH	70	48	11	0	86	3

[a]Structures outlined in Section 4.1 (page 73). Reaction Conditions: 3 mL solvent, "$RuCl_2${(S)-BINAP}":**1a** = 1:100. [b]Including both keto and enol tautomers. [c]At 40 °C.

As expected, the reaction efficiency is affected a great deal by the hydrogen pressure. EtOAc and CH_2Cl_2 have more favourable enantioselectivity at lower and

higher H_2 pressures, respectively. In MeOH, the enantioselectivity is unaffected but the selectivity for hydrogenation over decarboxylation is improved significantly by the increased H_2 pressure. As determined by Ohta,[35] this enantioselectivity difference could be caused by two competing mechanism pathways, namely the hydrogenation and hydrogenolysis pathways (Section 4.1.6).

Although decarboxylation occurs to some extent in every solvent tested, this is not expected to be a significant barrier to future applications because very little of the ketone that is re-formed by decarboxylation is hydrogenated during the process; the yield of 1-phenylethanol is ≤3 % in most cases. "$RuCl_2${(S)-BINAP}" is an inefficient hydrogenation catalyst for unfunctionalized ketones due to the lack of an "anchoring" heteroatom.[30]

4.2.2 Base Effect on Hydrogenation of Benzoylacetic Acid

The effect of base on hydrogenation is of particular importance because it would be experimentally preferable to perform the carboxylation and hydrogenation in a one-pot system without requiring isolation of the unstable β-keto acid.

Numerous studies involving the effect of base on the hydrogenation of a variety of substrates are available. Saburi *et al.*[40] determined that the hydrogenation of α-fluoro-α,β-unsaturated acids occurs with greater than 90 % ee using the Ru_2Cl_4{(S)-BINAP}$_2$(NEt_3) dimer. Similarly, Crameri *et al.*[41] established that the hydrogenation of α,β-unsaturated acids using $Ru(OAc)_2${(R)-MeOBIPHEP} in the presence of NEt_3 increased both conversion and enantioselectivity. Such base additions

presumably favour the formation of the active (hydride-containing) hydrogenation catalyst. However, the successful hydrogenation of β-keto acids (Table 4.1 and Table 4.3) in the present study in both protic and aprotic solvents demonstrates that an active catalyst is formed in our system in the absence of a base.

In fact, the addition of base is quite inadvisable. With no CO_2 present, the hydrogenation of **2a** in the presence of DBU failed, producing only the decarboxylation product. From ^1H NMR spectroscopy decarboxylation experiments, the $t_{1/2}$ of benzoylacetic acid decarboxylation in the presence of DBU and in the absence of CO_2 is determined to be less than 5 min. Therefore, base addition greatly accelerates decarboxylation and is therefore counterproductive. However, previous work by the Jessop group determined that with 20 bar CO_2, the attempted one-pot hydrogenation of the carboxylate anion using $Ru(OAc)_2$\{(R)-tolBINAP\} in MeOH gave a promising 17 % yield and 42 % ee.[42] This proves that the carboxylate anion can be hydrogenated without free acid isolation. Therefore, further research into this reaction is needed.

4.2.3 Asymmetric Hydrogenation of Other β-Keto Acids

Other β-ketocarboxylic acids were then tested under similar conditions, using CH_2Cl_2 or MeOH as the solvent (Table 4.3). For time efficiency, initial hydrogenation reactions of four different substrates were performed in parallel in one autoclave vessel. Such experiments were found to be irreproducible, probably because of inconsistent stirring, causing mass transfer problems; as such, all future experiments, including all data presented in Table 4.3, were run independently at 250 rpm.

Substituents on the 4-position of the phenyl ring should affect the electrophilicity of the β-carbon. The hydrogenation of **2b** (Table 4.3, entries 1, 2), with its electron-withdrawing chloride substituent, shows both good yields and excellent enantioselectivity in both CH_2Cl_2 and MeOH. The electron-donating methoxy group of **2c** (entries 3, 4), in contrast, decreases the carbonyl reactivity towards hydride attack, resulting in low hydrogenation yields.

Steric effects of phenyl substituents have a strong effect on the reaction performance. Although **2d** (entries 5, 6) is electronically similar to **2a**, the hydrogenation of **2d** does not proceed at all in CH_2Cl_2 and only with very poor enantioselectivity in MeOH. This result could be rationalized by steric effects offered by the *o*-Me substituent. Depending on the location of the methyl and its proximity to the metal, the methyl could provide steric repulsion via two modes: (i) methyl to ligand repulsion, increasing the reactivity of the diastereomeric metal-substrate complex, and (ii) methyl to metal repulsion, hindering metal hydride attack. The location of the *o*-Me would create four binding motifs instead of the expected two. Of these motifs, two must contain similar energies in order to synthesize an almost racemic mixture. For conclusive evidence, 3-(2',6'-dimethylphenyl)-3-oxo-propanoic acid should be tested to determine the *ortho* steric effect on the hydrogenation; if hydrogenation does not occur, this would suggest that the methyl group hinders hydride attack.

Substrate **2e** (entries 7-9), which is electronically and sterically similar to **2a**, was hydrogenated with good enantioselectivity in CH_2Cl_2. Because of its degree of aromaticity, **2e** was also hydrogenated in toluene, producing a very low yield.

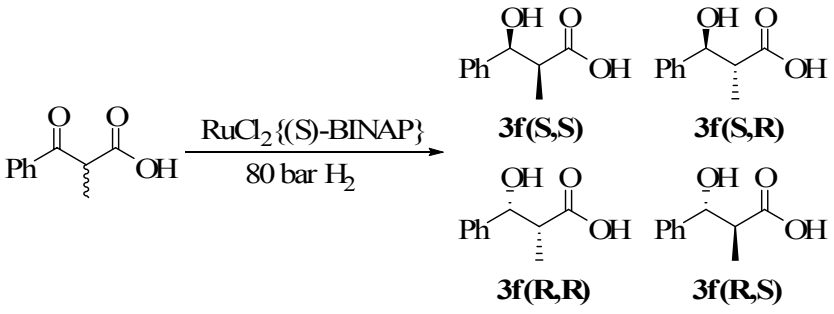
Table 4.3. Hydrogenation of Other β-Ketocarboxylic Acids.[a]

Entry	Substrate	Solvent	P_{H2} (bar)	Time (h)	Yield (%)[b]	% ee[c]
1	**2b**	MeOH	80	56	63	99
2	**2b**	CH_2Cl_2	80	70	87	94
3	**2c**	MeOH	80	68	10	nd[d]
4	**2c**	CH_2Cl_2	80	72	0	--
5	**2d**	MeOH	80	68	82	6
6	**2d**	CH_2Cl_2	70	54	0	--
7	**2e**	MeOH	80	56	55	48
8	**2e**	CH_2Cl_2	80	63	57	96
9	**2e**	PhMe	80	46	7	nd[d]
10	**2f**	EtOAc	70	72	0	--
11	**2f**	EtOAc	5	72	0	--
12	**2f**	MeOH	80	73	91[e]	--[g]
13	**2f**	CH_2Cl_2	80	68	20[e]	--[g]
14	**2g**	MeOH	80	72	75	97
15	**2g**	CH_2Cl_2	80	74	4	nd[d]
16	**2h**	EtOAc	5	72	84[f]	nd[d]
17	**2h**	MeOH	80	28	77[ef]	97[h]
18	**2h**	CH_2Cl_2	80	28	73[ef]	91[h]
19	**5/6**	MeOH	80	88	27	--[i]
20	**5/6**	MeOH	80	50	2	--[i]
21	**5/6**	CH_2Cl_2	80	88	0	--
22	2-oxocyclohexanoic acid	MeOH	80	92	87	--[j]
23	2-oxocyclohexanoic acid	CH_2Cl_2	80	92	65	--[j]

[a]Structures outlined in Section 4.1 (page 73). Reaction Conditions: "$RuCl_2${(S)-BINAP}":**2** = 1:100 in 4 mL solvent. [b]^{1}H NMR yield. [c]Determined by SFC. [d]nd = not determined. [e]"$RuCl_2${(S)-BINAP}":**2** = 2:100 in 8 mL solvent. [f]Calculated using 2-propanol as internal standard. [g]See Scheme 4.6. [h]Benzyl ester derivative. [i]See Scheme 4.8. [j]See Scheme 4.7.

Hydrogenation of substrate **2f** (entries 10-13) is slow in CH_2Cl_2, but proceeds in good yield in MeOH. This difference in reactivity may be caused by steric problems. The steric bulk of the extra methyl group is unlikely to be so large as to prevent binding of the acid to the Ru(II) centre; tiglic acid, $CH_3CH{=}C(CH_3)CO_2H$, is hydrogenated readily by Ru(II) BINAP catalysts.[43]

The diastereomeric ratio for **3f** was determined by ^{1}H NMR spectroscopy, but establishing the enantiomeric excess proved to be more difficult (Scheme 4.6). Enantiomer peak separation of **3f** by SFC was not possible, so three alternative methods for determining the ee were tried. First, the benzyl ester was synthesized using benzyl bromide in DMF and basic conditions, but the SFC chromatograph of the benzyl esters was complicated by extra UV-active species, and the reaction scale was too small for flash chromatography. Second, the synthesis of the methyl ester was synthesized using iodomethane, but separation on the SFC was still unattainable. Lastly, the ee for the major diastereomers of the **3f** methyl ester was successfully determined by ^{1}H NMR spectroscopy using 0.1 equivalent of $Eu(hfc)_3$ as a chiral shift reagent; the α-CH_3 peak of the major diastereomer showed the best separation under these conditions. The ee for the minor diastereomers was determined using only 0.007 eq of $Eu(hfc)_3$; in this case, the β-CH displayed the best separation.



	Yield (%)	dr (anti : syn)	ee (syn)	ee (anti)
MeOH	91	1 : 6.6	10	nd
CH_2Cl_2	20	1 : 5.7	74	~50

Scheme 4.6. Hydrogenation of 2-Methyl-3-Oxo-3-Phenylpropanoic Acid.

The observed enantioselectivity for **3f** offers additional information about the hydrogenation mechanism. Because of keto/enol tautomerization, the hydrogenation could be occurring via either dynamic kinetic resolution or standard kinetic resolution. By definition for dynamic kinetic resolution, the rate of tautomerization must be higher than the rate of hydrogenation; however, it was shown in Chapter 3 that tautomerization was slow in MeOH-d_4 for **2f** (producing 50 % deuteration within 780 min). Therefore, due to the comparable rates of hydrogenation and tautomerization, hydrogenation is more likely occurring by kinetic resolution.

MeOH is an effective solvent for hydrogenation of **2f**, as evidenced by the 91 % yield of β-hydroxy acid; however, the enantioselectivity of hydrogenation was low. Because the reaction was run to completion, the less reactive enantiomer is also hydrogenated, lowering the ee. Any future experiments should, therefore, be stopped at ≤50 % conversion. In the case of CH_2Cl_2, the rate of hydrogenation decreases with the inclusion of the α methyl. In theory, the more reactive enantiomer hydrogenates and the less reactive enantiomer has more time to decarboxylate, accounting for the higher enantioselectivity.

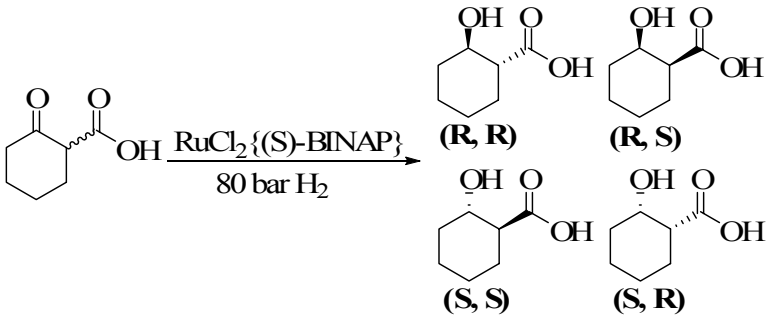
Although the hydrogenation of **2h** (Table 4.3, entries 16-18) shows good conversion and high enantioselectivity, the isolation and ee determination of the β-hydroxy acid proved to be very difficult. The decarboxylation product, acetone, is removed during workup, so an internal standard is needed for the ^{1}H NMR spectrum. Because this substrate lacks a chromophore, ee determination via SFC using a UV detector is not possible. On a commercial racemic sample, ee determination by ^{1}H NMR

spectroscopy using (+)-α-methylbenzylamine[44] in an acid:amine ratio of 1:0.4 was successful; advantageously with this method, **3h** would not need purification. However, attempts using the crude hydrogenation mixture did not produce the necessary peak splitting. Both ^{13}C NMR spectroscopy with diastereomeric salt formation, and chiral GC were also attempted and were ineffective in determining the ee.

The hydrogenation was then scaled up in size and the catalyst loading was increased. The benzyl ester was successfully synthesized, and with a chromophore present, enantiomer peak separation by SFC proved possible. However, the peak assigned to one of the enantiomers overlaps with benzyl alcohol, which is produced from hydrolysis of excess benzyl bromide. A Biotage Horison High Performance Flash Chromatography (HPFC) system (5:1 hexane:EtOAc) was used to provide the purified benzyl β-hydroxy ester, and SFC was then used to determine the ee. Note that the yield of **3h** was lower for the larger-scale hydrogenation in MeOH because of excessive formation of the methyl ester.

The hydrogenation of 2-oxocyclohexanoic acid (Table 4.3, entries 22, 23) proceeds in good yields for both CH_2Cl_2 and MeOH; however, the diastereoselectivity changes depending on the solvent choice (Scheme 4.7). It may be surprising that the diastereoselectivity for 2-oxocyclohexanoic acid is *anti* and for **2f** is *syn*. However, this same diastereoselective trend is observed for the hydrogenation of β-keto esters; methyl 2-oxocyclopentanecarboxylate ester was hydrogenated with 99:1 (anti:syn) selectivity, and methyl 2-acetamido-3-oxobutanoate was hydrogenated with 99:1 (syn:anti) selectivity.[32] In MeOH, 4 % formation of 1,1-dimethoxy cyclohexane as a byproduct was

detected in the ^{1}H NMR spectrum, resulting from decarboxylation and subsequent nucleophilic attack of methanol on cyclohexanone. No methyl ester formation was observed.

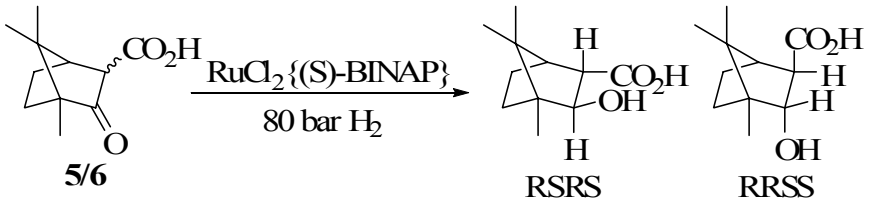


		dr		
	Yield (%)	anti		syn
MeOH	87	4.2	:	1
CH_2Cl_2	65	0.68	:	1

Scheme 4.7. Hydrogenation of 2-Oxocyclohexanoic Acid.

The attempted hydrogenation of a mixture of **5** and **6** (Table 4.3, entries 19-21) in CH_2Cl_2 failed, with no decarboxylation or hydrogenation observed after 88 h (Scheme 4.8). Interestingly, only the *trans* diastereomers are produced upon hydrogenation in MeOH, lending evidence to solvent dependent hydrogenation mechanisms. Unfortunately, rapid tautomerization makes it difficult to discern which isomer is reacting. The 7:3 ratio between **5** and **6** was maintained even after partial hydrogenation of the sample. If the assumption is made that the epimerization between **5** and **6** is slow relative to hydrogenation and that the RSRS product is derived from **5**, then 27 % overall conversion should have consumed half of the amount of **6** originally present. That the 7:3 ratio was preserved suggests that epimerization is rapid enough in this case to keep the **5**:**6** ratio in equilibrium. Furthermore, the significant difference between the observed

rate of hydrogenation, 88 h for 27 % yield, and the high rate of epimerization in MeOH-d_4 (shown by the rapid deuteration, 20 min for full deuteration) suggests that hydrogenation occurs by dynamic kinetic resolution.



	Yield (%)	RSRS : RRSS
MeOH	27	0.72 : 1
CH_2Cl_2	0	-

Scheme 4.8. Hydrogenation of Camphoric Acid.

4.2.4 Synthesis of 2,2-$^2H_2$-Benzoylacetic Acid

The synthesis of 2,2-$^2H_2$-benzoylacetic acid was of interest for elucidating the hydrogenation mechanism. Because of the acidic α-proton and prevalent tautomerization of benzoylacetic acid, the first attempted synthesis of 2,2-$^2H_2$-benzoylacetic acid involved deuterium exchange of benzoylacetic acid with MeOH-d_4. Unfortunately, decarboxylation proved to be problematic in this solvent, so product isolation was impossible. Self-catalyzed methyl ester formation was not observed during the reaction.

A synthesis involving the deuteration and subsequent hydrolysis of the ethyl ester derivative was attempted. Ethyl 2,2-$^2H_2$-benzoylacetate was obtained with 5 % protonation by using NEt_3 in MeOH-d_4. Subsequent hydrolysis of the ester produced the corresponding 2,2-$^2H_2$-benzoylacetic acid with 66 % protonation at the α-location.

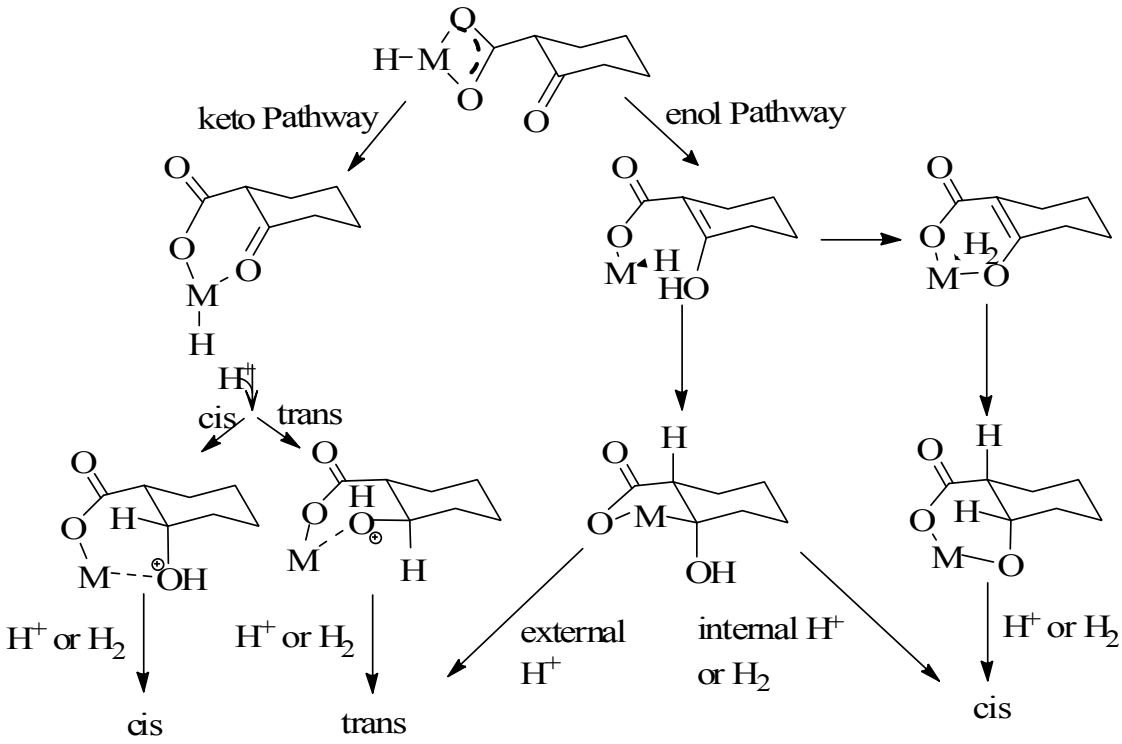
Another attempt to synthesize 2,2-$^{2}H_2$-benzoylacetic acid involved the carboxylation of 2,2,2-$^{2}H_3$-acetophenone, which was obtained with 4 % protonation by using NaOH in MeOH-d_4. Using the standard DBU/CO_2 carboxylation conditions (using D_2O and DCl), 2,2-$^{2}H_2$-benzoylacetic acid was synthesized in 28 % yield with 27 % protonation. This degree of protonation was higher than desired for the purpose of investigating the hydrogenation mechanism but future hydrogenation reactions were still attempted (Section 4.2.5).

4.2.5 Mechanism of Hydrogenation

Scheme 4.9 shows several possible hydrogenation pathways for the production of *cis* and *trans* diastereomers, based on the following findings from previous studies: (i) binding of the carboxylate moiety to the Ru(II) catalyst is possible and favoured,[30,35] and (ii) the hydrogenation of β-keto esters[24] and α,β-unsaturated acids[45] proceeds through a monohydride ruthenium mechanism. As speculated by Halpern *et al.*[45] for α,β-unsaturated acids, coordination occurs first by the carboxylate functional group. Next, either keto and/or enol hydrogenation can occur. Coordination to the metal could dramatically change the keto/enol ratio of the bound substrate relative to that of the free compound.

In the keto hydrogenation mechanism, bidentate binding by the carboxylate and keto groups requires that the carboxylate moiety be located in an equatorial position of the 2-oxocyclohexanoic acid; if located axially, metal coordination would create a very strained non-chair conformation. Such bulky groups are normally found equatorially due

to the decreased repulsion with axial protons.[46] Protonation of the carbonyl oxygen would produce a more electrophilic carbonyl carbon and a favourable geometry for hydride attack.[33] Depending on the location of the metal-bound hydride, attack from the bottom or top of the carbonyl can result in either *trans* or *cis* geometry, respectively. Because of reduced steric repulsion and the formation of a favourable chair intermediate, the *trans* product would be favoured.



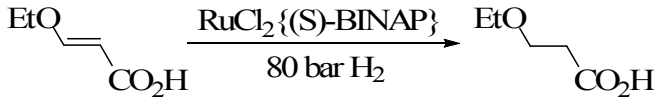
Scheme 4.9. Possible Hydrogenation Pathways.

For the enol pathway, both axial and equatorial carboxylate coordination geometries allow for olefin insertion, producing a five-membered metallocycle ring. For simplicity, only axial hydride attack is shown in Scheme 4.9, while equatorial attack is possible as well. In either case, metal coordination occurs with *cis* configuration to the

hydride. The hydroxy carbon can then be protonated by either a metal-bound proton source (MeOH or metal-bound H_2, for example), giving retention of stereochemistry and therefore the *cis* product, or an external source, giving inversion at the hydroxy carbon and the trans product.

To determine whether the hydrogenation of the enol tautomer is a viable mechanism for this reaction, the hydrogenation of an enol ether was studied. The hydrogenation of *trans*-3-ethoxypropionic acid (Scheme 4.10) proceeded to completion in MeOH but failed entirely in CH_2Cl_2. This demonstrates that at least in MeOH, this catalyst is quite capable of the hydrogenation of an α,β-unsaturated carboxylic acid that has similar electronic properties to the enol tautomer. This was surprising because in the literature, only studies of the hydrogenation of α,β-unsaturated carboxylic acids with $Ru(OC(O)R)_2$(BINAP) have been reported, not with the dichloride.[30] However, the failure of the hydrogenation in CH_2Cl_2 suggests that either a) the hydrogenation of the enol form is not the operative pathway in CH_2Cl_2, or b) the enol hydroxy proton is necessary for the enol mechanism in CH_2Cl_2.

Lastly, to determine whether the hydrogenation of a β-ketocarboxylic acid is possible without access to an enol form, the hydrogenation of **2g**, which can not form an



7 **8**

Scheme 4.10. Hydrogenation of *trans*-3-Ethoxypropionic Acid.

enol, was performed. In CH_2Cl_2, conversion was 11 %, producing 4 % β-hydroxy acid **3g** and 7 % ketone. In MeOH, conversion was 100 %, producing 75 % β-hydroxy acid with 97 % ee, along with 20 % ketone, 4 % methyl ester of **3g**, and 1 % alcohol. This conclusively demonstrates that, in both solvents, hydrogenation of the keto acid is quite possible; enolization is not a prerequisite for hydrogenation. However, the keto pathway might not be the dominant mechanism for other substrates.

To determine whether the enol mechanism predominates for substrates capable of an enol tautomer, the hydrogenation of 2,2-$^2H_2$-benzoylacetic acid was attempted but was inconclusive due to the 27 % protonation already present. As an alternative, the hydrogenation using D_2 gas was attempted. Such a hydrogenation of benzoylacetic acid in CD_2Cl_2 was inconclusive due to extensive deuterium incorporation into **2a**. However, the hydrogenation of **2f** using D_2 in CD_2Cl_2 was expected to be more informative for two reasons. Firstly, **2f** contains a low enol concentration, so incorporation due to deuterium exchange and tautomerization should be minimal; furthermore, during the aforementioned decarboxylation experiments, deuterium exchange was not observed in CD_2Cl_2. Secondly, the enol form does not contain an α-proton; therefore, assuming no deuterium exchange between the acid substrate and CD_2Cl_2, any observed deuterium incorporation into this position should be a result of hydrogenation of the enol double bond. The potential complicating factors, such as kinetic isotope effect, and Ru-catalyzed isotope exchange between deuterium gas and enol hydroxy, should be recognized. Using 10 bar D_2 gas and CD_2Cl_2 for hydrogenation, ^1H NMR spectroscopy showed that both α and β positions were deuterated, containing only 4 % protonation in

the β and 10 % in the α position. The observed *cis*:*trans* diastereomeric ratio was 1:0.33. This strongly supports the hydrogenation of the enol tautomer as the dominant mechanism. For the hydrogenation of α,β-unsaturated acids, gaseous molecules are incorporated into the α location and solvent protons are incorporated into the β location.[35] To determine the deuteration source, hydrogenation of **2f** in CH_2Cl_2 using 10 bar D_2 was attempted. By ^1H NMR spectroscopy, 47 % deuteration occurred in the α location and 96 % in the β location, in disagreement with literature. However, the unreacted original β-ketocarboxylic acid was 92 % deuterated in the α position. The deuterium source for incorporation was *in situ* deuterons produced by the heterolytic cleavage of D_2 gas by Ru(II). Therefore, no conclusions regarding the hydrogenated species can be drawn from these experiments.

4.2.6 Potential Hydrogenation of Solid-State Substrates

During these experiments, it was noticed that the substrate did not fully dissolve in certain solvents before hydrogenation commenced. This raised questions regarding the *in situ* substrate concentration and the substrate solid-state tautomeric form. The substrate concentrations used in these hydrogenation reactions is ~0.07 M, which is comparable to the 0.08 M solutions used for decarboxylation. Although the decarboxylation rate was found to be first-order, this concentration was selected for hydrogenation to ensure good substrate solubility. To this end, it is known that the solubility of **2a** is low in toluene; however, other solubility situations were observed. In some cases, **2b** did not always efficiently dissolve in CH_2Cl_2 and MeOH. Waiting

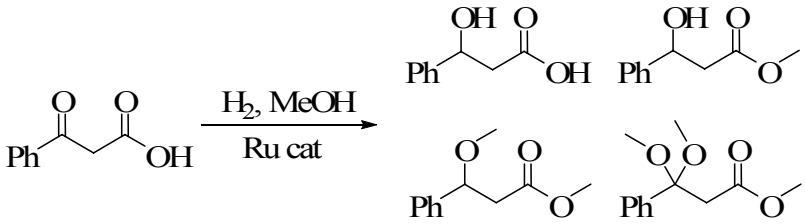
additional time before H_2 addition may ensure full dissolution, similar to the trend observed in the MeOH decarboxylation experiments. In other cases, the substrate was immediately soluble in the presence of $RuCl_2${*rac*-BINAP} but not "$RuCl_2${(S)-BINAP}".

In regards to the solid-state tautomeric form, β-keto acids have been found to exist in the enol tautomer.[47] Therefore, with solid present, hydrogenation can occur via the dissolved substrate or the solid state. To test this, the hydrogenation in CH_2Cl_2 was performed on a saturated solution of **2b**; excess solid was removed by filtration. Hydrogenation after 68 h still occurred with 96 % yield of the hydroxy acid, producing comparable results to the 87 % obtained with undissolved substrate present. For a decisive conclusion, the hydrogenation of the solid state substrate was also attempted under neat conditions. However, only decarboxylation was observed during this experiment. This proves that solvent molecules are involved in the hydrogenation mechanism in some manner, either in the formation of the active catalyst or in the protonation of the β-hydroxy acid.

4.2.7 Methyl Ester Production during Hydrogenation in MeOH

Because the hydrogenation is performed under acidic conditions with MeOH as the solvent, methyl ester production is not surprising. In addition to the ester, the self-catalyzed formation of the ketal and hemiacetal is also possible under these conditions (Scheme 4.11). No ketal or hemiacetal formation is observed by 2D NMR, but the methyl ester is formed in varying yields, depending on the reaction time and H_2

pressure used (Table 4.4). Methyl ester production is also increased as the substrate concentration and catalyst loading is increased.



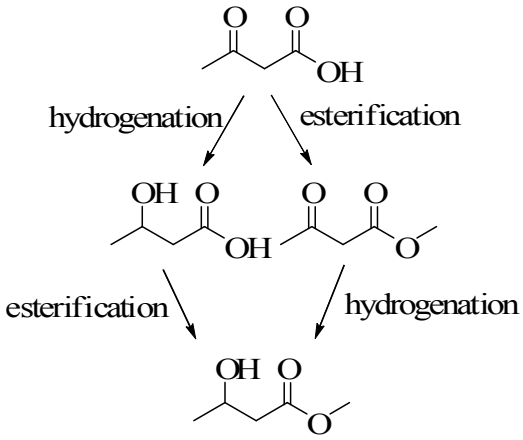
Scheme 4.11. Possible Products from a Hydrogenation Reaction in Methanol.

Table 4.4. Methyl Ester Formation of **2a**.

Pressure (bar)	Time (h)	-CO_2Me Yield[b] (%)
5	27	17
5	72	83
70	25	30
70	48	66

[a]Reaction Conditions: "$RuCl_2${(S)-BINAP}":**2a** = 1:100 in 4 mL solvent at room temperature. [b]NMR yield.

For future applications, the formation of side products causes undesirable additional steps and waste; therefore, in order to minimize the formation of the methyl ester, the operating conditions and the actively esterified species must be determined. Because the hydrogenation of β-keto esters is well known to be catalyzed by "$RuCl_2$(BINAP)",[37] esterification could be occurring either before or after hydrogenation (Scheme 4.12).



Scheme 4.12. Potential Pathways for Methyl Ester Formation.

To ascertain this information, the esterification of 3-oxobutanoic acid and 3-hydroxybutanoic acid was attempted in the absence of catalyst by stirring in MeOH. After 22 h, no esterification was observed in either case. This means that the precatalyst, active catalyst, or oxidized catalyst is required for the esterification to occur, probably as a Lewis acid catalyst. To eliminate the precatalyst as the required species, "hydrogenation" reactions were performed using 80 bar nitrogen instead of hydrogen. No esterification was observed after 52 h with higher catalyst loading or higher substrate concentration. Interestingly, the ketal product from the ketone was observed in both experiments with 11 % and 17 % yields, respectively. Therefore, it can be concluded that from these experiments, the precatalyst is not involved in esterification.

For the hydrogenation of **2f**, the diastereomeric ratios observed by ^{1}H NMR spectroscopy for the β-hydroxy acid and β-hydroxy ester are different. This finding means (i) that esterification occurs first, and the acid and ester are in competition for

hydrogenation, or (ii) the resulting β-hydroxy acid diastereomers have different rates of esterification, thereby, producing the different ratios.

4.3 Conclusions and Future Work

4.3.1 Conclusions

To begin with, the asymmetric hydrogenation of numerous β-ketocarboxylic acids has been shown to be successful with excellent ee's. CH_2Cl_2 and MeOH were selected as the best solvent choices due to short reaction times, good selectivity for hydrogenation, and high enantioselectivity. An electronic effect was observed by investigating the hydrogenation of aryl-substituted benzoylacetic acids. This can be related to the electrophilicity of the carbonyl carbon. By increasing the steric bulk at the α location with methyl groups, a significant decrease in reactivity is observed in CH_2Cl_2.

Hydrogenation is expected to be preceded by binding of the substrate as a carboxylate, in analogy to the known mechanisms of hydrogenation of α,β-unsaturated carboxylic acids. However, the hydrogen transfer may take place while the substrate is in the form of a ketocarboxylate or an enolcarboxylate tautomer. Evidence suggests that both the enol and keto pathways are possible in MeOH; however, the fact that an enol ether substrate could not be hydrogenated in CH_2Cl_2 suggests (but does not prove) that the enol pathway does not operate in CH_2Cl_2. Unfortunately, the attempted deuterium labelling experiments for **2a** and **2f** did not provide any conclusive answers due to heterolytic cleavage of D_2 by Ru(II).

Hydrogenation of a variety of β-keto acids, including alkyl, aryl, cyclic, and bicyclic, demonstrates a broad reaction scope. This reaction system is industrially advantageous due to the limited number of reactants required, their low-cost, and the ability to recycle unused ketone.

4.3.2 Future Work

Expansion of the substrate scope to improve application viability should be top priority. To be truly applicable and viable, the conditions required for a one-pot hydrocarboxylation synthesis also need to be determined.

Primarily for academic interest, the actively hydrogenated species could be determined. By knowing this information, informed decisions regarding the types of potential substrates can be made.

The enantioselectivity for the hydrogenation of **2f** in MeOH with ≤50 % conversion should be determined. Observation of a high ee would lend evidence for a kinetic resolution. This experiment would also provide information about the rate of hydrogenation, which is of interest in order to rule out dynamic kinetic resolution as a possibility. Also, the rate of tautomerization, as measured by deuterium incorporation, can be determined in CD_2Cl_2 by adding a small amount of MeOH-d_4. If incorporation is rapid, hydrogenation in CH_2Cl_2 may be expected to occur by dynamic kinetic resolution.

The ee of the methyl ester formed during the hydrogenation of **3f** in MeOH should be determined. If the acid and ester have the same values, it is strong evidence that hydrogenation may occur before the esterification. On the other hand, no additional

information would be derived if the values are different. For **2f**, simply running the ^{1}H NMR spectrum with 0.1 eq Eu(hfc)$_3$ should provide this answer.

4.4 Experimental

See Section 2.4 for a description of general experimental materials, equipment and techniques, and spectroscopy and chromatography. Any changes or additions to those procedures are described herein.

4.4.1 Materials

Diethyl ether, toluene, hexane and THF were dried by passage through activated alumina using a Solvent Purification System. Before bringing them into the glovebox, all solvents were degassed using three freeze-pump-thaw cycles.

Anhydrous DMF (Aldrich), "RuCl$_2${(S)-BINAP}" (Strem), *rac*-BINAP (Strem), (S)-BINAP (Strem), Eu(hfc)$_3$ (Aldrich), (+)-alpha-methylbenzylamine (Aldrich), benzyl bromide (Aldrich), iodomethane (Aldrich), deuterium chloride (35 wt% solution in D_2O, 99 % atom D) (Aldrich), and H_2 (Ultra High Purity 5.0 from Praxair) were used as received.

For chromatography purposes, both enantiomers of 3-hydroxy-3-phenylpropionic acid (Lancaster), both diastereomers of 2-hydroxycyclohexanoic acid (Aldrich), and *rac*-3-hydroxybutanoic acid (Aldrich) were purchased.

4.4.2 Spectroscopy and Chromatography

For purification of selected compounds, a Biotage Horizon™ High Performance Flash Chromatography was used with a FLASH 12+M™ column. Enantiomeric excess values were obtained using a supercritical fluid chromatograph with an Agilent 1100 Series UV-Vis broad spectrum analysis detector, an injection volume of 10 μL, a temperature of 40 °C, a CO_2 pressure of 100 bar, and either a CHIRALPAK® AD-H column with solvent flow of 4 mL/min and 5 % MeOH modifier, or a CHIRALPAK® OJ-H with solvent flow of 3 mL/min and 3 % MeOH modifier.

GC chromatographs were also obtained on the GC 17A Shimadzu containing a Varian CP-CHIRASIL DEX CB 0.25 mm x 0.l25 um x 25 m column.

4.4.3 General Considerations for the Hydrogenation of β-Keto Acids

A 31 mL steel vessel, vials, and syringes were dried in an oven at 130 °C overnight. In a N_2-filled glovebox, the catalyst, β-ketoacid substrate, stir bar, and 4 mL of solvent were added to a 4 dram vial and placed in the vessel. The vessel was then sealed, removed from the glove box, flushed with H_2 gas three times to remove any air, pressurized to the desired H_2 pressure, and stirred magnetically at 250 rpm for the desired reaction time. The vessel was then vented slowly and opened. The solvent was removed from the product mixture under vacuum. The ^{1}H NMR spectrum of the crude mixture was obtained to determine the extent of conversion. Unless otherwise stated, the product mixture was mixed with toluene and passed through a short Celite 545 column. The

β-hydroxy acid product, which was retained at the top of the column, was then washed through with diethyl ether. The organic solvent was removed by rotary evaporation.

4.4.4 3-Hydroxy-3-phenylpropanoic acid (3a)

The CHIRALPAK® AD-H column with solvent flow of 4 mL/min and 5 % MeOH modifier was used to determine the ee. The ^{1}H and ^{13}C spectra are comparable to those reported in the literature for this compound in $CDCl_3$.[48]

^{1}H NMR ($(CD_3)_2CO$): δ 7.42 (d, $^{3}J_{HH}$ = 7.6 Hz, 2H, 2′-C*H*), 7.33 (t, $^{3}J_{HH}$ = 7.6 Hz, 2H, 3′-C*H*), 7.25 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, 4′-C*H*), 5.13 (t, $^{3}J_{HH}$ = 6.4 Hz, 1H, C*H*), 2.67 (d, $^{3}J_{HH}$ = 6.0 Hz, 2H, CH_2); $^{13}C\{^{1}H\}$ NMR ($(CD_3)_2CO$): δ 172.8 (*C*O_2H), 145.5 (1′-C), 129.0 (3′-C), 128.0 (4′-C), 126.7 (2′-C), 70.9 (*C*H), 44.7 (*C*H_2).

4.4.5 3-Hydroxy-3-(4′-chlorophenyl)propanoic acid (3b)

The CHIRALPAK® AD-H column with solvent flow of 4 mL/min and 5 % MeOH modifier was used to determine the ee. The ^{1}H and ^{13}C spectra are comparable to those reported in the literature for this compound in $CDCl_3$.[49]

^{1}H NMR ($(CD_3)_2CO$): δ 7.46 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H, 2′-C*H*), 7.36 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H, 3′-C*H*), 5.14 (t, $^{3}J_{HH}$ = 6.4 Hz, 1H, C*H*), 2.68 (d, $^{3}J_{HH}$ = 6.8 Hz, 2H, CH_2); $^{13}C\{^{1}H\}$ NMR ($(CD_3)_2CO$): δ 176.7 (CO_2H), 143.5 (1′-C), 132.2 (4′-C), 129.1 (3′-C), 128.5 (2′-C), 69.5 (*C*H), 44.5 (*C*H_2).

4.4.6 3-Hydroxy-3-(4′-methoxyphenyl)propanoic acid (3c)

The CHIRALPAK® AD-H column with solvent flow of 4 mL/min and 5 % MeOH modifier was used to determine the ee. The ^{1}H NMR spectrum matches that reported in the literature.[50] The ^{13}C NMR spectrum was not obtained because of the low yield.

^{1}H NMR ($CDCl_3$): δ 7.30 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H, 2′-C*H*), 6.87 (d, $^{3}J_{HH}$ = 9.0 Hz, 2H, 3′-C*H*), 5.09 (s, 1H, C*H*), 3.78 (s, 3H, CH_3), 2.67 (m, 2H, CH_2).

4.4.7 3-Hydroxy-3-(2′-methylphenyl)propanoic acid (3d)

The CHIRALPAK® AD-H column with solvent flow of 4 mL/min and 5 % MeOH modifier was used to determine the ee.

^{1}H NMR ($CDCl_3$): δ 7.50 (d, $^{3}J_{HH}$ = 6.9 Hz, 1H, 6′-C*H*), 7.1-7.3 (m, 3H, aryl C*H*), 5.35 (dd, $^{3}J_{HH}$ = 2.5 Hz, 7.0 Hz, 1H, C*H*), 2.71 (m, 2H, CH_2), 2.32 (s, 3H, CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 177.2 (*C*O_2H), 140.1 (1′-*C*), 134.4 (2′-*C*), 130.6 (3′-*C*), 127.9 (5′-*C*), 126.5 (4′-*C*), 125.2 (6′-*C*), 66.9 (*C*H), 41.9 (*C*H_2), 19.0 (*C*H_3).

HR-MS, observed: *m/e* 180.0787 (M^+). Calculated for $C_{10}H_{12}O_3$: *m/e* 180.0786 (M^+).

EI-MS, observed: *m/e* 162.1 (M^+-H_2O), 121.1 (M^+-CH_2CO_2H), 117.1 (M^+-H_2O-CO_2H), 93.1 (M^+-CH_2CO_2H-CO), 91.0 (M^+-H_2O-CO_2H-$(CH)_2$), 77.0 (M^+-CH_2CO_2H-CO-CH_3).

4.4.8 3-Hydroxy-3-(2′-naphthyl)propanoic acid (3e)

The crude reaction mixture was mixed with CH_2Cl_2 and passed through a short Celite 545 column. The β-hydroxy acid product, which was retained at the top of the

column, was then washed through with acetone. The CHIRALPAK® AD-H column with solvent flow of 4 mL/min and 5 % MeOH modifier was used to determine the ee. The ^{1}H and ^{13}C spectra are comparable to those reported in the literature for this compound in $CDCl_3$.[51]

^{1}H NMR ($(CD_3)_2CO$): δ 7.8-8.0 (m, aryl 4H), 7.59 (dd, $^{3}J_{HH}$ = 1.5, 8.4 Hz, 1H, aryl H), 7.4-7.5 (m, 2H, aryl H), 5.31 (t, $^{3}J_{HH}$ = 6.4 Hz, 1H, C*H*), 2.79 (d, $^{3}J_{HH}$ = 7.2 Hz, CH_2); $^{13}C\{^{1}H\}$ NMR ($(CD_3)_2CO$): δ 172.8 (*C*O_2H), 143.0 (2′-*C*), 125.2-134.3 (9 aryl C), 71.1 (*C*H), 44.6 (*C*H_2).

4.4.9 3-Hydroxy-2-methyl-3-phenylpropanoic acid (3f)

For purification, $KHCO_3$ was added, and EtOAc was used to extract unreacted ketone and any methyl ester. The aqueous layer was acidified to pH 1 using 1 M HCl, and the product was extracted into EtOAc. Removal of the solvent provided the purified product. The ^{1}H NMR and ^{13}C NMR spectra match those reported in the literature.[52]

syn-product: ^{1}H NMR ($(CD_3)_2CO$): δ 7.40 (d, $^{3}J_{HH}$ = 7.6 Hz, 2H, 2′-C*H*), 7.32 (t, $^{3}J_{HH}$ = 7.2 Hz, 2H, 3′-C*H*), 7.23 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, 4′-C*H*), 5.04 (d, $^{3}J_{HH}$ = 5.6 Hz, 1H, 3-C*H*), 2.72 (m, 1H, 2-C*H*), 1.08 (d, $^{3}J_{HH}$ = 7.2 Hz, 3H, CH_3); $^{13}C\{^{1}H\}$ NMR ($(CD_3)_2CO$): δ 176.4 (*C*O_2H), 144.4 (1′-C), 123.8 (aryl C), 127.9 (aryl C), 127.1 (aryl C), 74.5 (3-*C*H), 47.7 (2-*C*H), 11.7 (*C*H_3).

anti-product: ^{1}H NMR ($(CD_3)_2CO$): δ 7.40 (d, $^{3}J_{HH}$ = 7.6 Hz, 2H, 2′-C*H*), 7.32 (t, $^{3}J_{HH}$ = 7.2 Hz, 2H, 3′-C*H*), 7.23 (t, $^{3}J_{HH}$ = 7.2 Hz, 1H, 4′-C*H*), 4.72 (d, $^{3}J_{HH}$ = 8.8 Hz, 1H, 3-C*H*), 2.67 (m, 1H, 2-C*H*), 0.86 (d, $^{3}J_{HH}$ = 6.8 Hz, 3H, CH_3); $^{13}C\{^{1}H\}$ NMR

($(CD_3)_2CO$): δ 176.9 (*C*O_2H), 143.9 (1′-C), 129.0 (aryl C), 128.4 (aryl C), 127.8 (aryl C), 76.7 (3-*C*H), 48.2 (2-*C*H), 14.4 (*C*H_3).

4.4.10 Enantiomeric Excess Determination of 3f

The benzyl ester of **3f** was synthesized using benzylbromide, following the procedure by Wang *et al*.[17] The ^{1}H NMR spectrum of the ester matches that reported in the literature.

The methyl ester of **3f** was synthesized using iodomethane, following the procedure by Wang *et al*.[17] The ^{1}H NMR spectrum of the ester matches that reported in the literature.[53]

Me ester syn-product: ^{1}H NMR ($(CD_3)_2CO$): δ 7.24-7.34 (m, 5H, aryl H), 5.10 (d, $^3J_{HH}$ = 3.9 Hz, 1H, 3-C*H*), 3.67 (s, 3H, OC*H*$_3$), 2.80 (m, 1H, 2-C*H*), 1.13 (d, $^3J_{HH}$ = 7.2 Hz, 3H, C*H*$_3$).

Me ester anti-product: ^{1}H NMR ($(CD_3)_2CO$): δ 7.24-7.34 (m, 5H, aryl H), 4.75 (d, $^3J_{HH}$ = 7.0 Hz, 1H, 3-C*H*), 3.73 (s, 3H, OC*H*$_3$), 2.80 (m, 1H, 2-C*H*), 1.01 (d, $^3J_{HH}$ = 7.2 Hz, 3H, C*H*$_3$).

By adding 0.007 equivalents of europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] to the methyl ester of **3f** and acquiring the ^{1}H NMR spectrum, splitting of the β-CH peak was observed. The ee was determined from the integration ratio of these peaks.

By adding 0.1 equivalents of europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] to the methyl ester of **3f** and acquiring the ^{1}H NMR spectrum, splitting of the α-methyl peak was observed. The ee was determined from the integration ratio of these peaks.

4.4.11 3-Hydroxy-2,2-dimethyl-3-phenylpropanoic acid (3g)

The CHIRALPAK® AD-H column with solvent flow of 4 mL/min and 5 % MeOH modifier was used to determine the ee. The ^{1}H and ^{13}C NMR spectrum match those reported in the literature.[54]

^{1}H NMR ($CDCl_3$): δ 7.2-7.4 (m, 4H, aryl C*H*), 4.94 (s, 1H, C*H*), 1.19 (m, 6H, CH_3); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 181.9 (*C*O_2H), 139.5 (1'-*C*), 128.1 (aryl *C*), 127.9 (aryl *C*), 127.7 (aryl *C*), 78.8 (*C*H), 47.4 (*C*$(CH_3)_2$), 23.4 (*C*H_3), 18.9 (*C*H_3).

HR-MS, observed: *m/e* 194.0950 (M^+). Calculated for $C_{11}H_{14}O_3$: *m/e* 194.0943 (M^+).

EI-MS, observed: *m/e* 176.1 (M^+-H_2O), 132.1 (M^+-H_2O-CO_2), 117.1 (M^+-H_2O-CO_2-CH_3), 107.0 (M^+-$CH(CH_3)_2CO_2$), 79.0 (M^+-$CH(CH_3)_2CO_2$-CO), 77.0 (M^+-$CH(CH_3)_2CO_2$-CO-H_2).

4.4.12 3-Hydroxybutanoic acid (3h)

To determine the reaction yield, isopropanol (5 μL) is added as an internal standard. The ^{1}H NMR and ^{13}C NMR spectra match those reported in the literature.[55]

^{1}H NMR ($CDCl_3$): δ 4.24 (m, 1H, C*H*), 2.51 (m, 2H, CH_2), 1.26 (d, $^{3}J_{HH}$ = 6.4 Hz, 3H, CH_3); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 177.0 (*C*O_2H), 64.5 (*C*H), 42.7 (*C*H_2), 22.4 (*C*H_3).

4.4.13 Enantiomeric Excess Determination of 3h

The benzyl ester of **3h** was synthesized by the procedure of Wang *et al*.[17] The ^{1}H NMR spectrum of the ester matches that reported in the literature.[56]

^{1}H NMR ($CDCl_3$): 7.32-7.39 (m, 5 aryl H), 5.16 (s, 2H, OC*H*$_2$), 4.19-4.24 (m, 1H, 3-C*H*), 1.22 (d, $^{3}J_{HH}$ = 6.5 Hz, 3H, CH_3).

Purification of the benzyl ester of **3h** was performed by flash optimization chromatography, utilizing a 5:1 (hexane:EtOAc) solution. The CHIRALPAK® OJ-H column with solvent flow of 3 mL/min and 3 % MeOH modifier was used to determine the ee.

4.4.14 2-Hydroxycamphoric acid

The observed diastereomeric ratio of 2-exo-OH, 3-endo-CO_2H to 2-endo-OH, 3-exo-CO_2H was 0.719:1. The ^{1}H NMR and ^{13}C NMR spectra match those reported in the literature.[57]

2-exo-OH, 3-endo-CO_2H: ^{1}H NMR ($CDCl_3$): 3.96 (m, 1H, 2-endo-C*H*), 3.06 (m, 1H, 3-exo-C*H*), 2.0-2.1 (m, 1H, 4-C*H*), 1.1-2.0 (m, 4H), 0.7-1.1- (m, 6H).

2-endo-OH, 3-exo-CO_2H: ^{1}H NMR ($CDCl_3$): 4.33 (m, 1H, 2-exo-C*H*), 2.21 (m, 1H, 3-endo-C*H*), 2.17 (m, 1H, 4-C*H*), 1.1-2.0 (m, 4H), 0.7-1.1- (m, 6H).

4.4.15 2-Hydroxycyclohexanoic acid

The ^{1}H spectrum matches that reported in the literature.[58]

syn product: ^{1}H NMR ($CDCl_3$): 4.20 (m, 1H), 2.57 (m, 1H), 1.6-2.1 (m, 5H), 1.2-1.6 (m, 3H).

anti product: ^{1}H NMR ($CDCl_3$): 3.7-3.9 (m, 1H), 2.4-2.4 (m, 1H), 2.0-2.2 (m, 2H), 1.6-1.9 (m 2H), 1.1-1.5 (m, 4H).

4.4.16 *trans*-3-Ethoxyacrylic Acid

Ethyl 3-ethoxy-2-propenoate (0.5 mL) was added to water (5 mL) containing NaOH (1.5 g) and the mixture was allowed to stir at room temperature for 5 h. The unreacted ester was extracted using diethyl ether, and the aqueous layer was acidified to pH=1 using 1 M HCl. Extraction with diethyl ether, drying with $MgSO_4$, and removal of the solvent afforded the acid product (36 % isolated yield). The ^{1}H NMR spectrum matches that reported in the literature.[59]

^{1}H NMR ($CDCl_3$): δ 7.67 (d, $^{3}J_{HH}$ = 12.5 Hz, 1H, 3-H), 5.18 (d, $^{3}J_{HH}$ = 12.5 Hz, 1H, 2-H), 3.95 (q, $^{3}J_{HH}$ = 7.0 Hz, 2H, OCH_2), 1.36 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3).

^{13}C{^{1}H} NMR ($CDCl_3$): δ 173.6 (CO$_2$H), 164.4 (OCH), 96.7 (CHCO$_2$H), 67.1 (CH$_2$), 14.4 (CH$_3$)

4.4.17 3-Ethoxypropanoic Acid

The ^{1}H NMR spectrum matches that reported in the literature.[60]

^{1}H NMR ($CDCl_3$): 3.72 (t, $^{3}J_{HH}$ = 6.0 Hz, 2H, 3-CH$_2$), 3.53 (q, $^{3}J_{HH}$ = 7.0 Hz, 2H, CH_2CH$_3$), 2.64 (m, 2H, 2-CH_2), 1.21 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3).

4.4.18 "$RuCl_2${rac-BINAP}"[61]

In the glovebox, $[RuCl_2(benzene)]_2$ (65.3 mg, 0.13 mmol) and rac-BINAP (170.3 mg, 0.274 mmol) were added to DMF (10 mL). The resulting brown suspension was stirred at 100 °C for 15 min under nitrogen, producing a clear reddish brown solution. The solution was cooled to room temperature, and solvent was removed under vacuum at 50 °C. The reddish brown solid remaining was "$RuCl_2${rac-BINAP}" complex. $^{31}P\{^1H\}$ NMR spectrum matches that reported in literature.[61]

4.4.19 $Ru(OAc)_2${(R)-BINAP}[62]

In a large Schlenk tube in the glovebox, $[RuCl_2(benzene)]_2$ (20 mg, 0.04 mmol) and (R)-BINAP (47 mg, 0.076 mmol) was dissolved in DMF (2 mL) to produce a brown emulsion. The Schlenk tube was removed from glovebox and the solution was heated at 100 °C for 10 min, producing a clear brown solution. The solution was then cooled to room temperature. To the reaction solution was added a solution of KOAc (0.13 g, 1.59 mmol) in degassed and dry MeOH (1 mL), H_2O (3 mL), and toluene (2 mL). The aqueous layer turned yellow and the organic layer remained brown. The organic layer was removed by cannula, and the aqueous layer exctracted with toluene (2x2 mL). In a new Schlenk tube, the organic layers were combined and then washed with H_2O (3x2 mL). The organic solvent was removed under vacuum, and the Schlenk tube was returned to the glovebox. Toluene was added (2 mL) to dissolve the solid, and the solution very slowly layered with hexane (3 mL). Crystallization occurred over a 5 d period; the mother liquor was removed and the yellow solid was dried under vacuum. $^{31}P\{^1H\}$ NMR: 65.8 ppm.

4.4.20 Hydrogenation of 2a in the presence of DBU

Benzoylacetic acid was added (30.6 mg, 0.19 mmol) to CH_2Cl_2 (4 mL) to DBU (0.01 mL, 0.095 mmol) and the mixture was stirred for 24 h at room temperature and 80 bar H_2. Upon reaction completion, the solvent was removed, and the ^1H NMR spectrum was acquired using $CDCl_3$. The ^1H NMR spectrum of the crude material confirms the presence of only acetophenone, with no hydrogenation being observed.

4.4.21 Methyl Ester Formation

Self-catalyzed esterification: 3-oxobutanoic acid (25.4 mg, 0.25 mmol) was added to HPLC-grade MeOH (1 mL) and the reaction was stirred at room temperature for 22 h. The solvent was removed under vacuum, and the ^1H NMR spectrum using $CDCl_3$ shows no esterification product.

3-Hydroxybutanoic acid (25.0 mg, 0.24 mmol) was added to HPLC-grade MeOH (1 mL) and the reaction was stirred at room temperature for 22 h. The solvent was removed under vacuum, and the ^1H NMR spectrum using $CDCl_3$ shows no esterification product.

4.4.22 Hydrogenation with 80 bar nitrogen

To determine the effect of catalyst loading and substrate concentration, two experiments were prepared:

Higher catalyst loading: 2-methyl-3-oxo-3-phenylpropanoic acid (40.1 mg, 0.23 mmol) and "$RuCl_2${(S)-BINAP}" (9.1 mg, 0.01 mmol) were added to MeOH (4 mL) in a 31 mL autoclave and the vessel was pressurized to 80 bar N_2. After 52 h of stirring,

the vessel was vented, and the solvent removed under vacuum. The ^{1}H NMR spectrum of the crude material using $CDCl_3$ shows no esterification but did show the formation of the ketal in 11 % yield.

High substrate concentration: 2-methyl-3-oxo-3-phenylpropanoic acid (201.3 mg, 1.13 mmol) and "$RuCl_2${(S)-BINAP}" (8.8 mg, 0.01 mmol) were added to MeOH (8 mL) in a 31 mL autoclave and the vessel was pressurized to 80 bar N_2. After 52 h of stirring, the vessel was vented, and the solvent removed under vacuum. The ^{1}H NMR spectrum of the crude material using $CDCl_3$ shows no esterification but did show the formation of the ketal in 17 % yield.

4.4.23 Solution-state hydrogenation with filtering using 2b

3-(4'-chlorophenyl)-3-oxopropanoic acid (49.7 mg, 0.25 mmol) and "$RuCl_2${(S)-BINAP}" (1.9 mg, 0.002 mmol) were added to CH_2Cl_2 (4 mL). The mixture was stirred for 5 min to ensure that a saturated solution was produced; the undissolved solid was filtered off using a Shur-wipe® (Georgia-Pacific) pipette filter. The hydrogenation was performed for 68 h, the solvent was removed under vacuum, and the ^{1}H NMR spectrum of the crude material using $CDCl_3$ shows hydrogenation in 96 % yield.

4.4.24 Hydrogenation of 2b in the solid-state

3-(4'-chlorophenyl)-3-oxopropanoic acid (48.6 mg, 0.24 mmol) and "$RuCl_2${(S)-BINAP}" (1.8 mg, 0.002 mmol) were added to a 31 mL autoclave and the vessel was pressurized to 80 bar H_2. The reaction was stirred for 68 h, but the ^{1}H NMR

spectrum of the crude material using $CDCl_3$ shows no hydrogenation product, only decarboxylation.

4.4.25 Deuterium Labelling Experiments

Synthesis of 2,2-$^2H_2$-Benzoylacetic Acid.

Method 1: Deuteration and carboxylation of acetophenone

Under nitrogen, acetophenone (3.00 mL, 25.64 mmol) was added to MeOH-d_4 (4.5 mL) in a round bottom flask. NaOH (2.0 g, 50.00 mmol) was added to the solution and allowed to stir at room temperature for 17 h, producing a brown solution. The MeOH-d_4 was removed under vacuum, and added D_2O (10 mL). Diethyl ether (15 mL) was used to extract the 2,2,2-$^2H_3$-acetophenone; the organic layer was dried with $MgSO_4$, filtered, and removed under vacuum. ^1H NMR spectroscopy using $CDCl_3$ confirmed 84 % deuteration at the methyl group. Adding additional NaOH (1.0 g, 25.0 mmol) and stirring for overnight in 10 mL MeOH-d_4 produced 2,2,2-$^2H_3$-acetophenone with 96 % deuteration. 2,2-$^2H_2$-Benzoylacetic acid was prepared from 2,2,2-$^2H_3$-acetophenone (1.19 mL, 9.7 mmol) and DBU (3.0 mL, 20.0 mmol) by Method A in Section 2.4.4 at room temperature. ^1H NMR spectroscopy using $CDCl_3$ confirmed product formation, but the deuteration was only 73% at the α carbon (28 % isolated yield).

Method 2: Deuteration and hydrolysis of ethyl benzoylacetate

Ethyl benzoylacetate (1.00 mL, 5.81 mmol) was added to a solution of dried MeOH-d_4 (4.0 mL) and NEt_3 (1.81 mL, 13.0 mmol) and the reaction was stirred for 24 h at room temperature. The solvent was removed under vacuum and an extraction with D_2O and diethyl ether was performed. The organic layer was removed under vacuum,

leaving an orange liquid. ^{1}H NMR spectroscopy using $CDCl_3$ confirmed formation of ethyl 2,2-$^{2}H_2$-benzoylacetate with 91 % deuteration and the presence of unreacted NEt_3. Additional MeOH-d_4 (2.5 mL), and D_2O (2.0 mL) were added and the reaction was stirred overnight. The solvent was removed under vacuum, and extracted with D_2O and diethyl ether. Drying the organic layer with $MgSO_4$ followed by removal under vacuum yielded a brown liquid, confirmed by ^{1}H NMR spectroscopy using $CDCl_3$ to be ethyl 2,2-$^{2}H_2$-benzoylacetate with 95 % deuteration at α the location.

Ethyl 2,2-$^{2}H_2$-benzoylacetate (0.6 mL, 3.6 mmol) was added to a solution of D_2O (3 mL) and NaOH (0.2395 g, 6.0 mmol) and stirred for 8 h at room temperature. Unreacted material was removed by extraction with diethyl ether, and the aqueous layer was acidified to pH=1. Diethyl ether was used for extraction, dried with $MgSO_4$, and removed under vacuum. ^{1}H NMR spectroscopy using $CDCl_3$ confirmed 2,2-$^{2}H_2$-benzoylacetic acid formation with 34 % deuteration at the α location.

Hydrogenation with Deuterium Gas.

2,3-$^{2}H_2$-2-Methyl-3-hydroxy-3-phenylpropanoic acid was prepared from the general procedure using 10 bar D_2, in CD_2Cl_2 or CH_2Cl_2, at room temperature. If CD_2Cl_2 was utilized, the ^{1}H NMR spectrum was obtained from crude reaction mixture without solvent removal. If CH_2Cl_2 was utilized, the reaction solvent was removed before the ^{1}H NMR spectrum was obtained using CD_2Cl_2. The degree of deuteration at the α and β positions of for 2,3-$^{2}H_2$-2-methyl-3-hydroxy-3-phenylpropanoic acid was determined by independently comparing the integration of these peaks to the 2-methyl peak.

4.5 References

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Chapter 5
Conclusions

5.1 Summary of Key Thesis Results

Although conclusions and future work have been discussed within each chapter, some significant points and future work are summarized here.

In this thesis, an effective strategy for the conversion of inexpensive ketones into optically active β-hydroxycarboxylic acids using a homogeneous metal catalyst was presented. For the carboxylation step, two equivalents of DBU, no solvent, dry substrates, and 60 bar CO_2 were determined to be effective conditions for a variety of aliphatic and aromatic ketones, although much lower CO_2 pressures and a lower concentration of DBU may suffice.

The *in situ* decarboxylation of the synthesized β-ketocarboxylic acids was monitored by ^{1}H NMR spectroscopy. It was found that the rate of decarboxylation generally increased with solvent polarity, but decreased in the presence of a Lewis basic solvent, including $(CD_3)_2CO$, EtOAc, and THF. Aromatic substituents did not affect the decarboxylation rate, and increasing the steric bulk on either the *ortho*- aromatic or the α-position decreased the rate of decarboxylation.

For the asymmetric hydrogenation, CH_2Cl_2 and MeOH were selected as the best solvent choices. Hydrogenation is expected to be preceded by binding of the substrate as a carboxylate, in analogy to the known mechanisms of hydrogenation of α,β-unsaturated carboxylic acids. However, the hydrogen transfer may take place while the substrate is in

a ketocarboxylate or an enolcarboxylate tautomer. Evidence suggests that both the enol and keto pathways are possible in MeOH; however, the fact that an enol ether substrate could not be hydrogenated in CH_2Cl_2 suggests (but does not prove) that the enol pathway does not operate in CH_2Cl_2. This hydrogenation was successfully used on a variety of β-keto acids, including alkyl, aryl, cyclic, and bicyclic.

5.2 Future Work

The carboxylation of a select group of ketones, including α,β-unsaturation, such as 3-penten-2-one and methylvinylketone, should be repeated using a saturated $CaCl_2$ solution during extraction.

Although the effect of *para* aromatic substitution has been well studied, further investigation on the effect *ortho* aromatic substitution should be performed. The decarboxylation of benzoylacetic acid should be attempted under CO_2 pressure; this information will be important in determining the validity of a one-pot hydrocarboxylation reaction.

Using the standard conditions determined for the carboxylation and hydrogenation reactions, a one-pot hydrocarboxylation method can be attempted. For this one-one port method, an attached vessel containing the best hydrogenation solvent, catalyst, and H_2 gas would be opened to the carboxylation vessel; therefore, the carboxylate salt would be hydrogenated without the isolation of the unstable β-ketocarboxylic acid. This would be experimentally preferred.

For mechanistic and academic interest, the actively hydrogenated species could be determined. Hydrogenating β-ketocarboxylic acids that favour the enol tautomer could provide information regarding the importance of the hydroxy proton.

Because of the surprisingly low enantioselectivity from the hydrogenation of **2f** in MeOH, a reaction run to ≤50 % conversion should be attempted. This result would provide information regarding the existence of either dynamic kinetic resolution or kinetic resolution for this substrate. Because of the different rates of tautomerization and hydrogenation observed between **2f** and **5/6**, a full evaluation of the kinetic resolution and dynamic resolution should be investigated.

From the studies performed on α,β-unsaturated acid and β-keto esters, it is known that $Ru(OAc)_2$(BINAP) favours hydrogenation of olefin bonds over carbonyl.[1] With this in mind, the hydrogenation the β-ketocarboxylic acids using $Ru(OAc)_2${(S)-BINAP} should be attempted.

5.3 References

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Appendix 1: Selected Spectra from Chapter 2

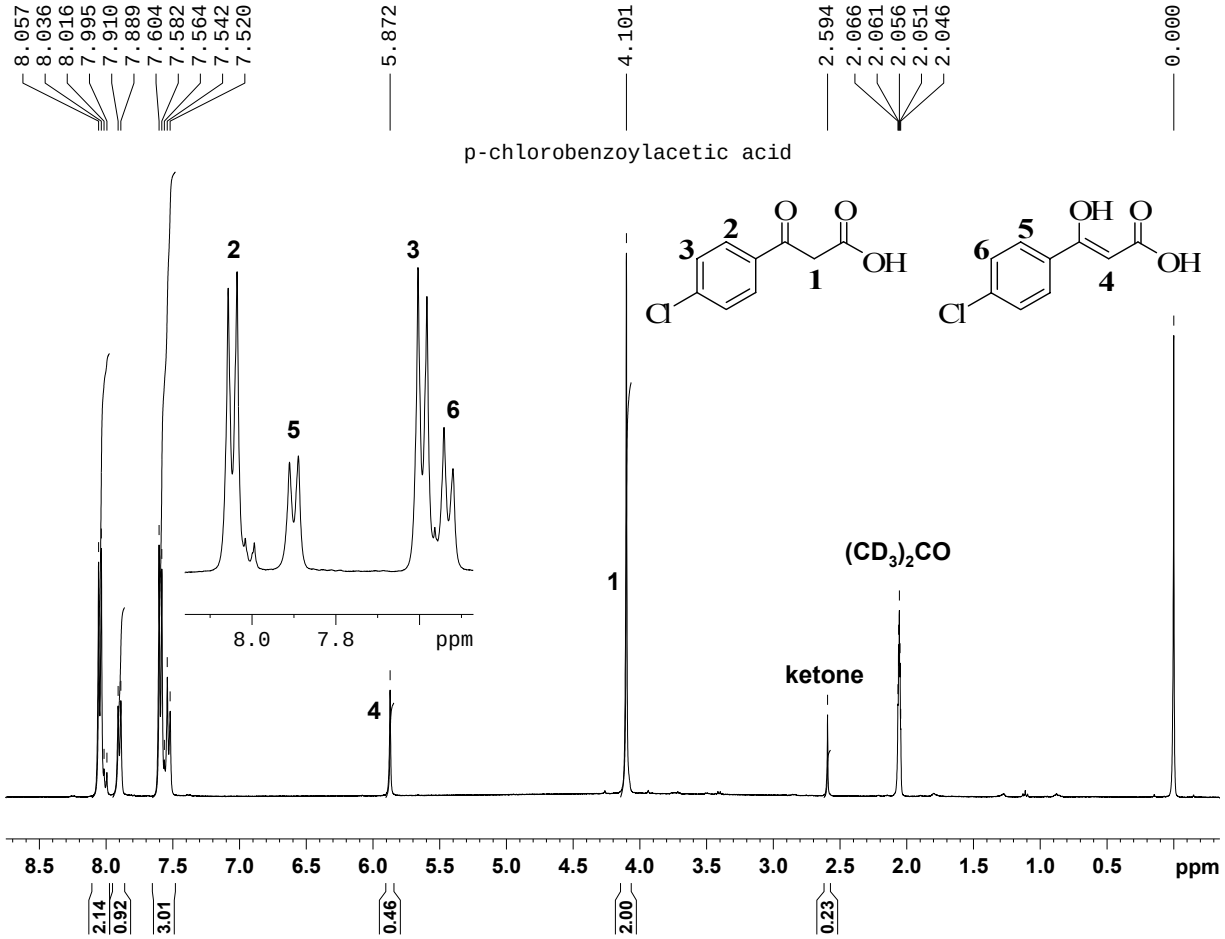

Figure A1.1. ^{1}H NMR spectrum of 4'-chlorobenzoylacetic acid (**2b**) in $(CD_3)_2CO$.

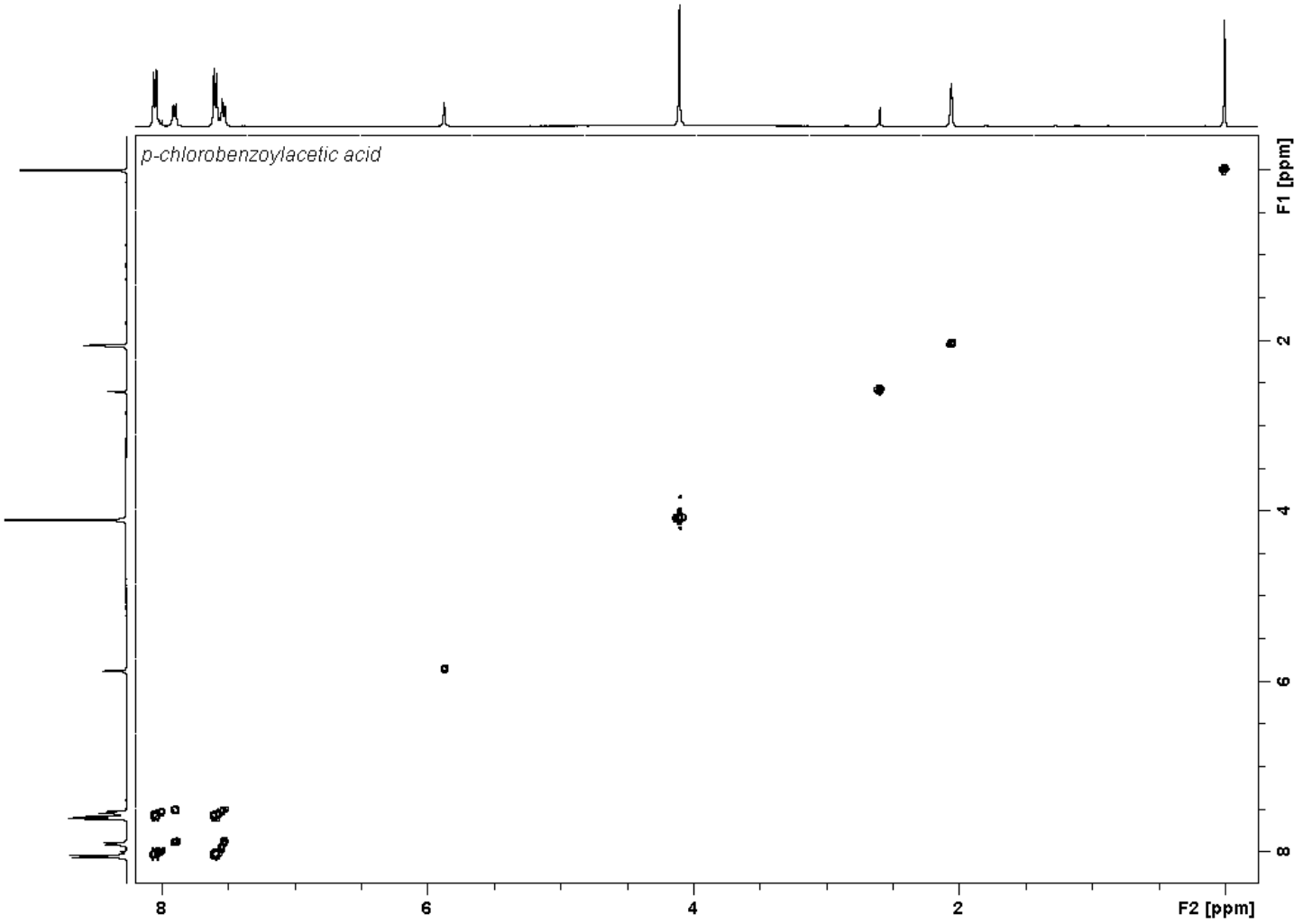

Figure A1.2. ^{1}H-^{1}H COSY NMR spectrum of 4'-chlorobenzoylacetic acid (**2b**) in $(CD_3)_2CO$.

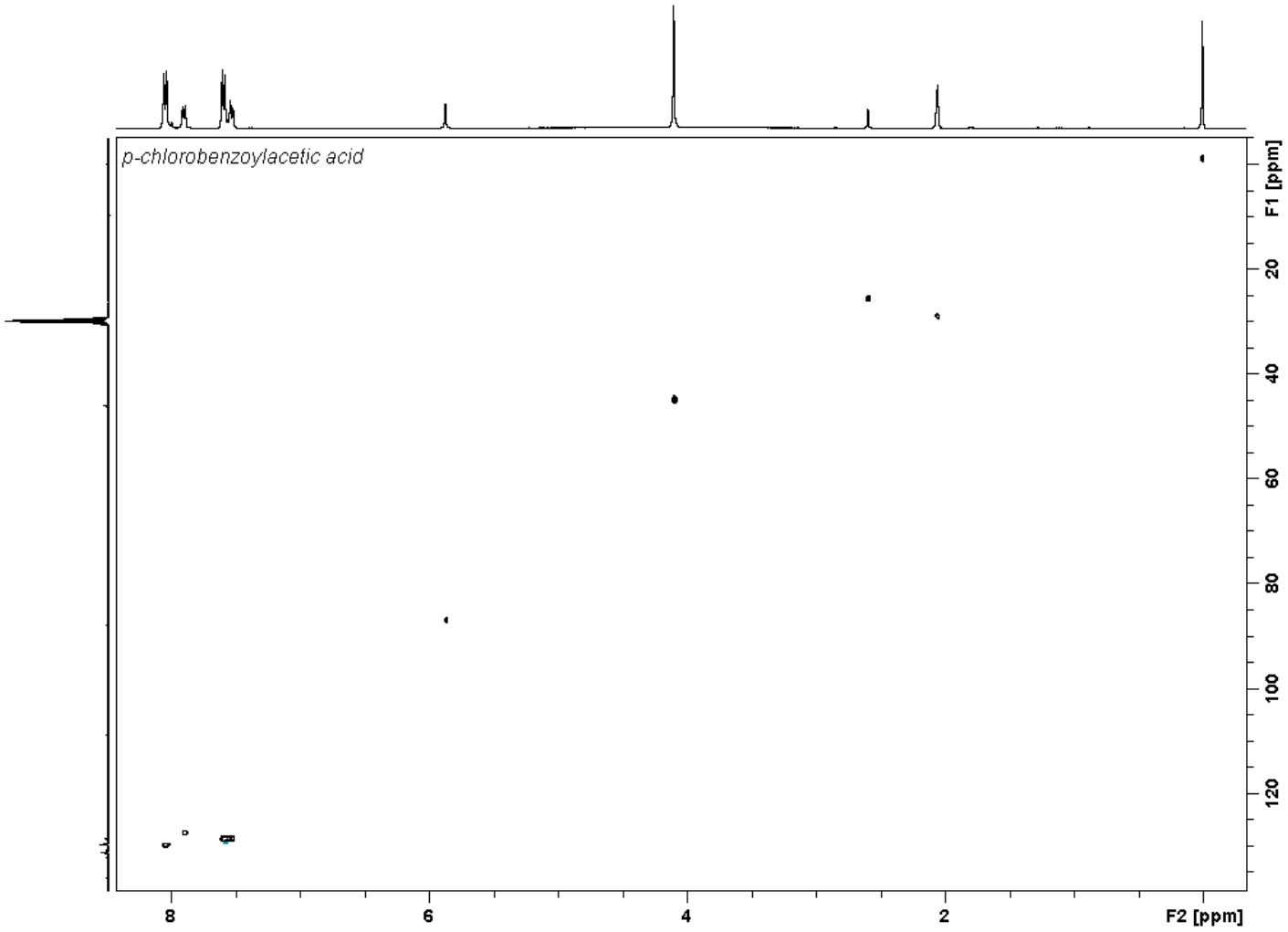

Figure A1.3. ^{1}H-^{13}C HSQC NMR spectrum of 4'-chlorobenzoylacetic acid (**2b**) in $(CD_3)_2CO$.

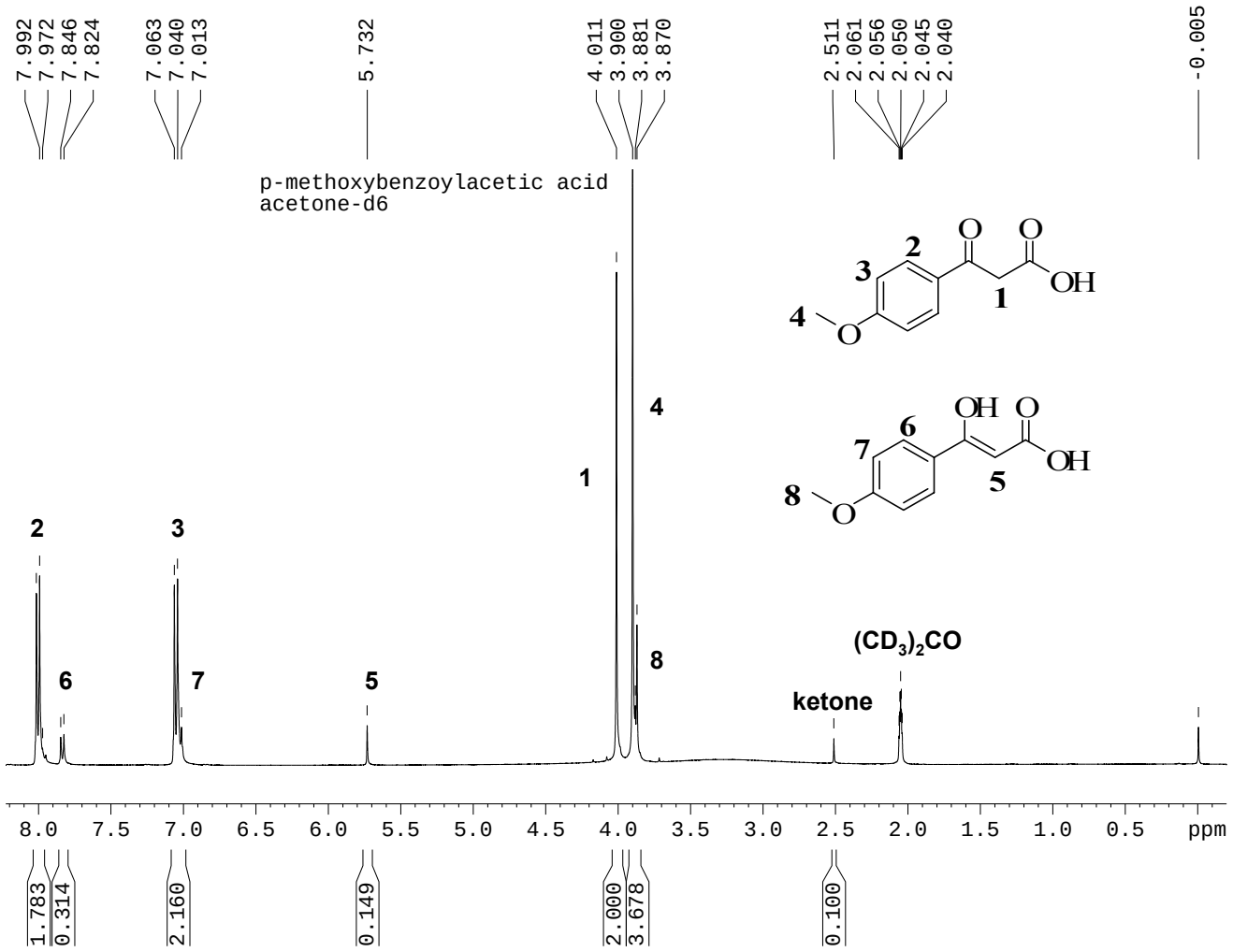

Figure A1.4. ^{1}H NMR spectrum of 4'-methoxybenzoylacetic acid (**2c**) in $(CD_3)_2CO$.

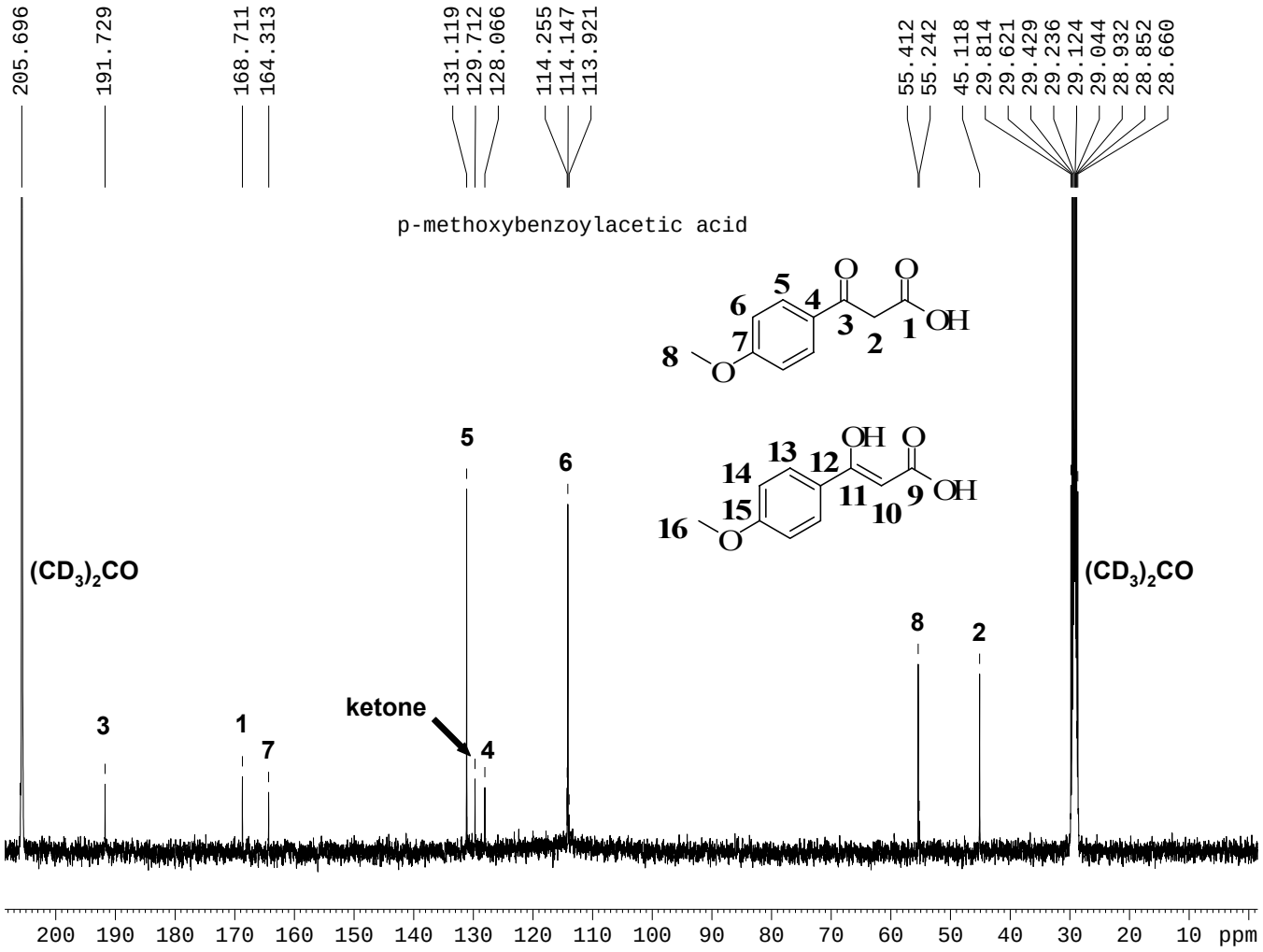

Figure A1.5. ^{13}C NMR spectrum of 4'-methoxybenzoylacetic acid (**2c**) in $(CD_3)_2CO$.

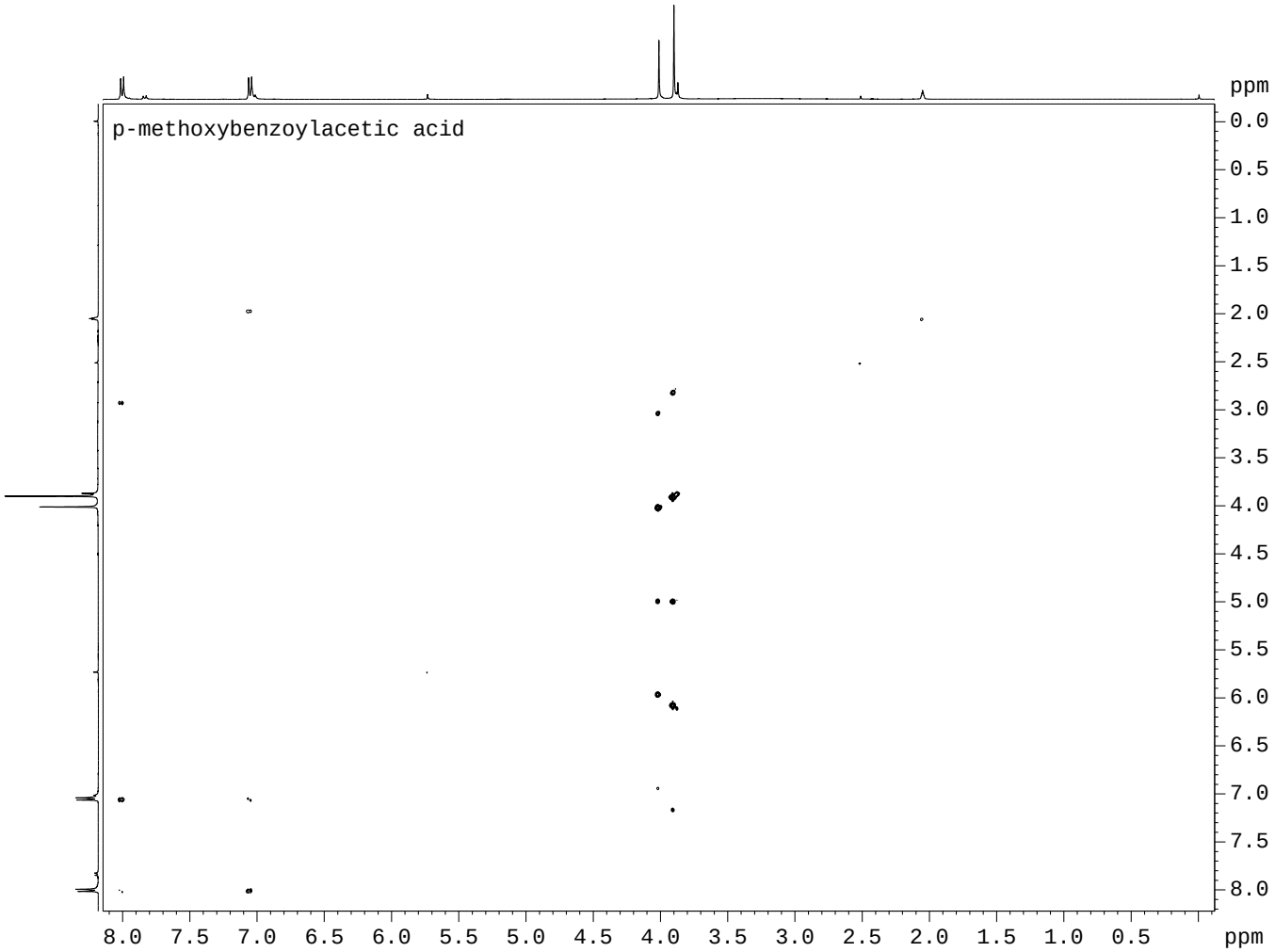

Figure A1.6. ^{1}H-^{1}H COSY NMR spectrum of 4'-methoxybenzoylacetic acid (**2c**) in $(CD_3)_2CO$.

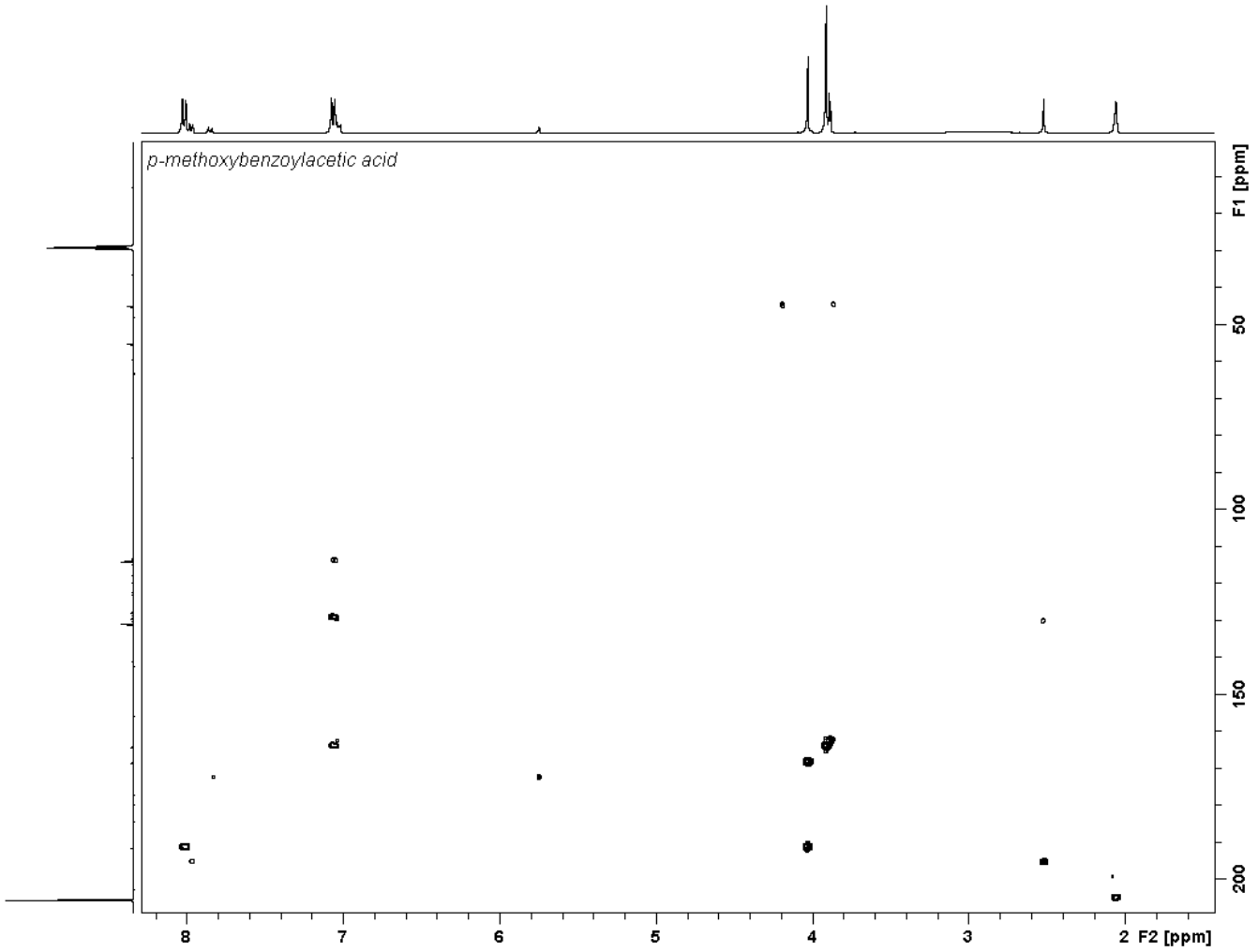

Figure A1.7. ^{1}H-^{13}C HSQC NMR spectrum of 4'-methoxybenzoylacetic acid (**2c**) in $(CD_3)_2CO$.

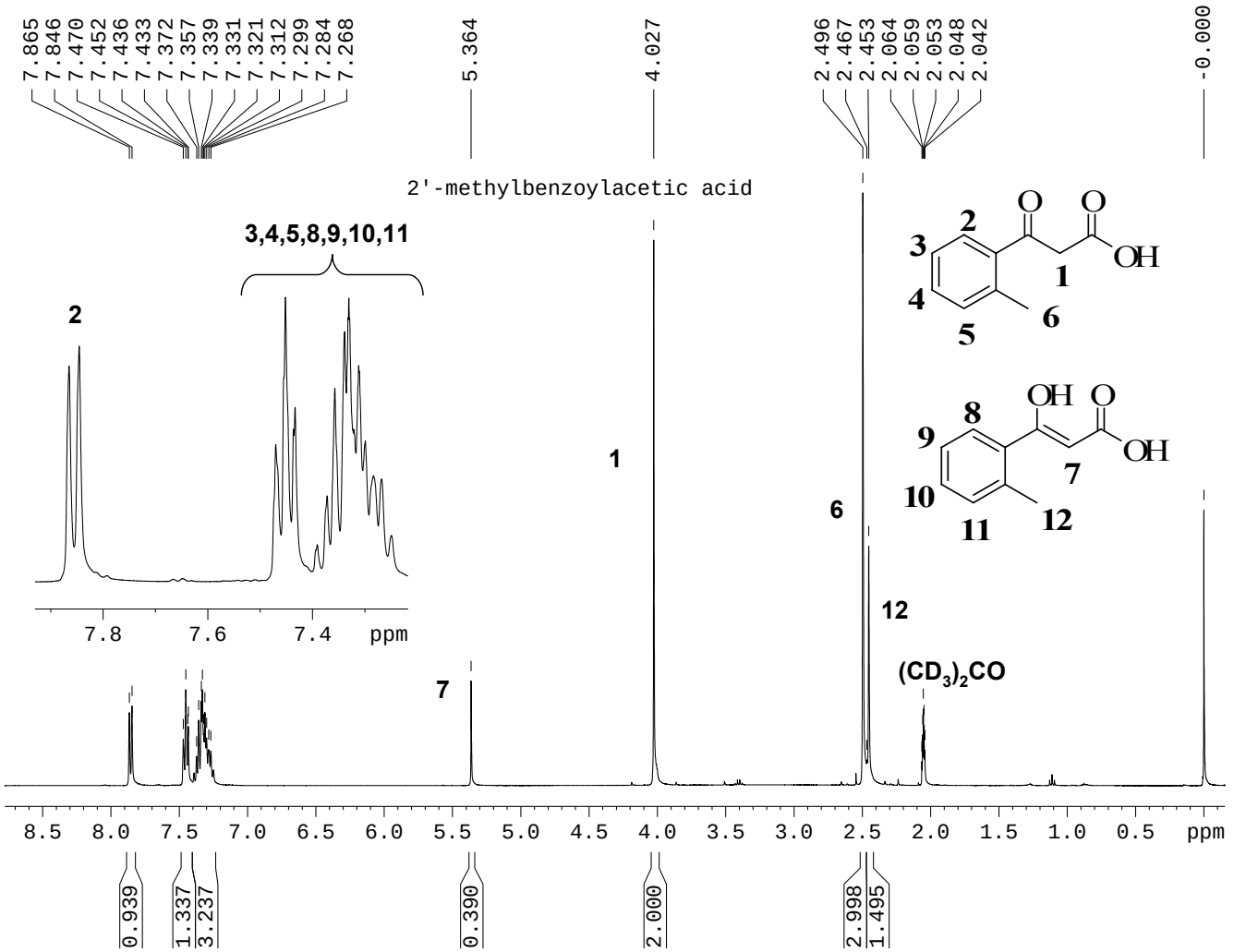

Figure A1.8. ^{1}H NMR spectrum of 2'-methylbenzoylacetic acid (**2d**) in $(CD_3)_2CO$.

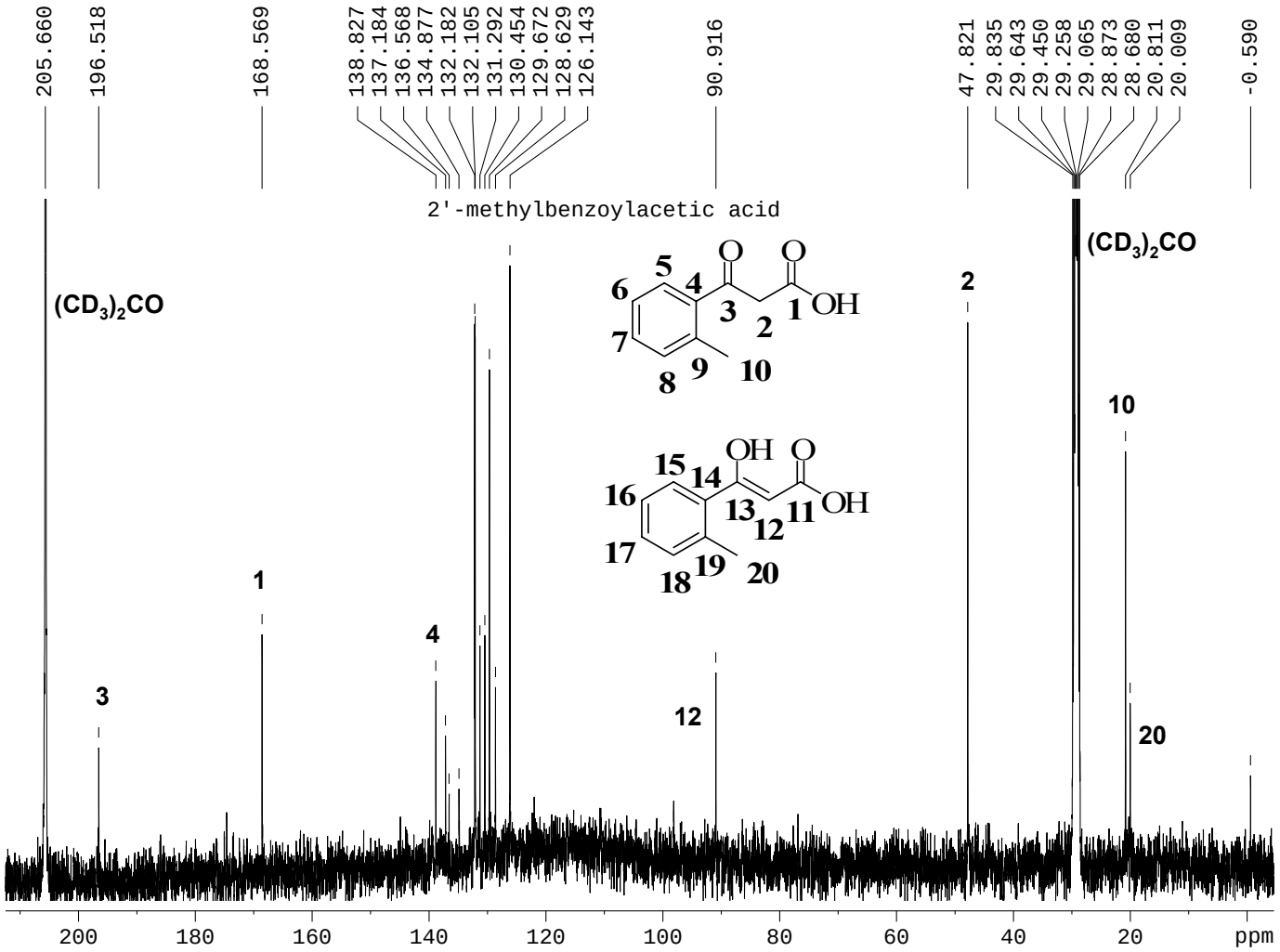

Figure A1.9. ^{13}C NMR spectrum of 2'-methylbenzoylacetic acid (**2d**) in $(CD_3)_2CO$.

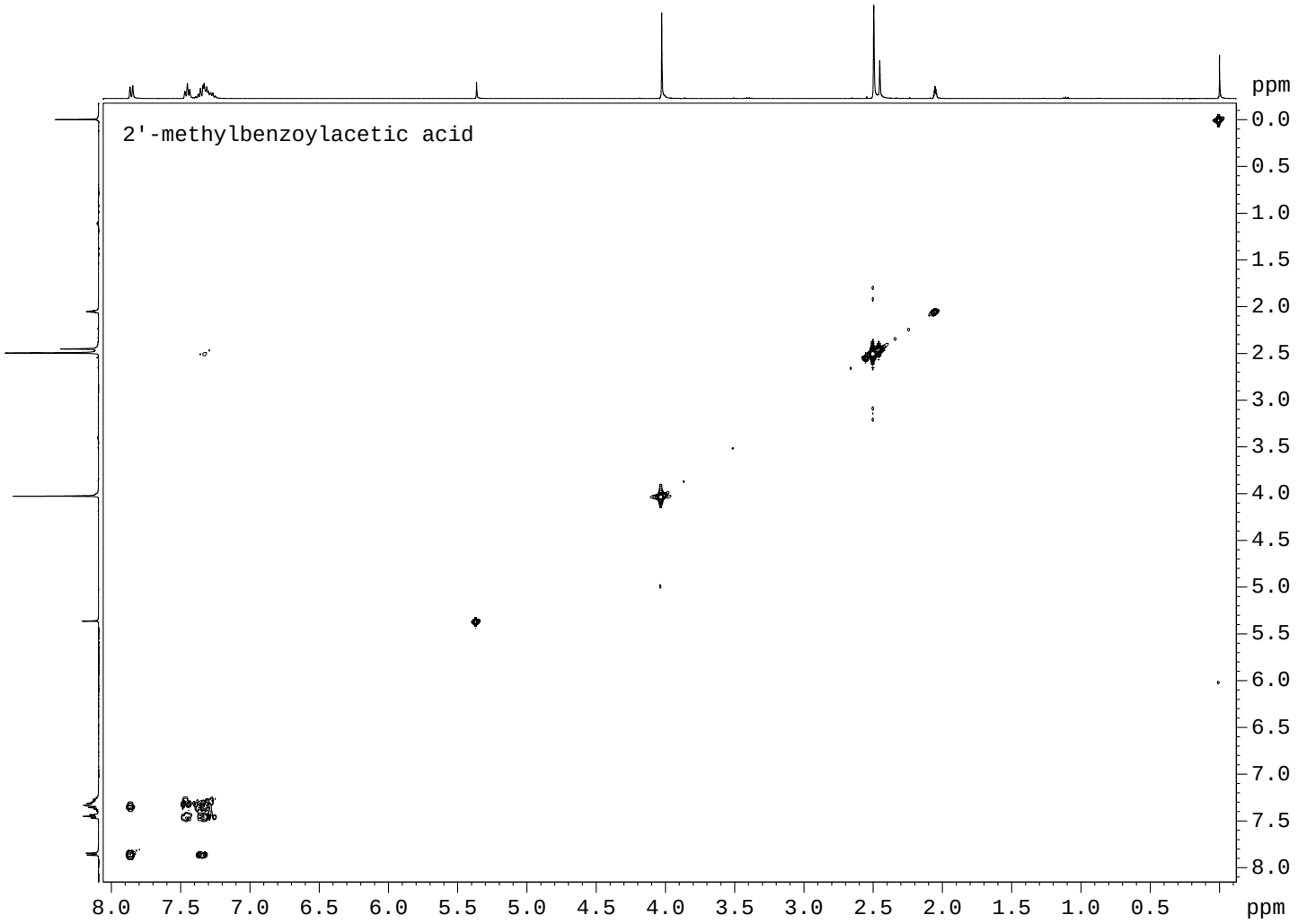

Figure A1.10. ^{1}H-^{1}H COSY NMR spectrum of 2'-methylbenzoylacetic acid (**2d**) in $(CD_3)_2CO$.

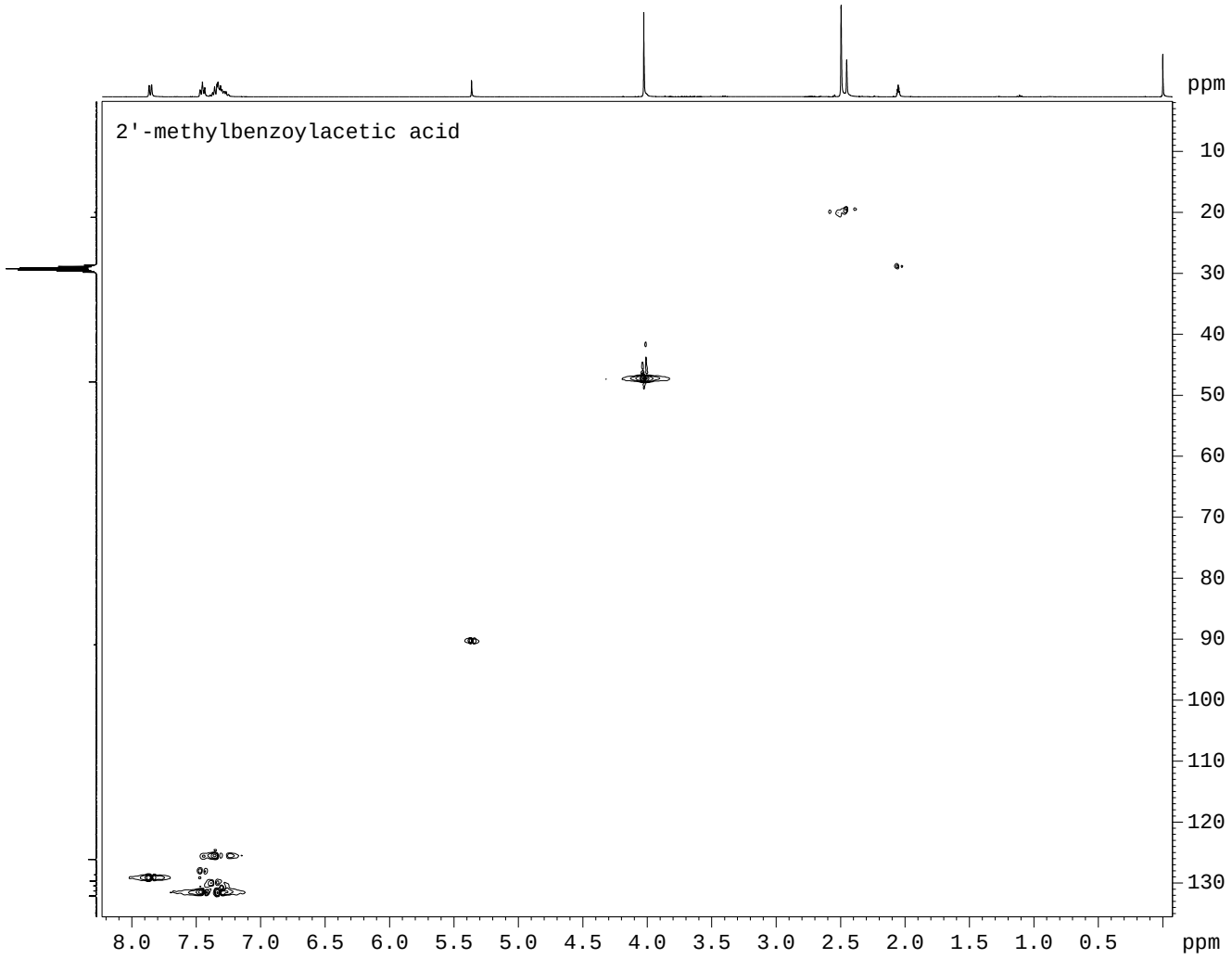

Figure A1.11. ^{1}H-^{13}C HSQC NMR spectrum of 2'-methylbenzoylacetic acid (**2d**) in $(CD_3)_2CO$.

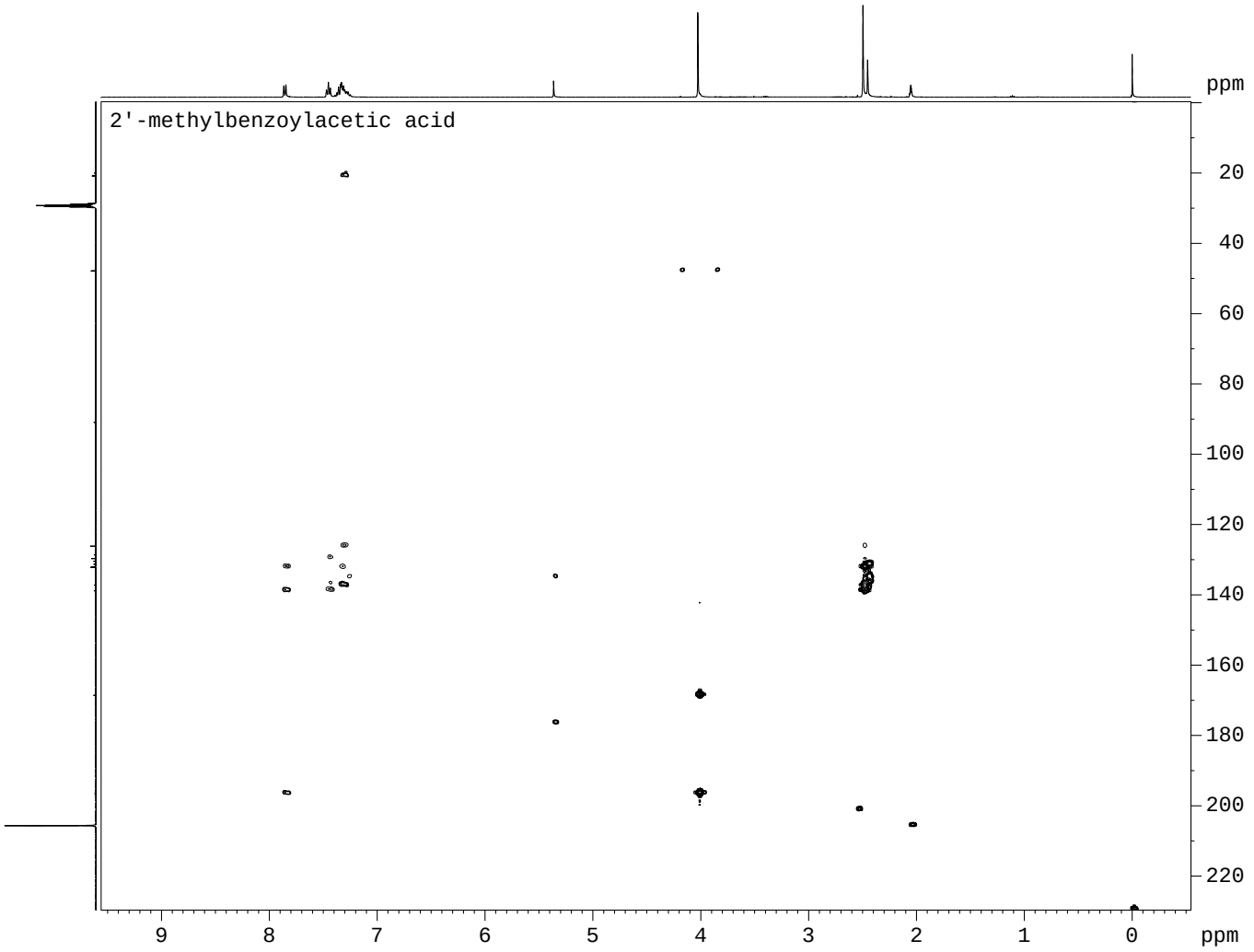

Figure A1.12. ^{1}H-^{13}C HMBC NMR spectrum of 2'-methylbenzoylacetic acid (**2d**) in $(CD_3)_2CO$.

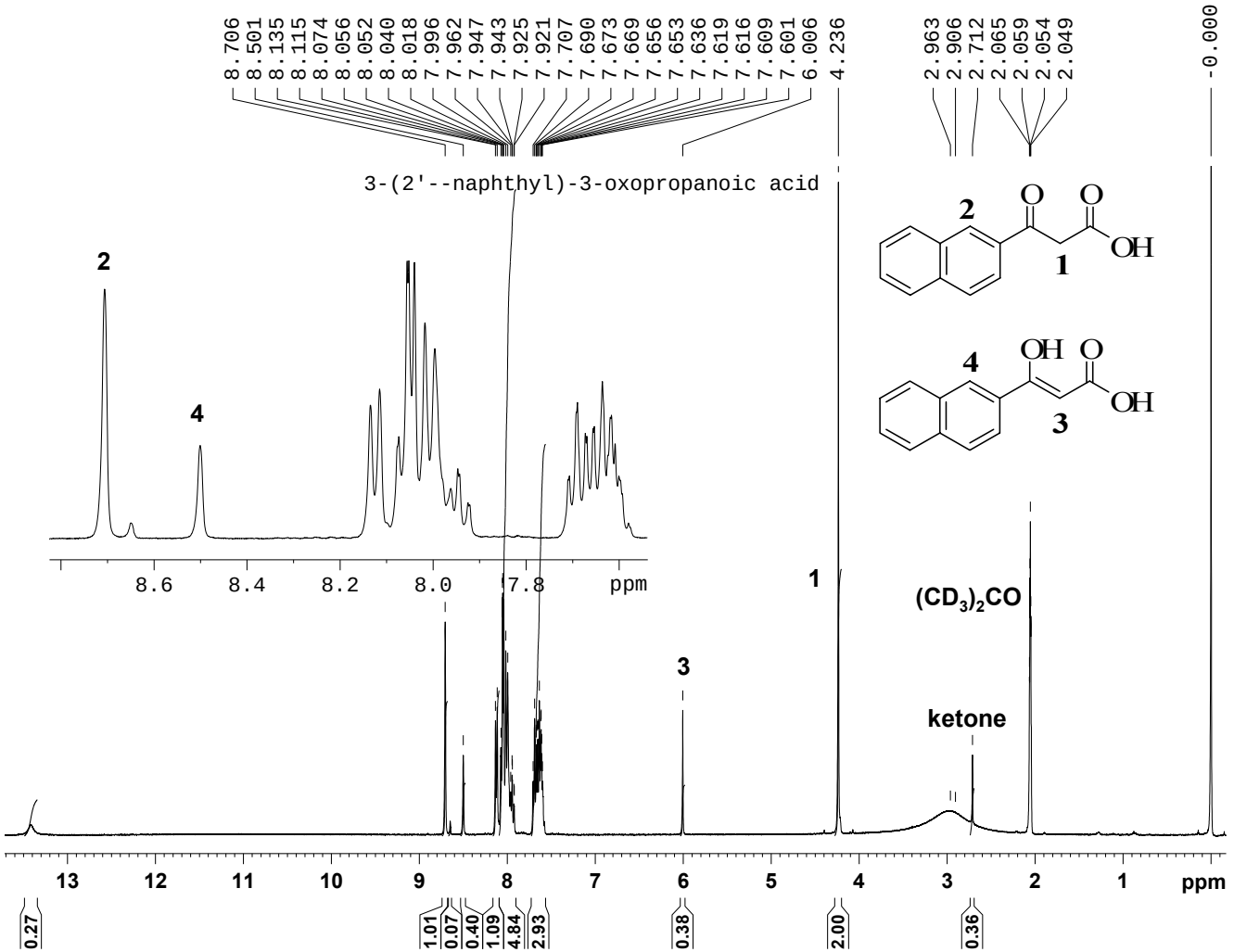

Figure A1.13. ^{1}H NMR spectrum of 3-(naphthalen-2′-yl)-3-oxopropanoic acid (**2e**) in $(CD_3)_2CO$.

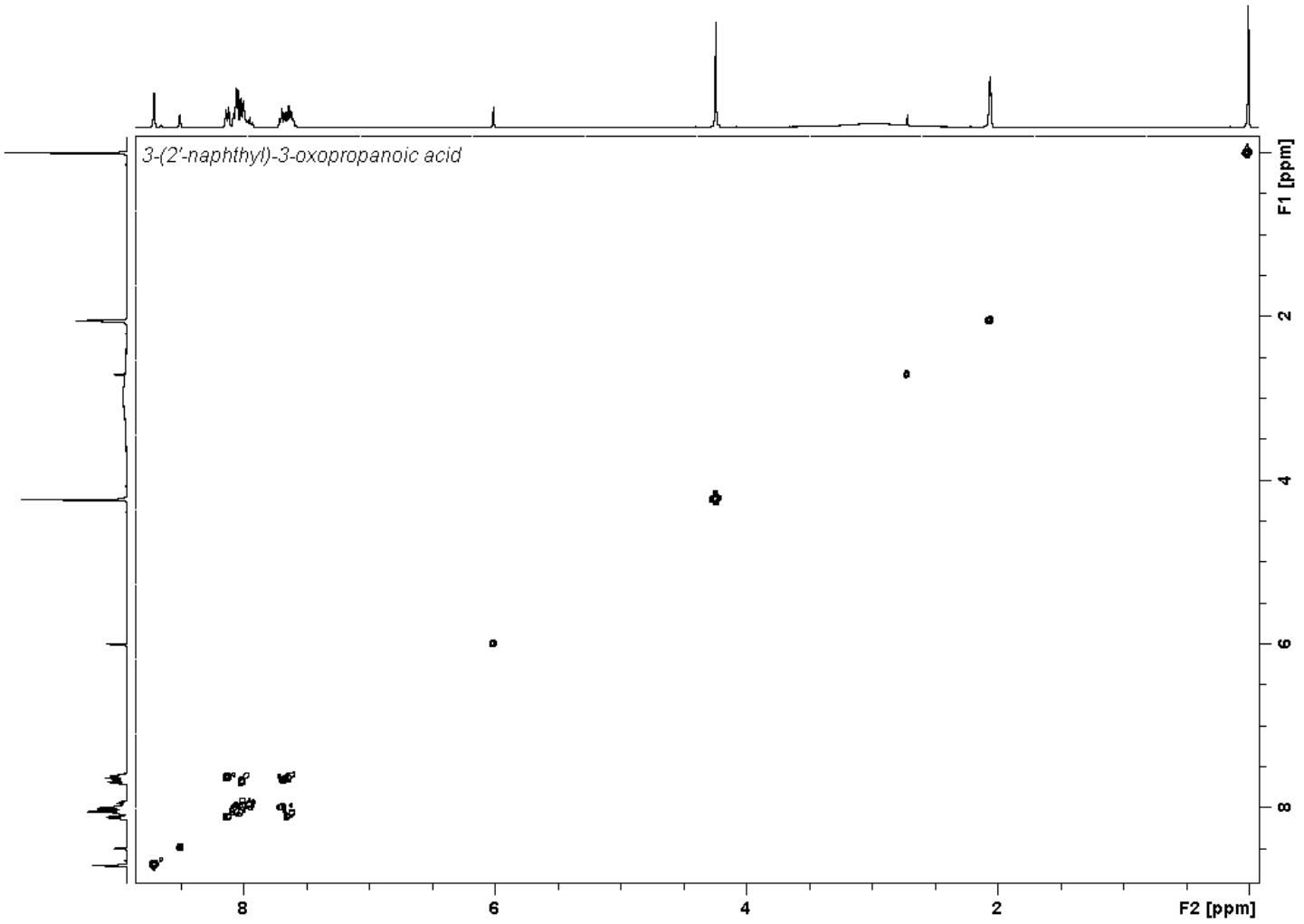

Figure A1.14. ^{1}H-^{1}H COSY NMR spectrum of 3-(naphthalen-2′-yl)-3-oxopropanoic acid (**2e**) in $(CD_3)_2CO$.

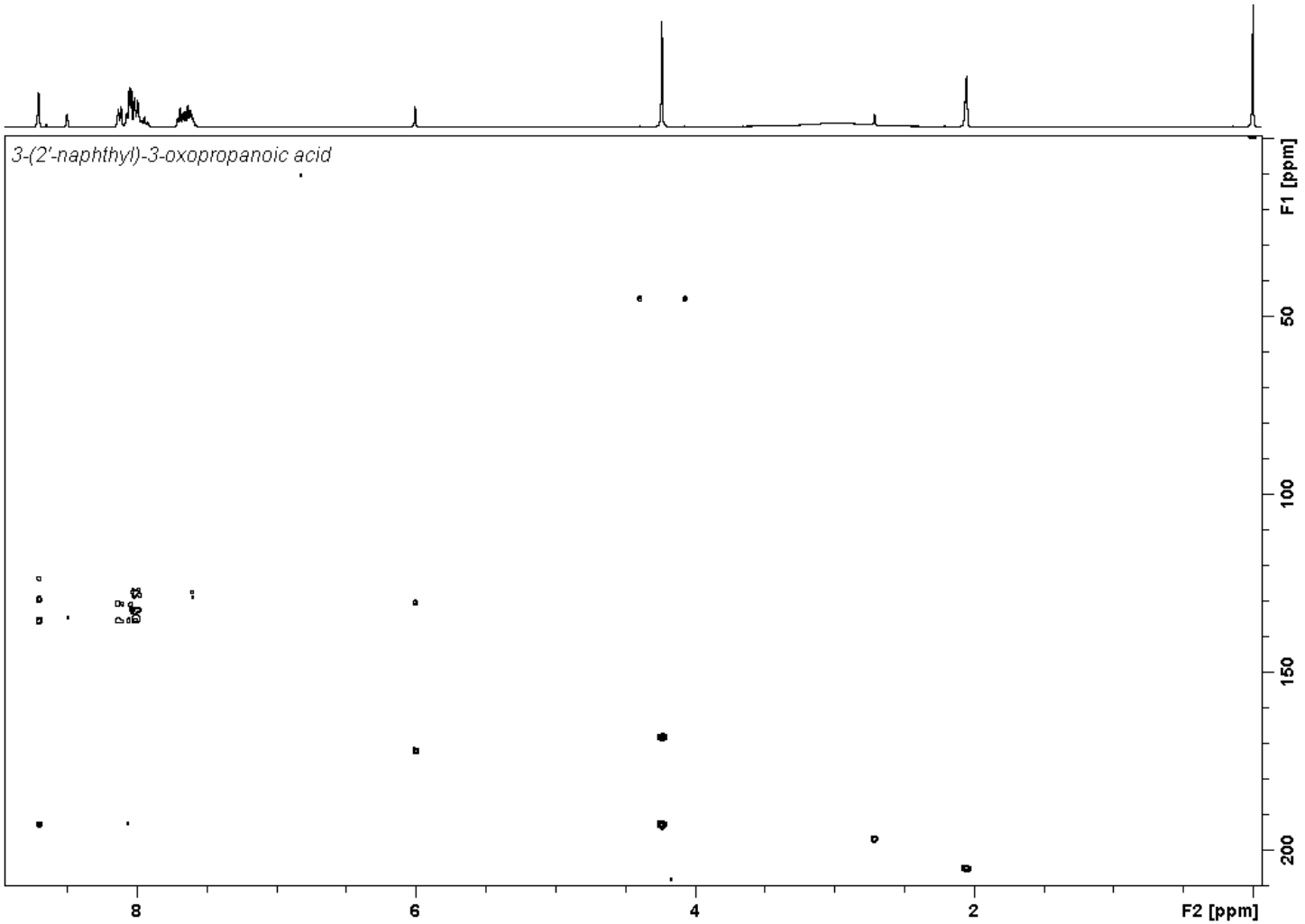

Figure A1.15. ^{1}H-^{13}C HMBC NMR spectrum of 3-(naphthalen-2′-yl)-3-oxopropanoic acid (**2e**) in $(CD_3)_2CO$.

Table A1.1. Unsuccessful DBU-Promoted Carboxylations of Other Ketones.

Entry	Ketone	CH pK_a (DMSO)	Temp (°C)	Time (h)	Yield (%)
1	2-acetylpyrrole (MeCN)	na	23	24	0
2	3-pentene-2-one	na	23	24	0
3	methylvinylketone	na	0	50	0
4	acetylacetone	13.2	40	25	0
5	acetylacetone	13.2	23	29	0
6	deoxybenzoin (MeCN)	17.7	23	25	0
7	cyclopropylphenylketone	28.2	23	24	0
8	ethylmethylketone	na	23	29	0
9	diisopropylketone	28.2	40	24	0
10	diisopropylketone	28.2	0	25	0
11	diisopropylketone	28.2	23	19	0
12	tert-butylmethylketone	27.7	23	23	0
13	tert-butylmethylketone	27.7	40	20	0
14	1,1,1-trifluoroaceteon	na	23	24	0

Appendix 2: Selected Data from Chapter 3

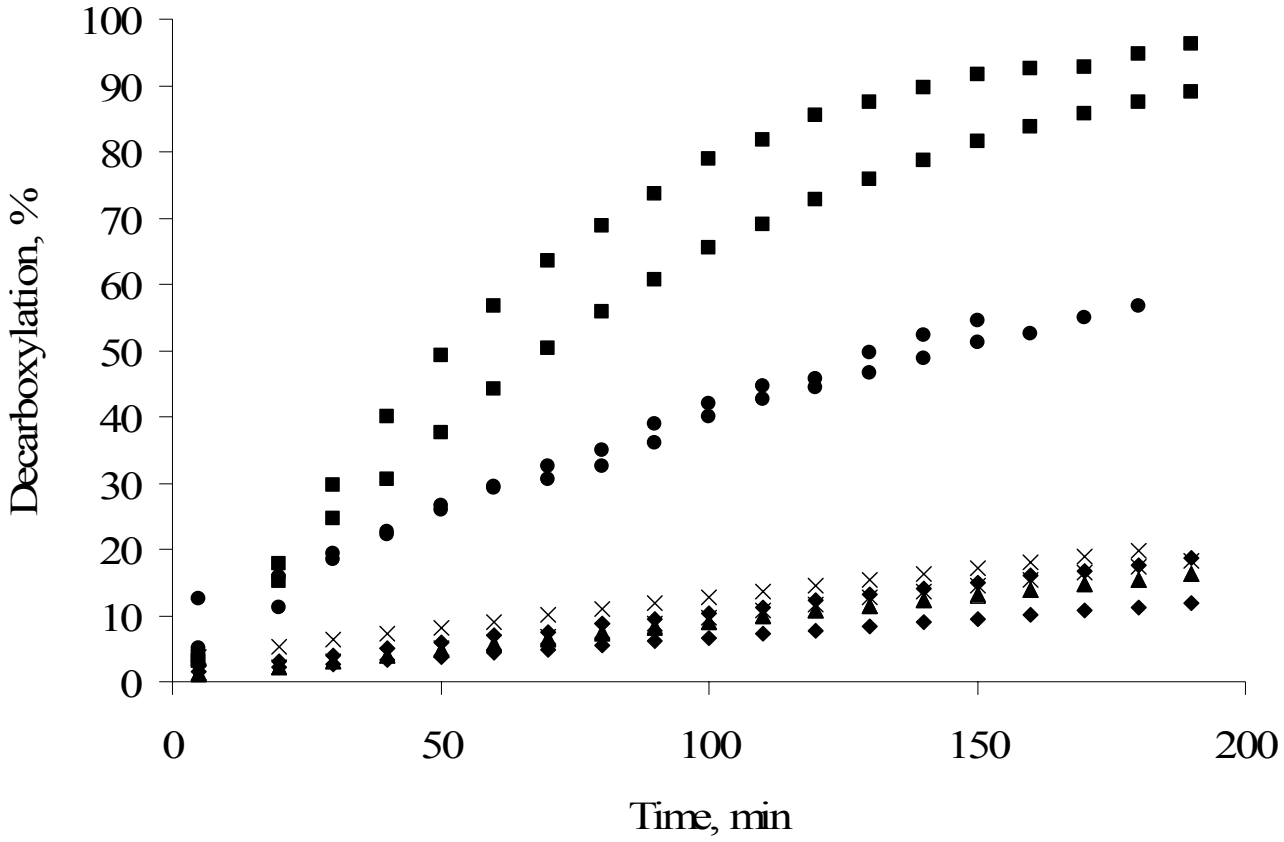

Figure A2.1. Duplicate Observed Decarboxylation Data of Benzoylacetic Acid (**2a**).

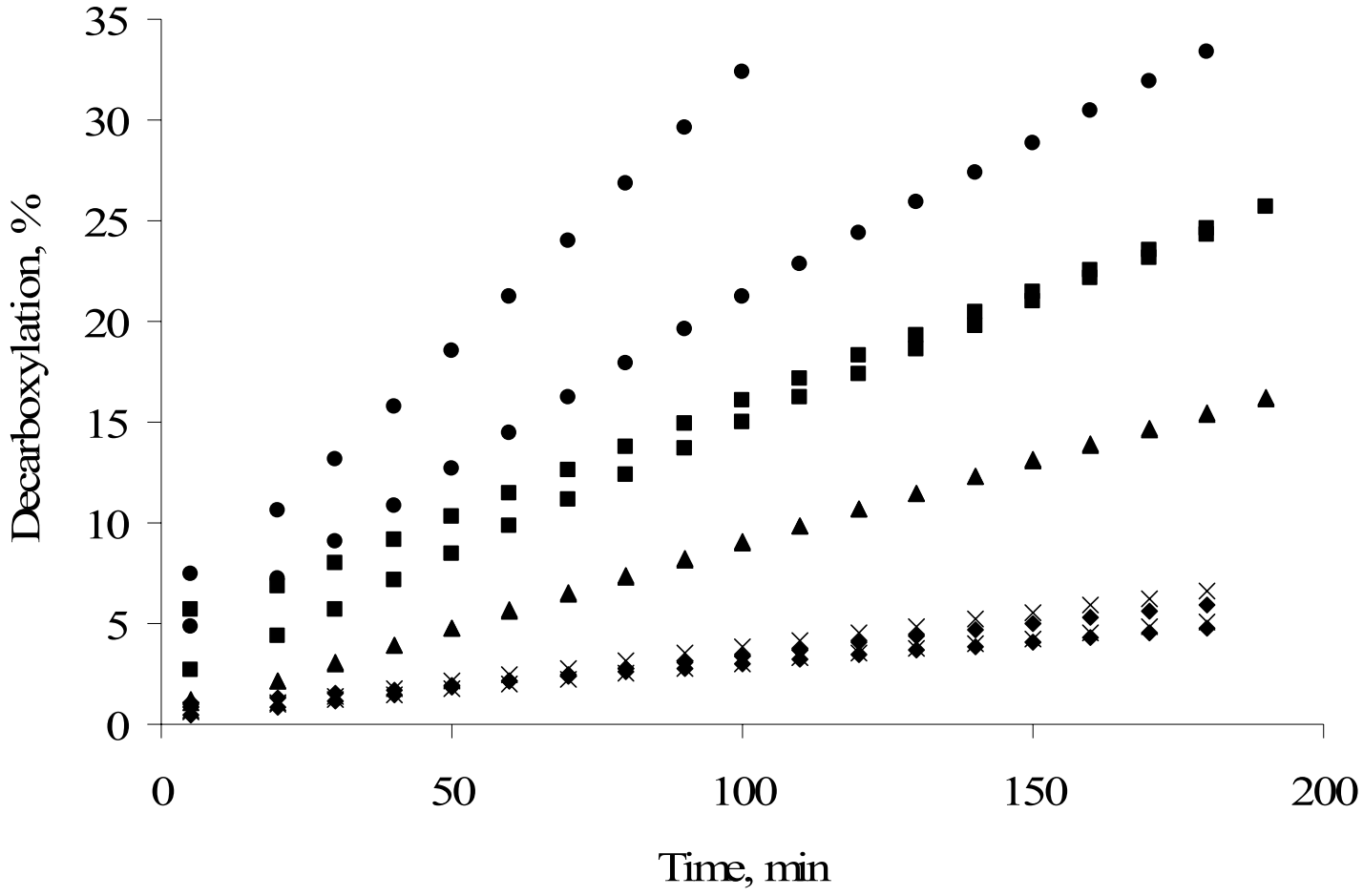

Figure A2.2. Duplicate Observed Decarboxylation Data of **2a**, **2b**, **2c**, **2d**, and **2h**.

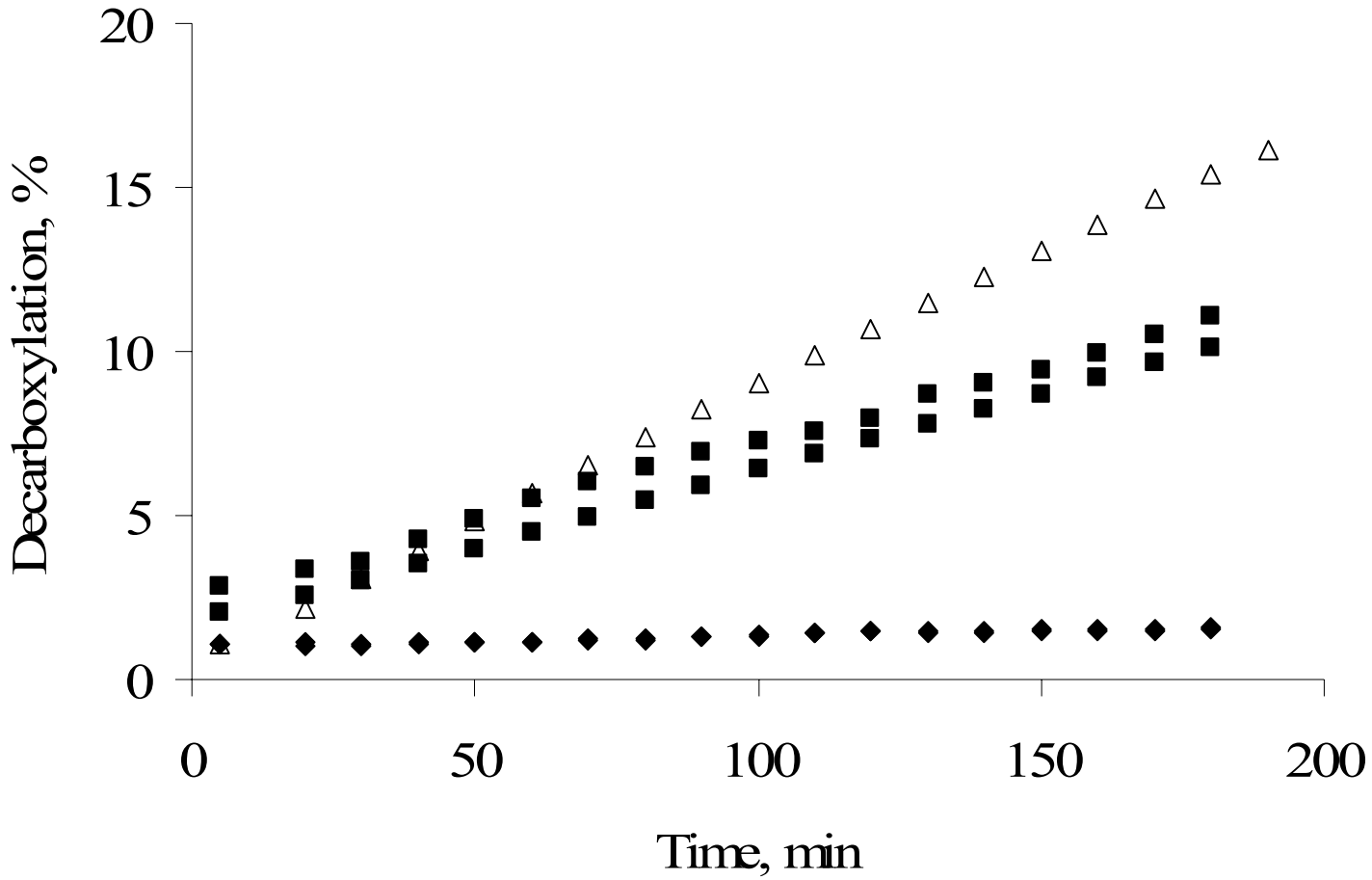

Figure A2.3. Duplicate Observed Decarboxylation Data of **2a**, **2f**, and **2g**.

Appendix 3: Selected Spectra from Chapter 4

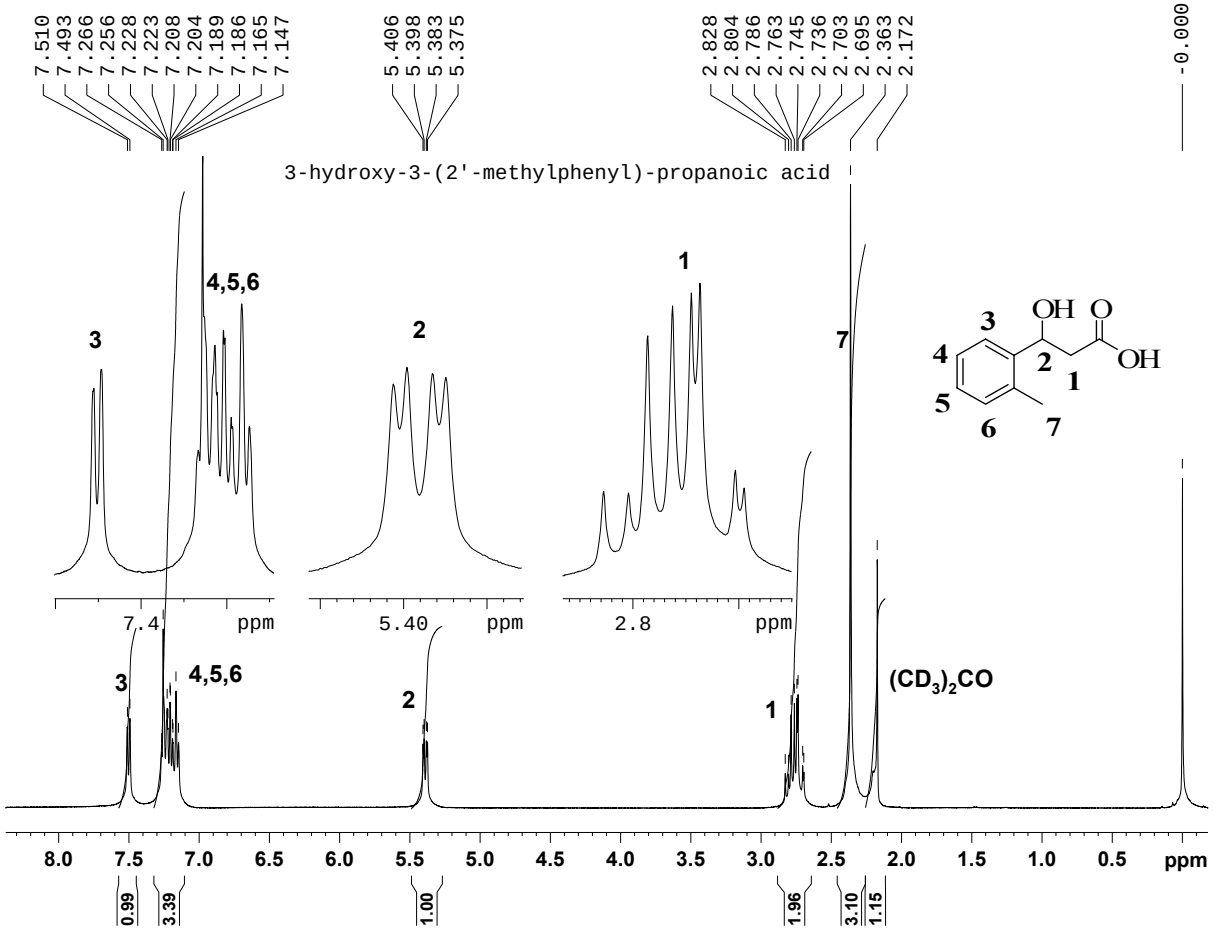

Figure A3.1. ^{1}H NMR spectrum of 3-hydroxy-3-(2'-methylphenyl)propanoic acid (**3d**) in $(CD_3)_2CO$.

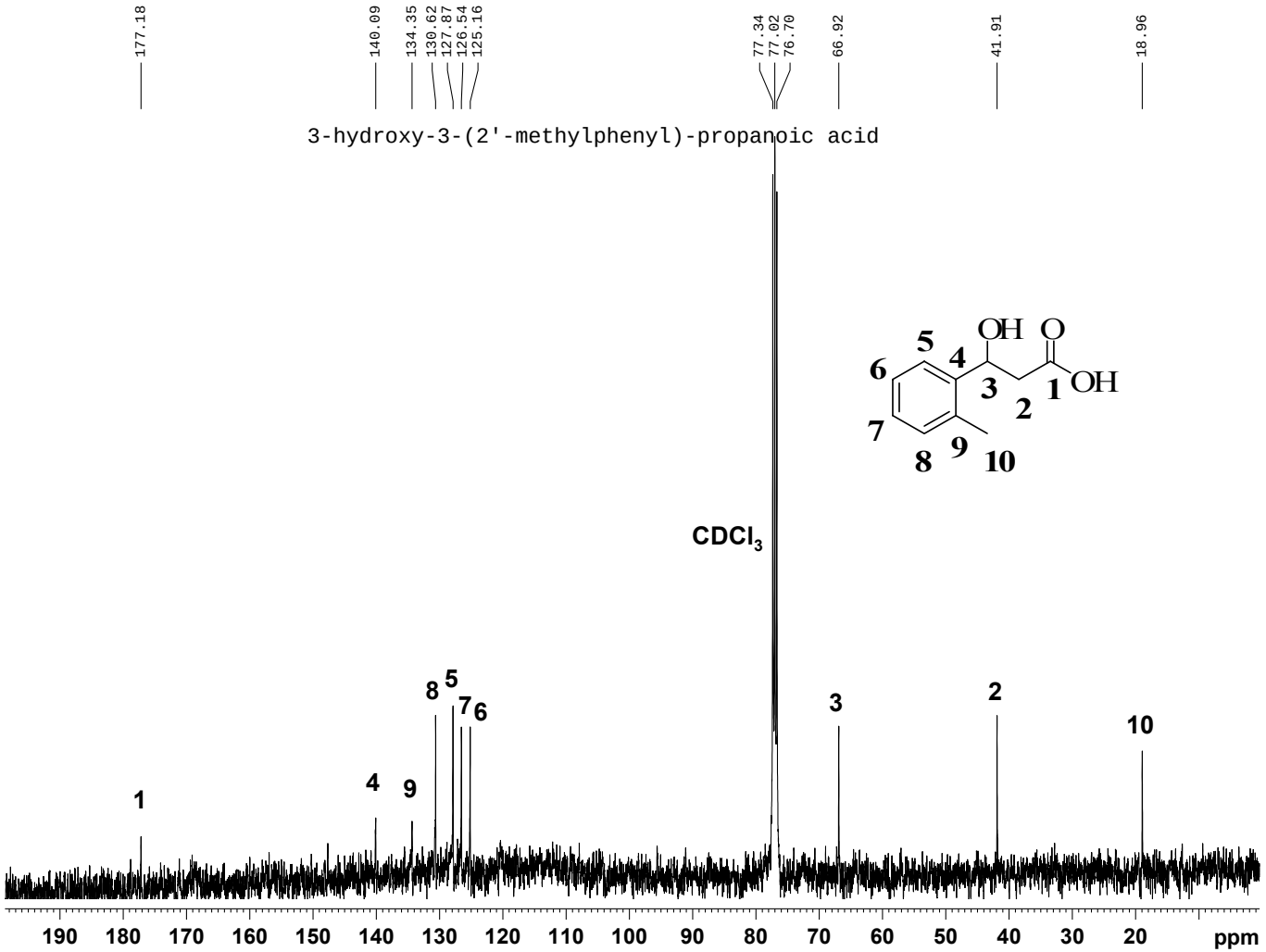

Figure A3.2. ^{13}C NMR spectrum of 3-hydroxy-3-(2'-methylphenyl)propanoic acid (**3d**) in $(CD_3)_2CO$.

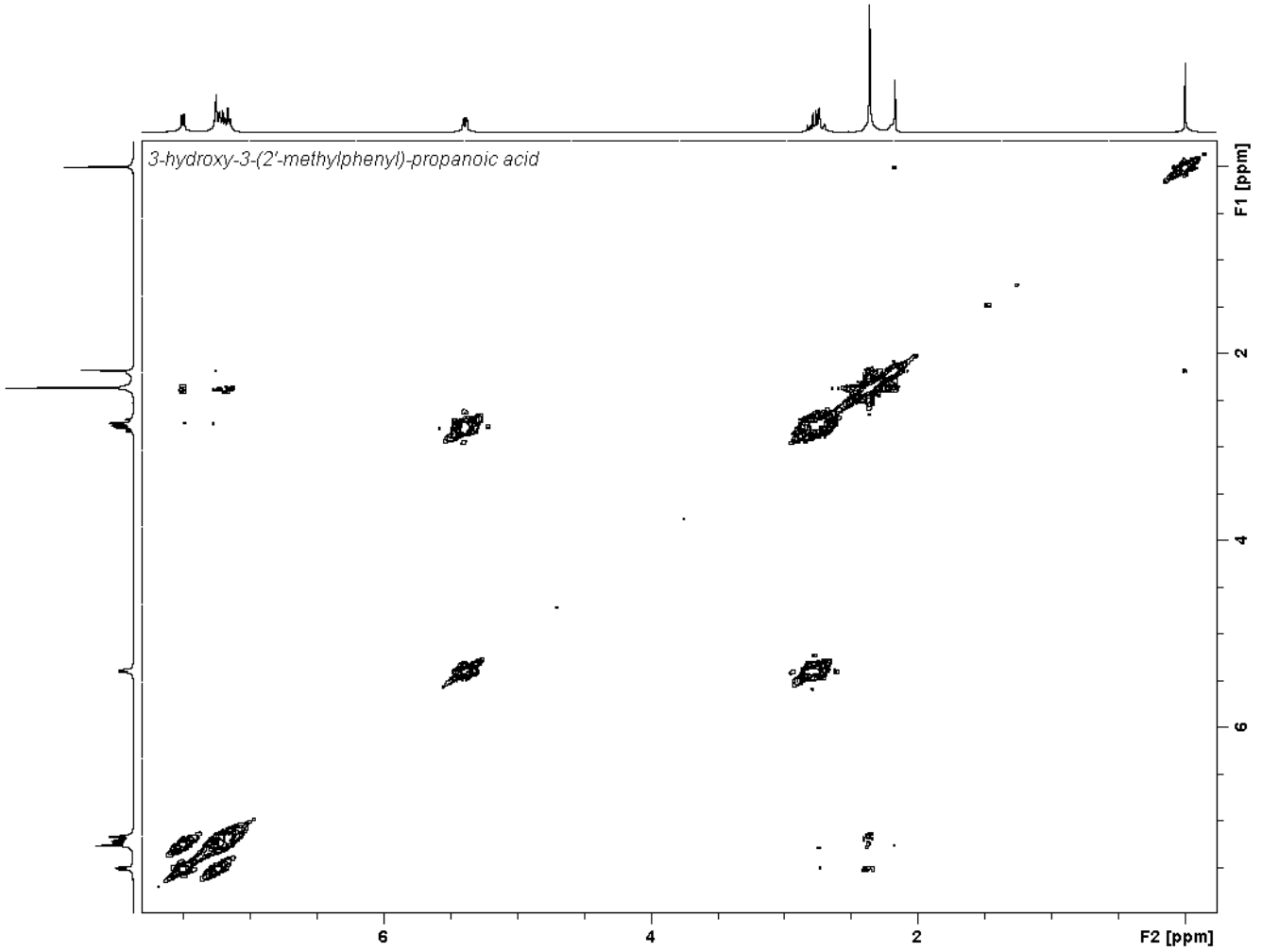

Figure A3.3. ^{1}H-^{1}H COSY NMR spectrum of 3-hydroxy-3-(2'-methylphenyl)propanoic acid (**3d**) in $(CD_3)_2CO$.

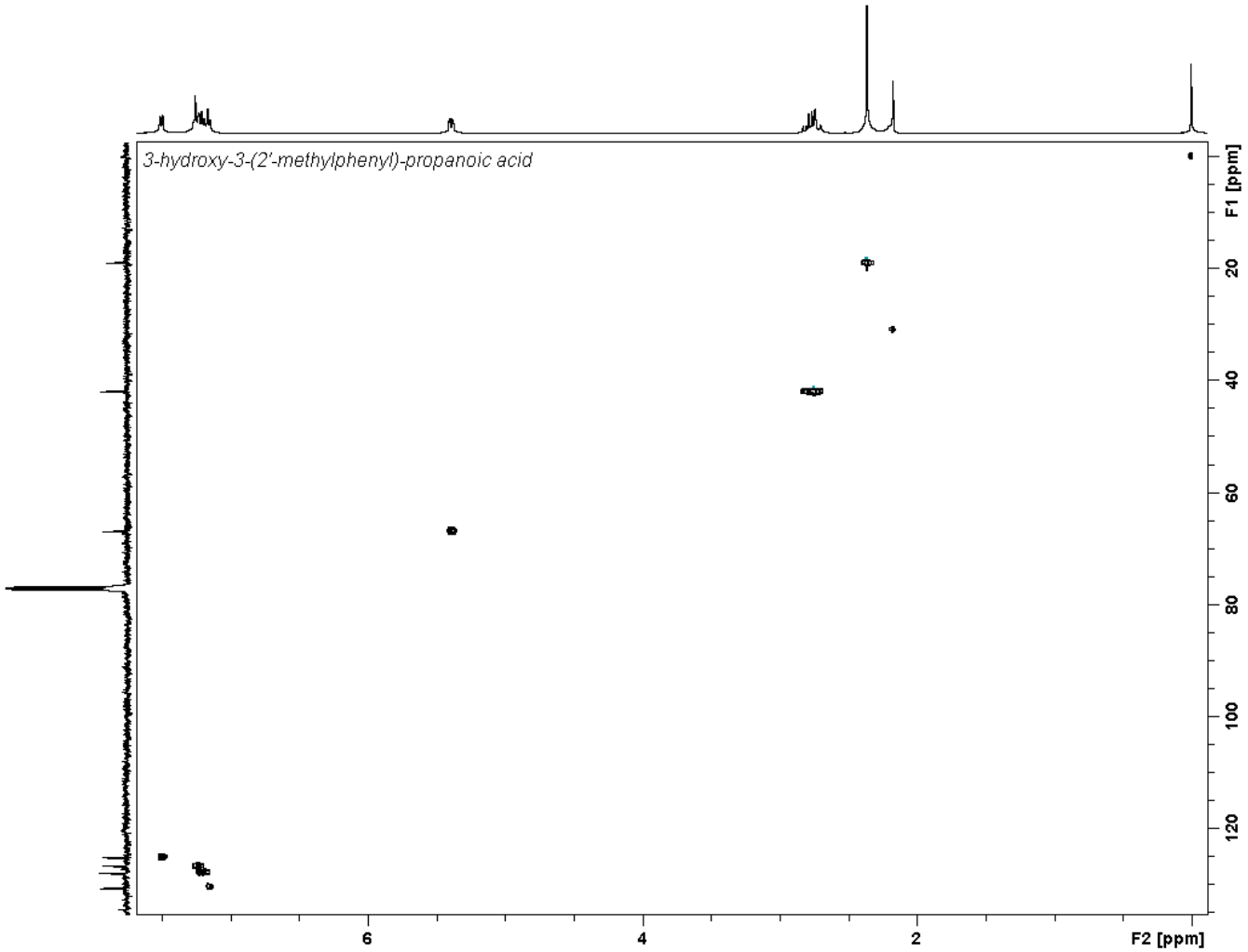

Figure A3.4. ^{1}H-^{13}C HSQC NMR spectrum of 3-hydroxy-3-(2'-methylphenyl)propanoic acid (**3d**) in $(CD_3)_2CO$.

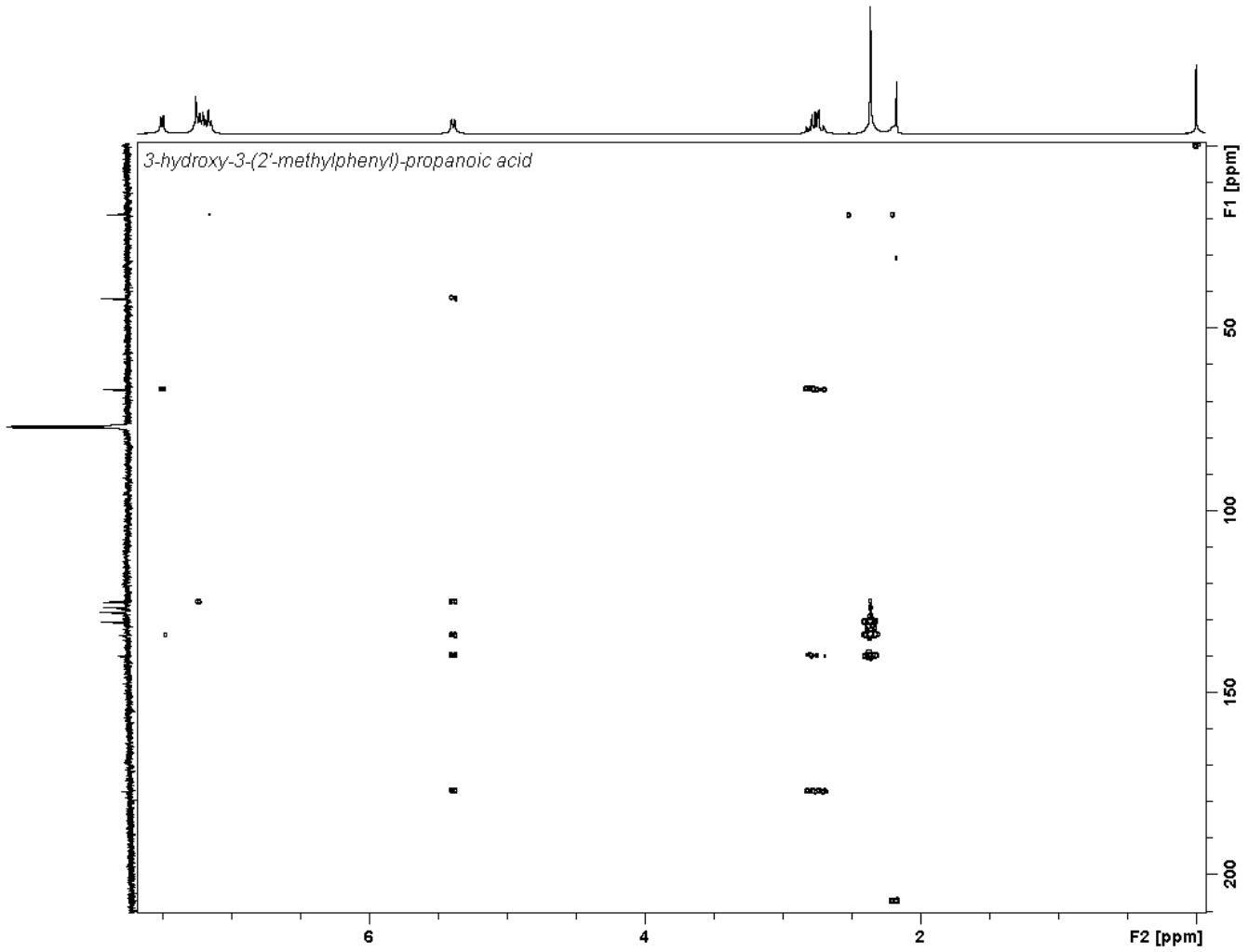

Figure A3.5. ^{1}H-^{13}C HMBC NMR spectrum of 3-hydroxy-3-(2'-methylphenyl)propanoic acid (**3d**) in $(CD_3)_2CO$.

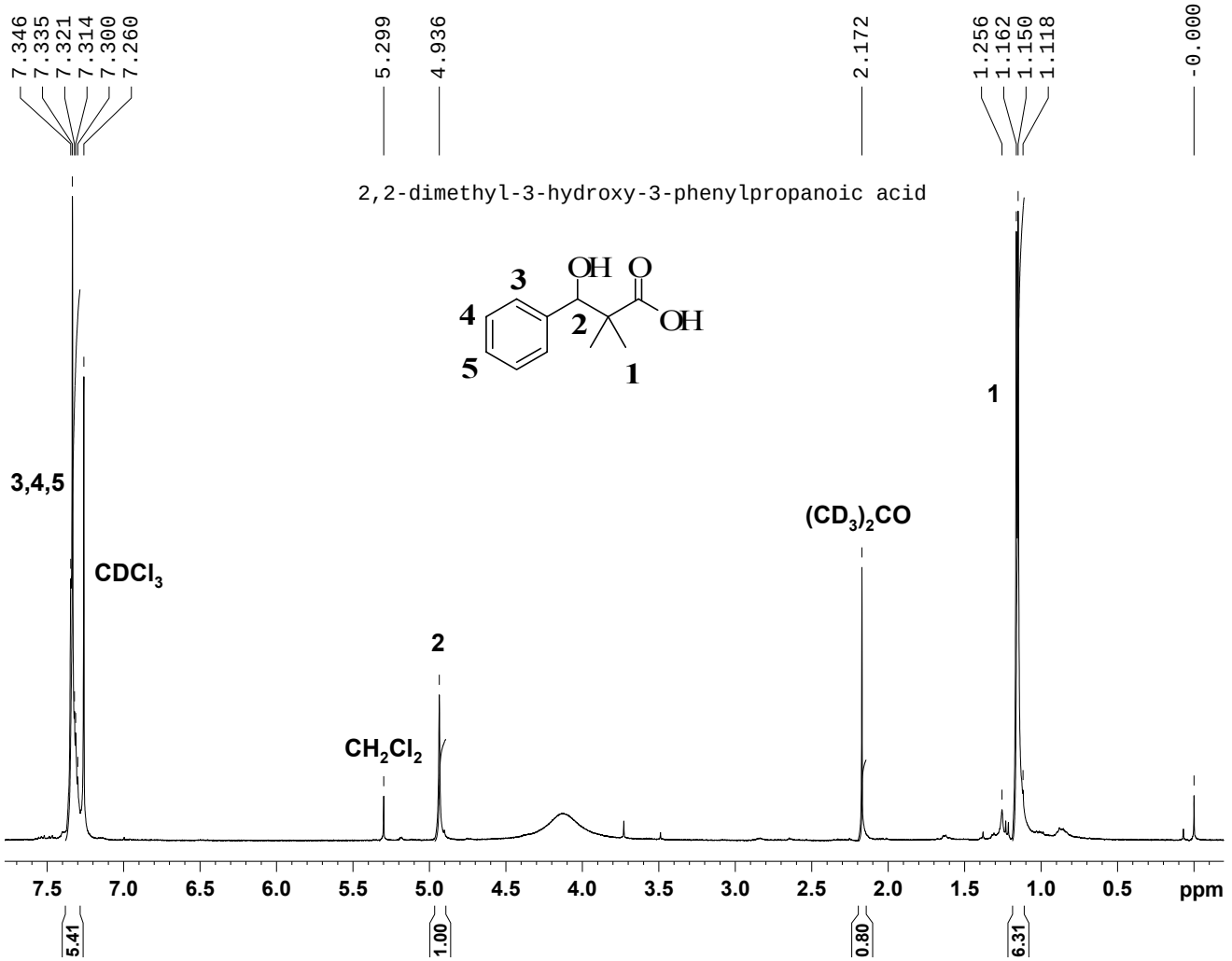

Figure A3.6. ^{1}H NMR spectrum of 3-hydroxy-2,2-dimethyl-3-phenylpropanoic acid (**3g**) in $(CD_3)_2CO$.

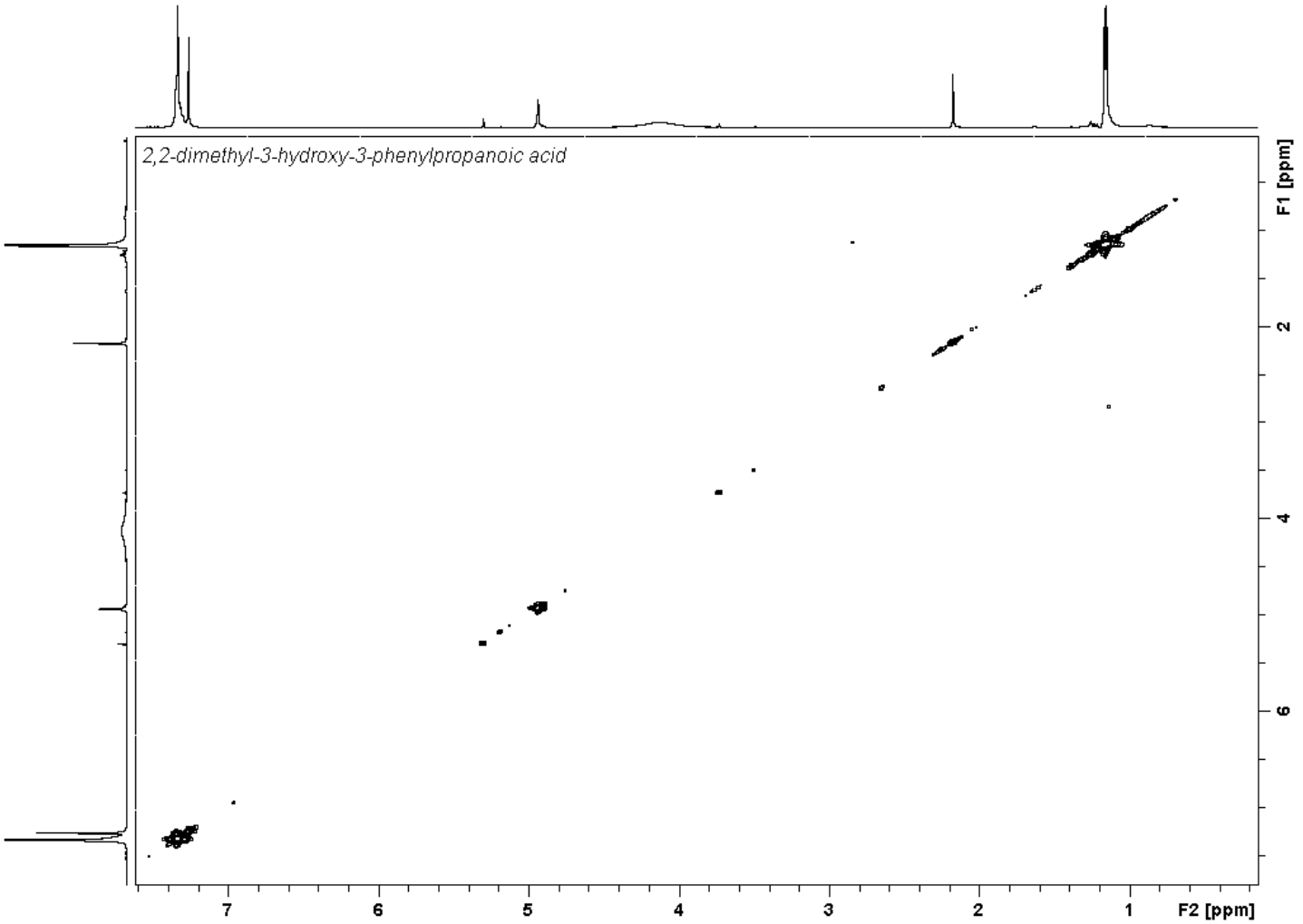

Figure A3.7. ^{1}H-^{1}H COSY NMR spectrum of 3-hydroxy-2,2-dimethyl-3-phenylpropanoic acid (**3g**) in $(CD_3)_2CO$.

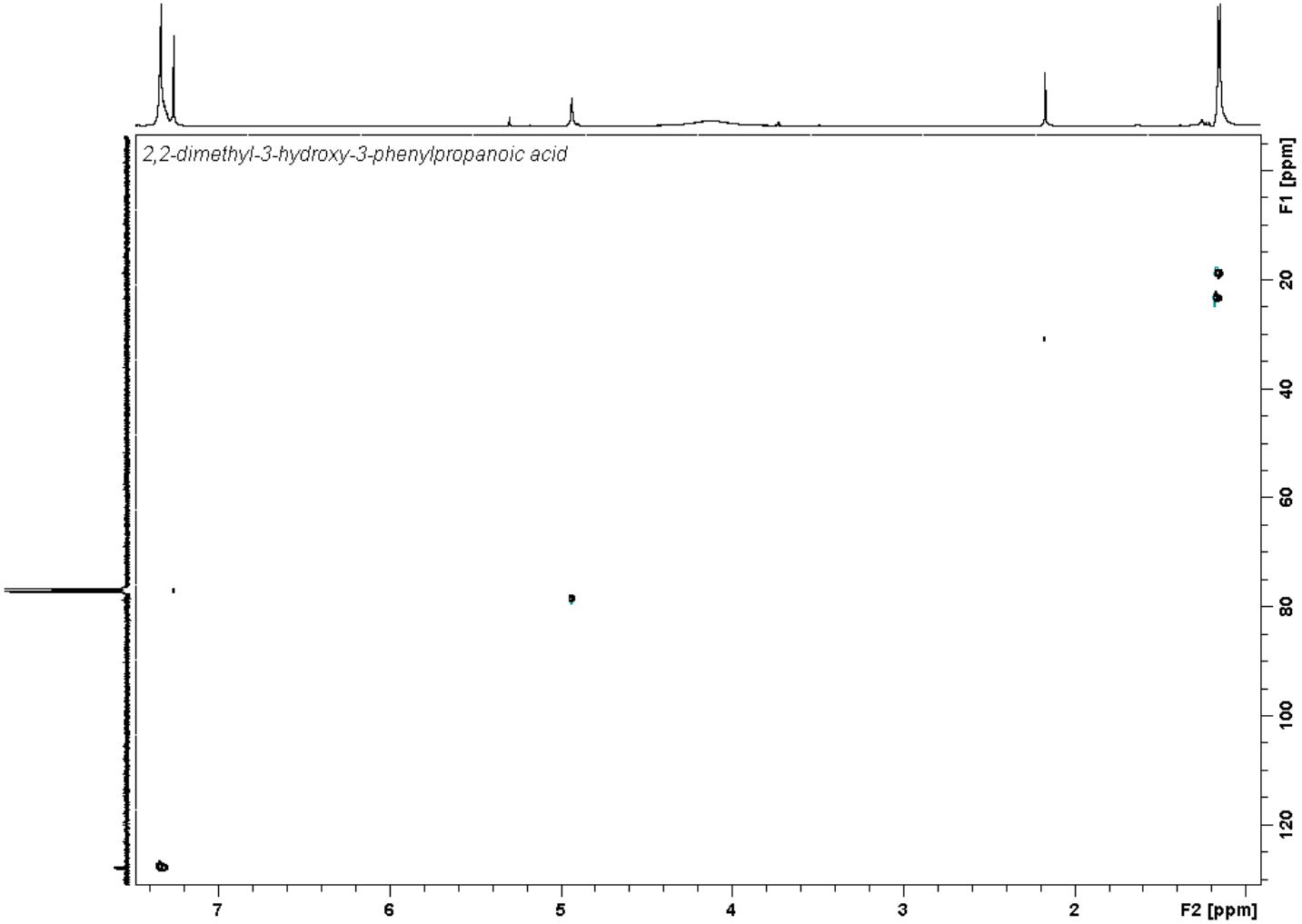

Figure A3.8. ^{1}H-^{13}C HSQC NMR spectrum of 3-hydroxy-2,2-dimethyl-3-phenylpropanoic acid (**3g**) in $(CD_3)_2CO$.

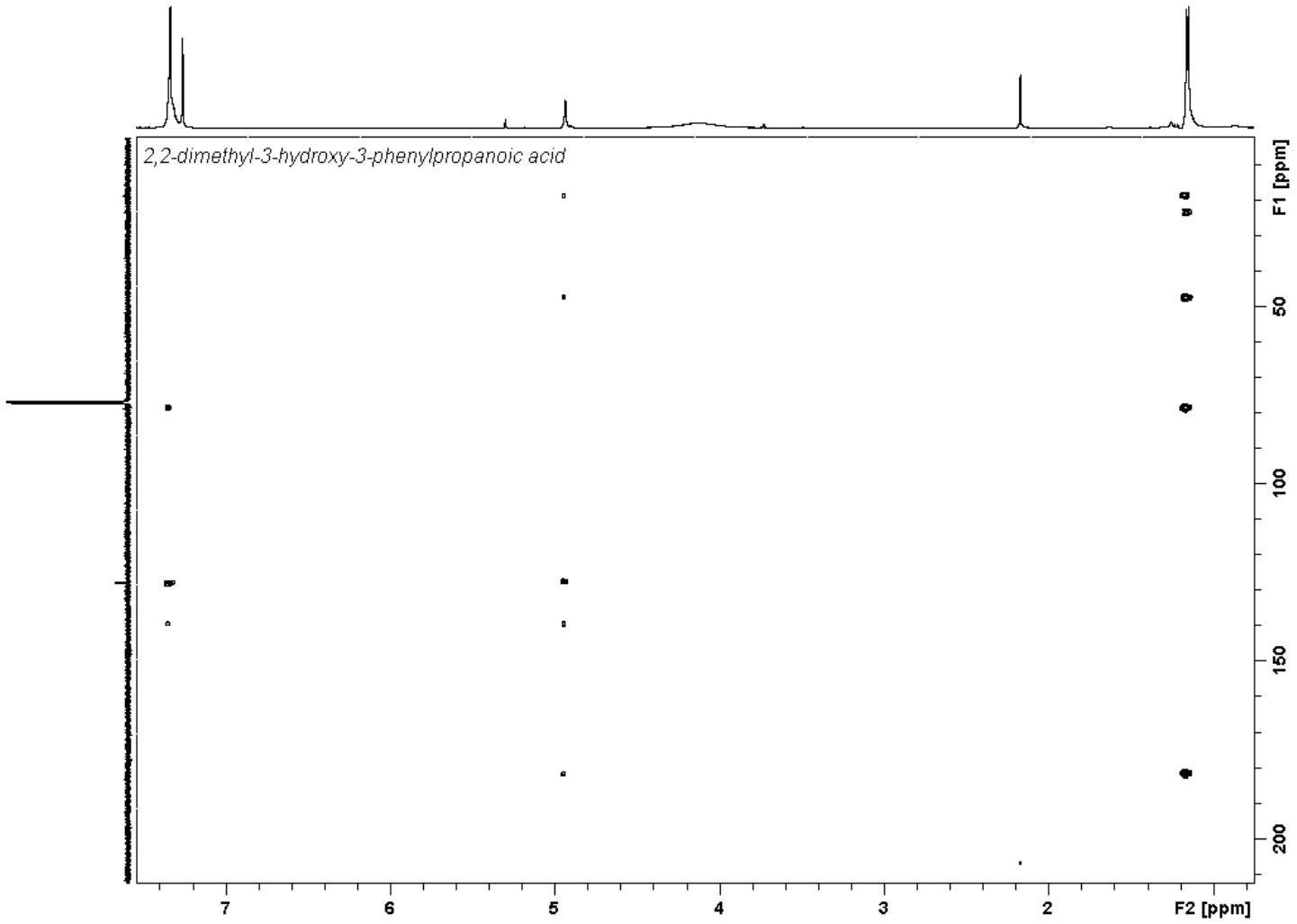

Figure A3.9. ^{1}H-^{13}C HMBC NMR spectrum of 3-hydroxy-2,2-dimethyl-3-phenylpropanoic acid (**3g**) in $(CD_3)_2CO$.

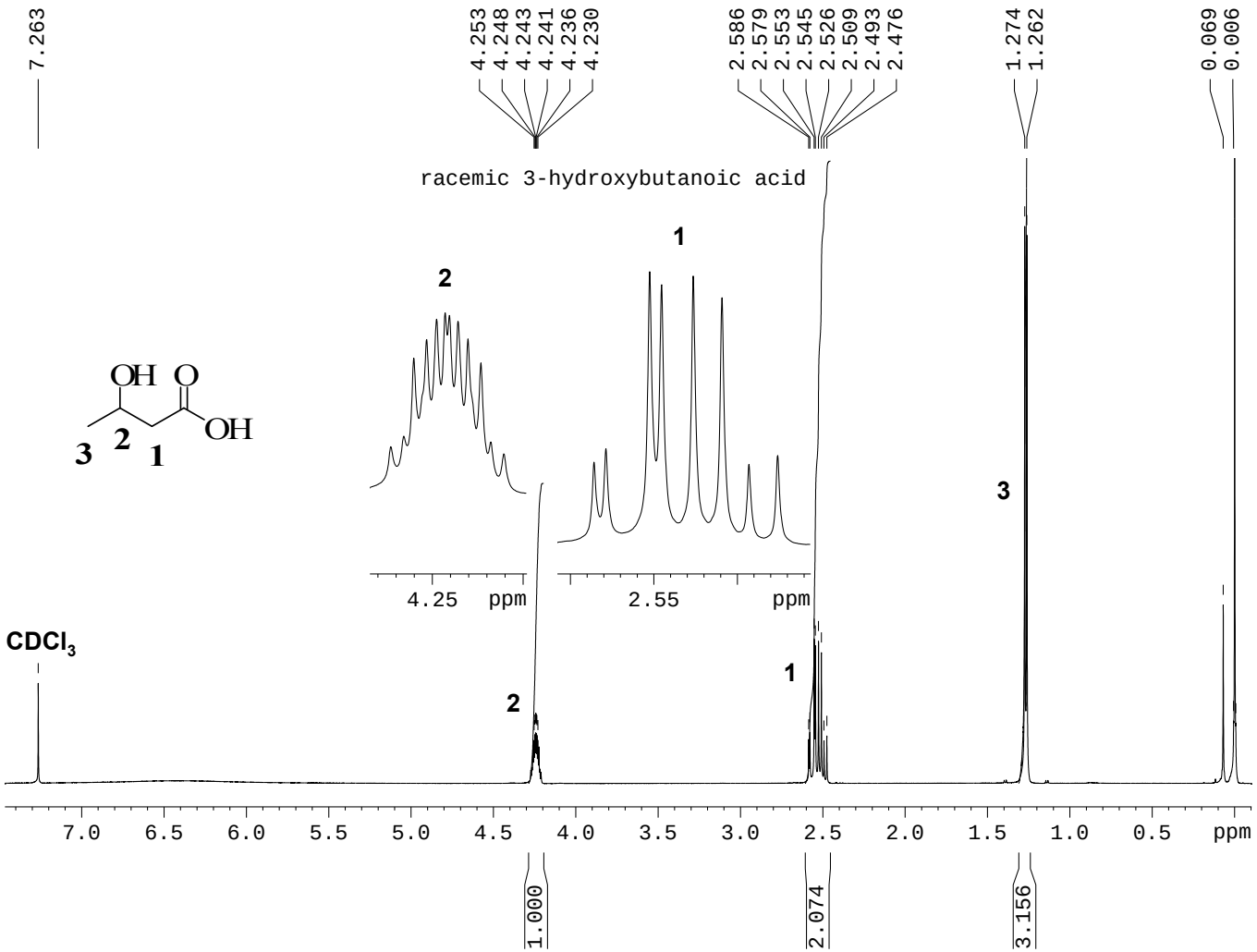

Figure A3.10. ^{1}H NMR spectrum of 3-hydroxybutanoic acid (**3h**) in $CDCl_3$.

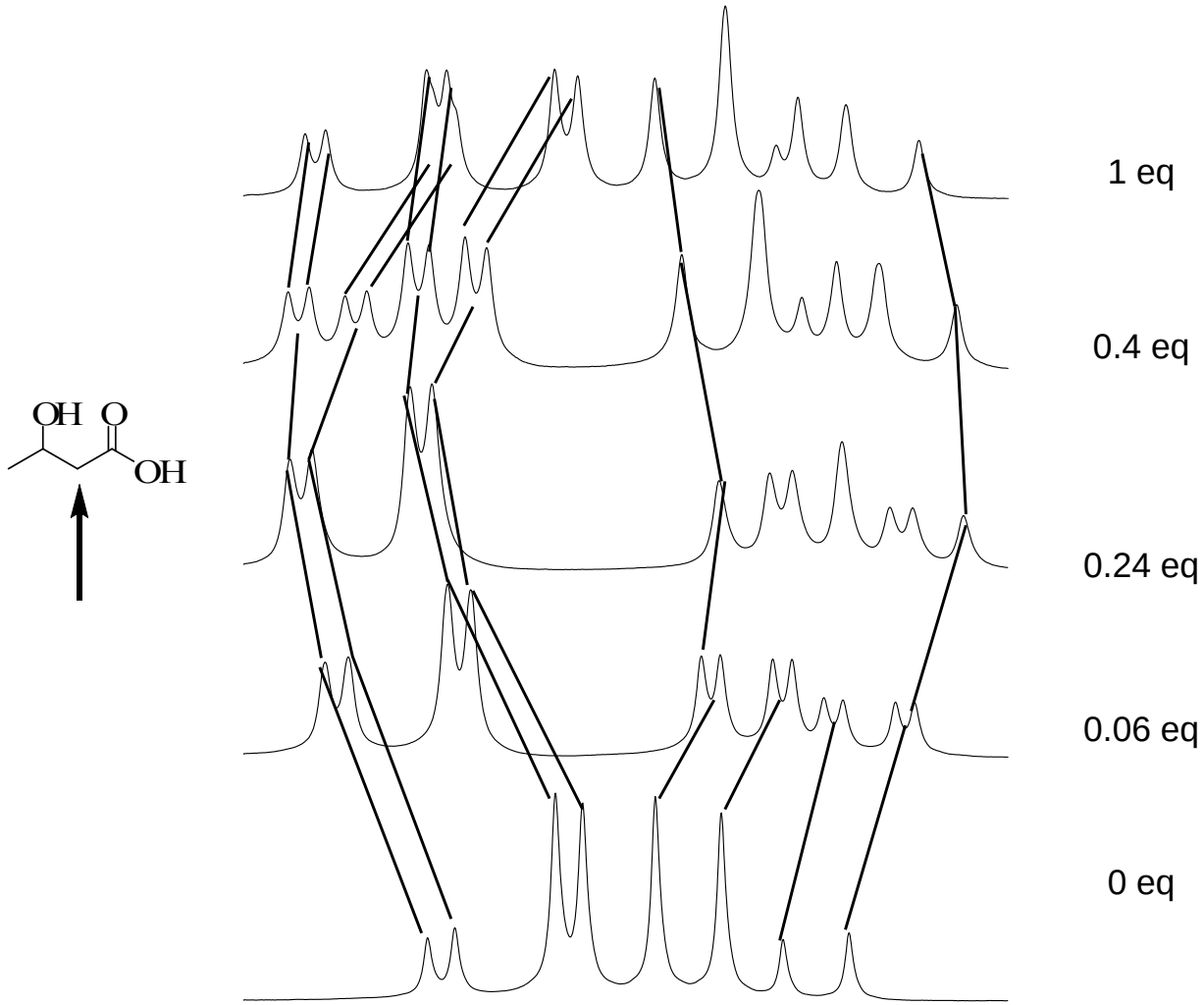

Figure A3.11. Observed splitting pattern for 3-hydroxybutanoic acid (**3h**) CH_2 moiety with (+)-alpha-methylbenzylamine in $CDCl_3$.

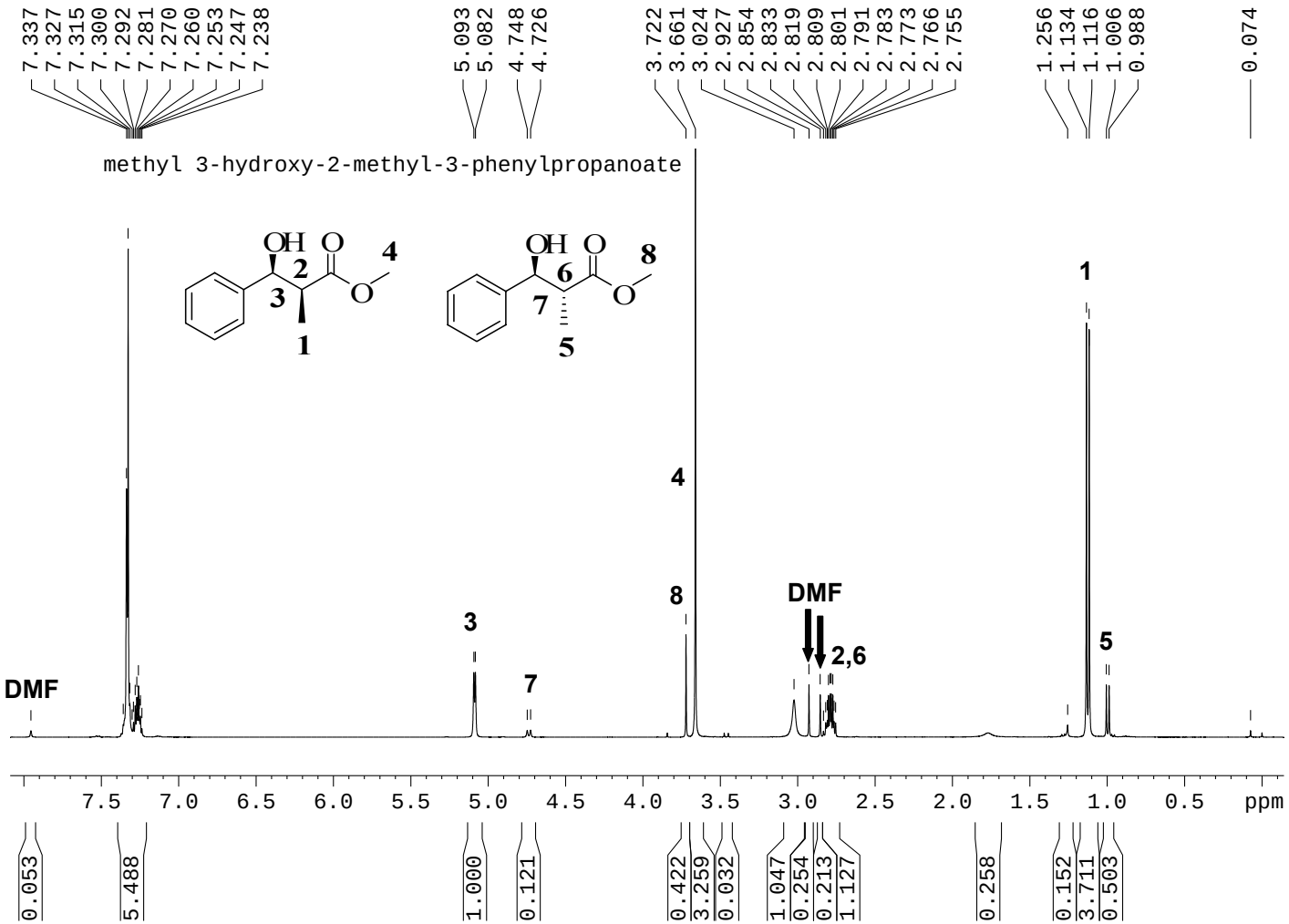

Figure A3.12. ^{1}H NMR spectrum of methyl ester of **3f** in $CDCl_3$.

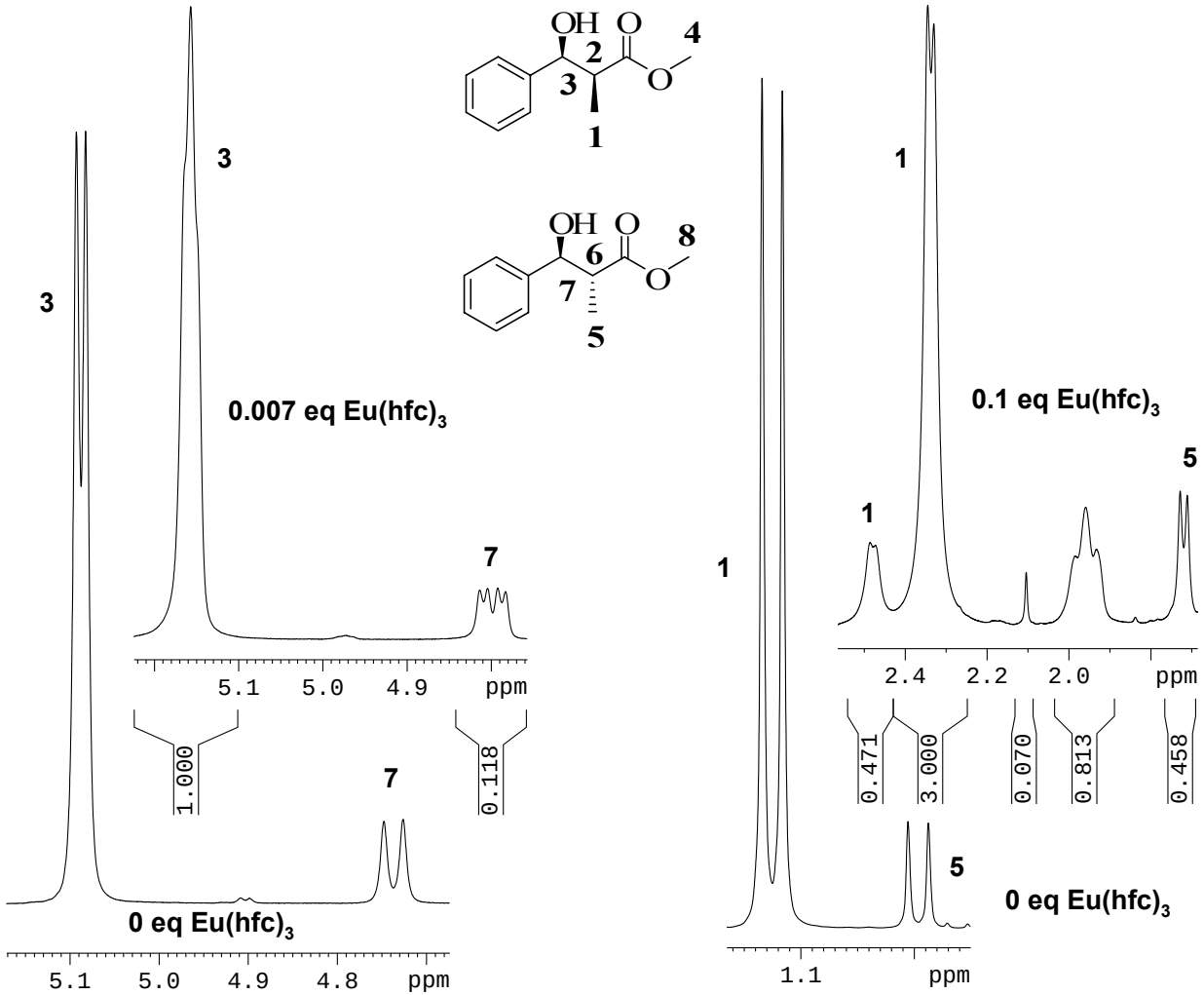

Figure A3.13. Observed splitting pattern for methyl ester of **3f** with $Eu(hfc)_3$ added in $CDCl_3$.