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Techniques for the Enantioselective Asymmetric Synthesis of Benzyl Substituted Malonic Acid Esters

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Techniques for the Enantioselective Asymmetric Synthesis of Benzyl Substituted Malonic Acid Esters

by

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ABSTRACT

A popular method for the enantioselective synthesis of substituted malonic half esters is hydrolysis via Pig Liver Esterase (PLE), however some substrates produce low enantiomeric excess, namely benzyl-substituted malonic esters. Presented here are alternative methods explored for this synthesis, the first being phase-transfer catalyzed hydrolysis via *N*-benzyl quaternary ammonium salts derived from cinchona alkaloids. The second method utilized chiral auxiliary directed benzylation with auxiliaries including menthol and oxazolidinones. Though unsuccessful, this research provided valuable groundwork in the investigation for the enantioselective asymmetric synthesis of benzyl-substituted malonic acid esters.

Keywords: Pig Liver Esterase, Enantioselectivity, Phase-Transfer Catalysis, Cinchona Alkaloids, Quaternary Ammonium Salts, Chiral Auxiliary, Menthol, Oxazolidinones

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LIST OF ILLUSTRATIONS

LIST OF ABBREVIATIONS

*	Denotes Chiral Center
APCI-MS	Atmospheric Pressure Chemical Ionization Mass Spectrometry
BnBr	Benzyl Bromide
$CDCl_3$	Deuterated Chloroform
$CHCl_3$	Chloroform
$(COCl)_2$	Oxalyl Chloride
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DI	Deionized
DIPA	Diisopropyl Amine
DMF	Dimethylformamide
DPPA	Diphenylphosphoryl Azide
ESI-MS	Electrospray Ionization Mass Spectrometry
EtOAc	Ethyl Acetate
EtOH	Ethanol
H_L	Hydrophobic Large
H_s	Hydrophobic Small
HCl	Hydrochloric Acid
HPLC	High Performance Liquid Chromatography
IPA	Isopropyl Alcohol
IR	Infrared
KOH	Potassium Hydroxide

LDA	Lithium Diisopropylamide
LiOH	Lithium Hydroxide
MeOH	Methanol
$MgSO_4$	Magnesium Sulfate
MRG	Masterson Research Group
n-BuLi	*n*-Butyl Lithium
NaH	Sodium Hydride
$NaHCO_3$	Sodium Bicarbonate
$NaHSO_4$	Sodium Bisulfate
NH_4Cl	Ammonium Chloride
NMR	Nuclear Magnetic Resonance
P_B	Polar Back
P_F	Polar Front
PLE	Pig Liver Esterase
PMA	Phosphomolybdic Acid
ppm	Parts Per Million
PTC	Phase-Transfer Catalyst
RIC	Reconstructed Ion Chromatogram
$SOCl_2$	Thionyl Chloride
TBAB	Tetrabutylammonium Bromide
TEA	Triethanolamine
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography

CHAPTER I: INTRODUCTION

It is widely known that the function and properties of many biologically active molecules are heavily dependent upon their structure and three-dimensional orientation. Influencing their shape are often quaternary carbon stereocenters containing four different substituents. Due to steric hinderance and the necessity of building a carbon-carbon bond, their construction in a desired three-dimensional orientation had been a daunting task until recent developments in chemical catalysis.[1]

Some small molecules containing chiral centers serve as precursors for the synthesis of macromolecules, including the most abundant and functionally versatile, proteins.[2] Responsible for their structure are monomeric subunits, known as amino acids, that covalently bond together to form a peptide chain. The genetic information within cells is able to code for 20 common amino acids, who all share common structural features that are depicted in Figure 1.[3]

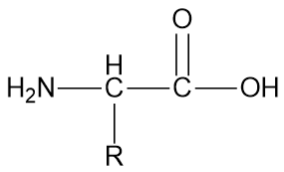
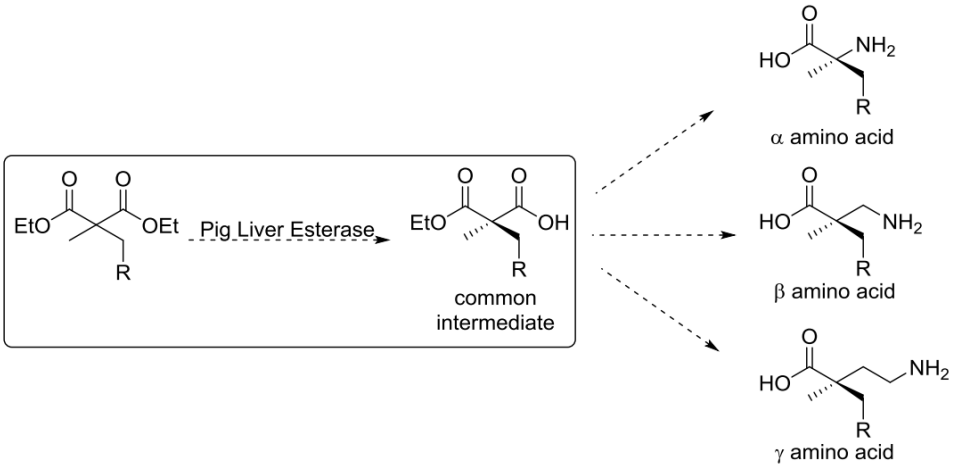


Figure 1. General structure of a proteinogenic, α-amino acid.

Popular in modern drug development is the use of non-proteinogenic, or unnatural, amino acids due to their structural and functional diversity and versatility.[5] Peptide drugs developed from these amino acids have proven successful in treating human diseases such as breast and prostate cancer, multiple sclerosis, and type 2 diabetes.[6] In vitro, both proteinogenic and non-proteinogenic amino acids may be

synthesized by the hydrolysis of malonic esters into enantioenriched half-esters, followed by installation of the amine by using diphenylphosphoryl azide (DPPA) to convert to an acyl azide, and a Curtius rearrangement to produce an isocyanate intermediate before generating the amino acid.[7, 30] A primary focus of the Masterson Research Group is the use of the serine protease Pig Liver Esterase (PLE) in this hydrolysis, forming the quaternary carbon center with relatively high enantioselectivity in most cases, as summazrized in Scheme 1.[4]



Scheme 1. Unnatural amino acid synthesis from enantioenriched half-ester intermediate.[4]

Despite PLE's favorability, certain substrates exhibit lower enantioselectivity likely due to their ability to bind to multiple sites within the active site, which was modeled by Jones et al. in 1990 and is shown in Figure 2.

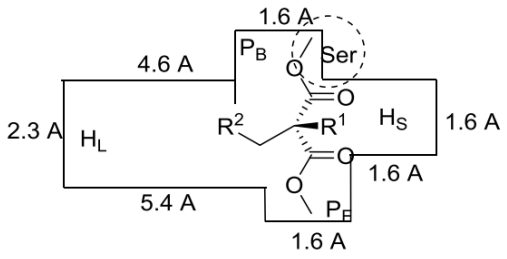
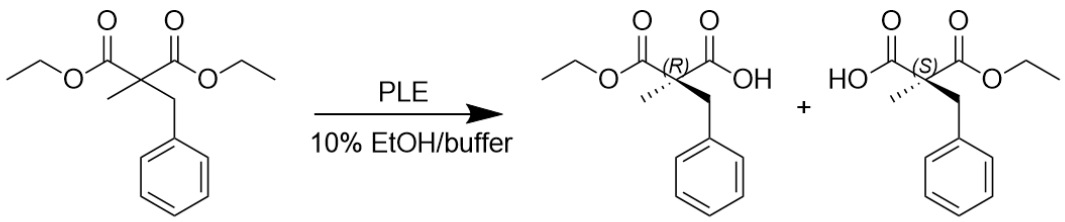


Figure 2. Jones Active Site Model fitted with a generic substrate.[4]

Within the Jones Active Site Model are four pockets, two of which are hydrophobic (H_L and H_S, hydrophobic large and hydrophobic small, respectively) while the remaining two are polar (P_F and P_B, polar front and polar back, respectively).[26] The serine residue performing the hydrolysis is thought to be located near the polar back (P_B) pocket, where the ester to be hydrolyzed fits, directing the remainder of the molecule to fill the remaining pockets.

As shown in Scheme 2, when hydrolyzed with PLE, the phenylalanine precursor 2-benzyl-2-methyl-malonic acid diethyl ester produces only a maximum enantiomeric excess of 17%.[4] It is proposed that, though hydrophobic, the benzyl side chain is small enough to fit in either hydrophobic pocket, resulting in near racemic hydrolysis.



Scheme 2. Hydrolysis of 2-benzyl-2-methyl-malonic acid diethyl ester with PLE and EtOH cosolvent, resulting in enantioenriched half esters.

Therefore, to create an enantiopure quaternary carbon center for the named substrate, other synthesis methods must be investigated. Presented here are several methods that were explored for more efficient enantioselective asymmetric synthesis of benzyl-substituted malonic half ester, including the use of phase-transfer catalysts and chiral auxiliaries.

Phase-Transfer Catalysis

A topic of growing popularity in synthetic organic chemistry is the use of phase transfer catalysts (PTCs) to allow for the migration of reactants between two non-miscible systems (i.e., aqueous and organic phases). Like PLE, these catalysts have been promoted in the practice of "green chemistry", which aims to reduce reaction time, the use of organic solvents, and the production of hazardous waste. PTCs satisfy these requirements because they often utilize water as a solvent and avoid the use of toxic heavy metals employed in other synthetic methods.[8, 9]

Specifically, chiral PTCs allow for the selective synthesis of one enantiomeric form of a desired product, and catalysts especially functional in hydrolysis reactions include the biologically derived cinchona alkaloids, shown in Figure 3.[10-12]

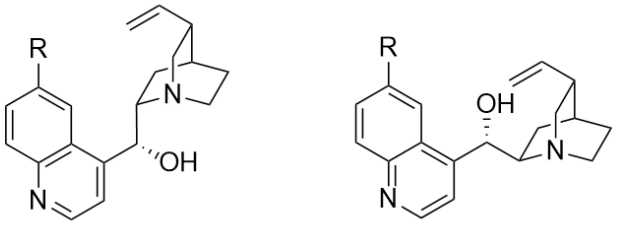


Figure 3. Four types of cinchona alkaloids.[27]

The first successful application of cinchona alkaloids in organocatalysis was reported in the 1970s in the asymmetric dihydroxylation of olefins. The tertiary amine of the alkaloid was later derivatized to provide quaternary ammonium salts that served as PTCs in the 1980s. Essentially, this quaternary ammonium cation forms an ionic complex with a nucleophile at the interphase of the organic and aqueous phases to provide the resulting products while generating a chiral environment where the least sterically hindered face is targeted by the nucleophile. Types of cinchona-based PTCs include *N*-Benzyl, *N*-9-Anthracenylmethyl, polymeric, electronic factor-based, and solid-supported, which are depicted in Figure 4.[27]

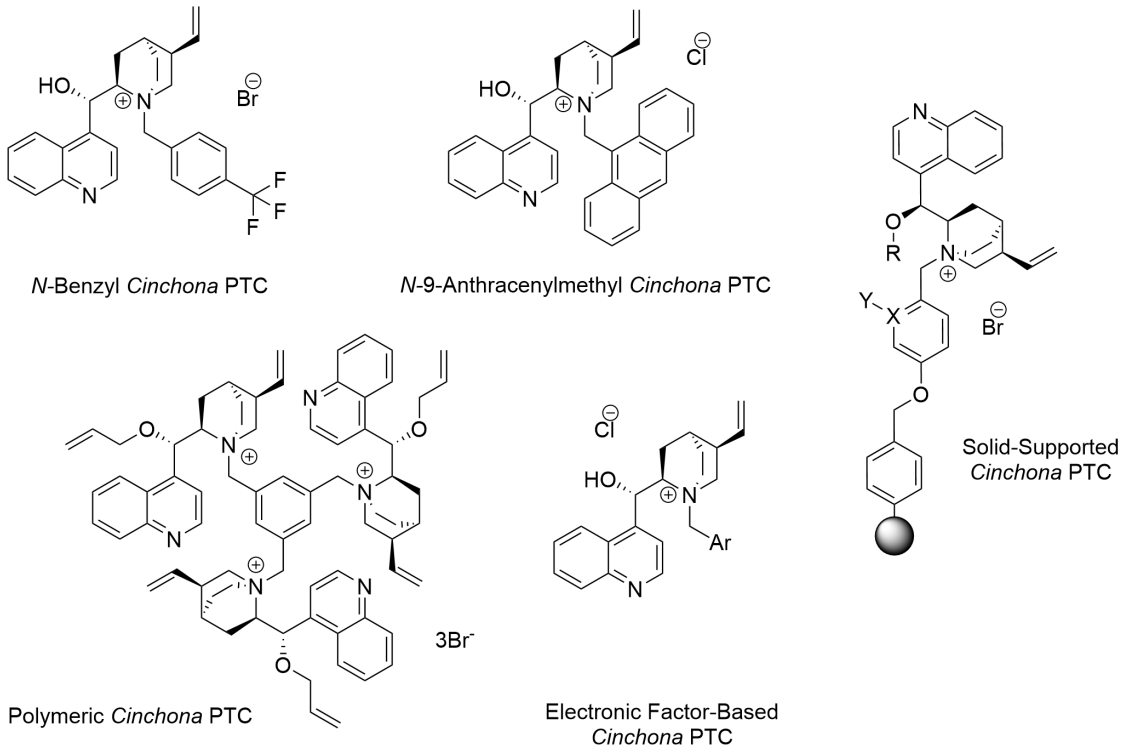
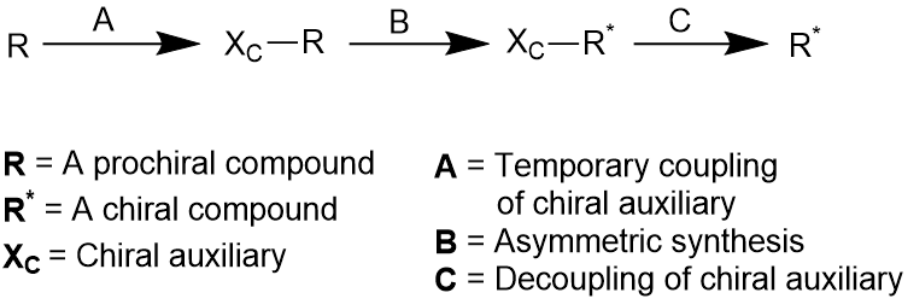


Figure 4. Types of cinchona-derived PTCs.[27]

These PTCs have been utilized in a wide variety of reactions including alkylation, Mannich reactions, Aldol reactions, hydrolysis, fluorination, and trifluoromethylation, but have remained most popular in alkylation.[10]

Chiral Auxiliaries

While catalyzed hydrolysis of prochiral compounds is a widely effective method in the synthesis of stereogenic quaternary centers and is preferred due to its lack of intermediate, it does not always produce desirable yields. Instead, another popular method based on traditional enolate chemistry, summarized in Scheme 3, may be employed: auxiliary-controlled alkylation.[14] This approach involves the temporary coupling of a chiral auxiliary to a prochiral compound to influence the stereoselectivity of a future reaction, in this case benzylation, followed by its subsequent removal and production of an enantiopure product.[13]



Scheme 3. General mechanism of chiral auxiliaries.[13]

Seminal work reported the formation of nonracemic stereogenic centers in enolates via auxiliary-directed alkylation using menthol and oxazolidinones as chiral auxiliaries, and an emerging method introduces imidazolidinones.[14, 21-25] Menthol, as depicted in Figure 5, is a naturally occurring crystalline monoterpenoid obtained from the

oils of mint species. It exists in nature as one pure stereoisomer, which is assigned the (1*R*, 2*S*, 5*R*) configuration.

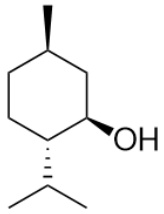


Figure 5. Natural menthol structure.

To date, a menthol ester auxiliary has only been employed once for use on malonates as reported by Ihara, et al., which utilized (-)-8-phenylmenthol.[21] Due to availability in laboratory stock, naturally occurring (-)-menthol was sampled for use in this project. The use of oxazolidinones, a synthetic chemical class with anti-microbial properties whose general structure is shown in Figure 6, was also explored due to their reported success by Evans.[22, 23, 28]

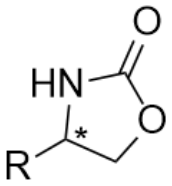


Figure 6. Generic structure of oxazolidinones.

Finally, imidazolidinones, a class of heterocycles related to imidazole with either a urea or amide functional group whose structures are shown in Figure 7, have been used in catalysis and the chiral auxiliary directed alkylation of malonates and are promising for use in the formation of 2-benzyl-2-methyl-malonic acid diethyl ester.[14, 29]

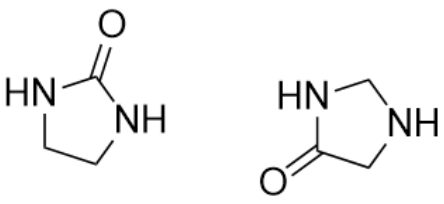


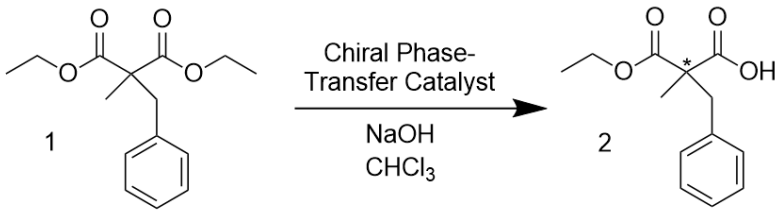
Figure 7. Structures of 2-imidazolidinone and 4-imidazolidinone.

These chiral auxiliaries, along with the phase transfer catalysts described above, were selected for use in this investigation, whose methods are described in the following chapter.

CHAPTER II: METHODOLOGY

Method 1: Cinchona-Derived Chiral Phase Transfer Catalysts

The first attempt in the enantioselective synthesis of benzyl-substituted malonic acid esters employed the use of cinchona alkaloids as chiral, asymmetric phase transfer catalysts in the hydrolysis of the synthesized substrate, as summarized in Scheme 4, due to their ability to interact with the organic phase, containing the substrate, and the aqueous phase, where hydrolysis occurs.



Scheme 4. General hydrolysis of substrate with chiral phase-transfer catalyst resulting in chiral half ester.

N-benzyl cinchona derived catalysts *N*-(4-trifluoromethylbenzyl)cinchoninium bromide, *N*-(2,3,4,5,6-pentafluorobenzyl)cinchoninium bromide, *N*-(4-methylbenzyl)cinchoninium bromide, *N*-benzylcinchoninium bromide, and *N*-(2-cyanobenzyl)cinchoninium bromide were selected for use in this project due to their reported success in catalyzing similar reactions and availability of materials for their synthesis.[15,17-20] The structure of the selected catalysts is summarized in Figure 8.

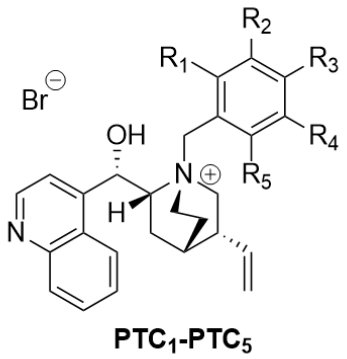


Figure 8. General structure of cinchona-derived phase transfer catalysts.

Entry	*Catalyst*	*R_1*	*R_2*	*R_3*	*R_4*	*R_5*
PTC_1	*N*-(4-Trifluoromethylbenzyl)cinchoninium bromide	H	H	CF_3	H	H
PTC_2	*N*-(2,3,4,5,6-Pentafluorobenzyl)cinchoninium bromide	F	F	F	F	F
PTC_3	*N*-(4-Methylbenzyl)cinchoninium bromide	H	H	CH_3	H	H
PTC_4	*N*-benzylcinchoninium bromide	H	H	H	H	H
PTC_5	*N*-(2-cyanobenzyl)cinchoninium bromide	CN	H	H	H	H

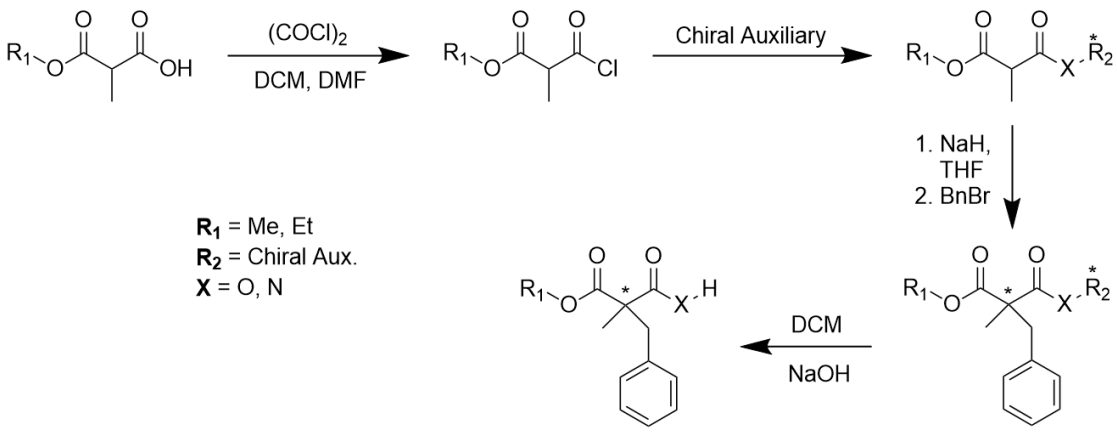
Table 1. Summary of cinchona-derived phase transfer catalyst R-groups.

To serve as a reference for enantiomeric excess determination in subsequent reactions with the catalysts, a racemic hydrolysis was performed on the synthesized substrate. The catalysts were then used in catalytic amounts of 10 and 25 mol %. Additionally, controls with less bulky materials—Aliquat® 336 and tetrabutylammonium bromide in place of the chiral PTC and diethyl 2-methylmalonate in place of substrate—were performed to confirm the efficacy of phase transfer catalysis. Results of these hydrolyses were analyzed using ^{1}H-NMR, infrared (IR) spectroscopy, chiral high-

performance liquid chromatography (HPLC), and atmospheric-pressure chemical ionization mass spectrometry (APCI-MS).

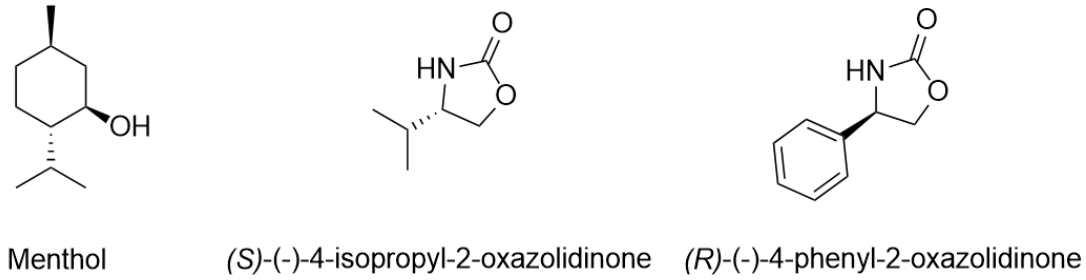
Method 2: Chiral Auxiliaries

The second method employed the use of chiral auxiliaries, requiring an adjustment of starting material. Instead of hydrolyzing the already benzyl-substituted malonic diester, an unsubstituted malonic half ester was coupled with a chiral auxiliary before benzylation, upon which later removal of the auxiliary may be performed. The general mechanism employed in this method is summarized in Scheme 5.



Scheme 5. General mechanism of chiral auxiliaries.

Chiral auxiliaries especially effective for use on malonates are menthol, oxazolidinones, and imidazolidinones, whose structures are depicted in Figure 9.[14, 21-25] Due to supply chain restrictions resulting from the COVID-19 pandemic, only menthol and two oxazolidinones, *(S)*-(-)-4-isopropyl-2-oxazolidinone and *(R)*-(-)-4-phenyl-2-oxazolidinone, were explored.



Menthol *(S)*-(-)-4-isopropyl-2-oxazolidinone *(R)*-(-)-4-phenyl-2-oxazolidinone

Figure 9. Structures of chiral auxiliaries used.

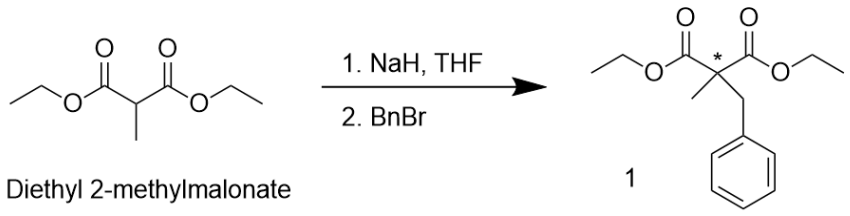
Detailed procedures for syntheses, phase-transfer catalyzed hydrolyses, chiral auxiliary directed benzylations, and subsequent analyses are defined in the following chapter.

CHAPTER III: EXPERIMENTAL

General

All reagents were provided by commercial sources and used as received. Anhydrous solvents were dried using an Innovative Technology PurSolv solvent purification system. Flash column chromatography was performed with Sorbent Technologies P-60 silica gel. NMR spectra were obtained with a 400 MHz Bruker NMR. Electrospray ionization mass spectrometry (ESI-MS) and Atmospheric-Pressure Chemical Ionization Mass Spectrometry (APCI-MS) were performed on a ThermoFinnigan LXQ ESI-Ion trap mass spectrometer. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were obtained on a Thermo Nicolet Nexus 470 FT-IR instrument. Catalysts **PTC_4** and **PTC_5** were provided by MRG member Allyson Bullock.

Substrate Synthesis

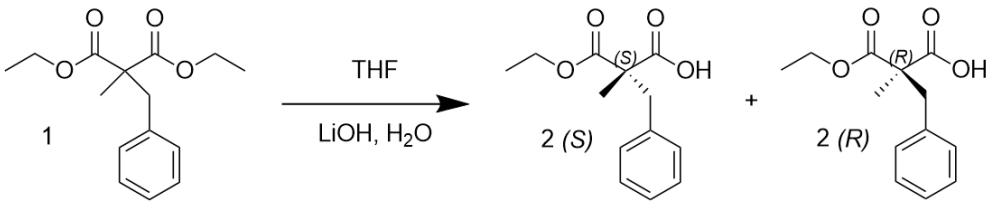


Scheme 6. Substrate synthesis from diethyl 2-methylmalonate.

To a single-neck round-bottom flask equipped with a stir bar were added sodium hydride (NaH) dispersion in mineral oil (1.3777 g, 34.45 mmol) and pentane. The mineral oil and pentane were then decanted, 35 mL anhydrous tetrahydrofuran (THF) was added to the washed NaH, and the reaction was cooled to 0 °C in an ice bath. Diethyl

2-methylmalonate (5.0 g, 28.7 mmol) was suspended in anhydrous THF and added to the reaction flask, followed by benzyl bromide (BnBr) (3.41 mL, 28.7 mmol), and allowed to stir for one hour. The flask was then removed from the ice bath and allowed to warm to room temperature before heating and allowing the solvent to reflux overnight. The mixture was then diluted in ice water and transferred to a separation funnel. The product was extracted with diethyl ether three times, and the organic layer was washed twice with deionized (DI) water and once with brine before drying with magnesium sulfate ($MgSO_4$). The solvent was then evaporated under vacuum before confirmation of product formation (6.24g, 27.1 mmol, 82% yield) with ^{1}H-NMR. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.24 (m, 6H), 4.19 (q, J = 7.26 Hz, 4H), 3.23 (s, 2H), 1.33 (s, 3H), 1.25 (t, J = 6.99 Hz, 3H).

Racemic Hydrolysis

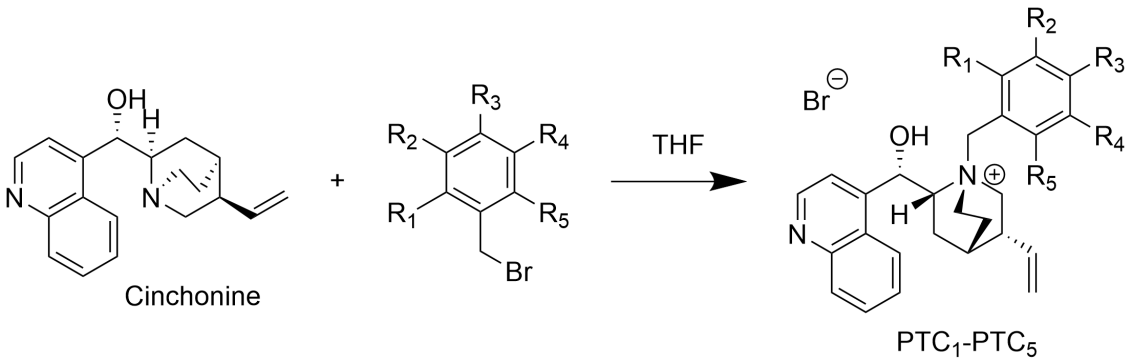


Scheme 7. Racemic hydrolysis of substrate.

To serve as a control for subsequent reactions with the catalysts, a racemic hydrolysis was performed on the substrate. To a single-neck round-bottom flask was added **1** (0.2621g, 0.99 mmol) dissolved in THF and 0.1 M lithium hydroxide (LiOH) (0.0244g, 1.02 mmol). The reaction was stirred for two hours. Thin-Layer Chromatography (TLC) with a solvent system of 10:1 ethyl acetate and hexanes and

staining with bromocresol green was used to monitor completion. Upon completion, the reaction was washed three times with diethyl ether followed by acidification of the aqueous layer with sodium bisulfate ($NaHSO_4$) until a pH of 2 was obtained. The product was then extracted with diethyl ether and dried with $MgSO_4$. The solvent was evaporated under vacuum before confirmation of product formation (32% yield) with ^{1}H-NMR. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 11.06 (br, 1H), 7.12-7.04 (m, 6H), 3.16 (dd, J = 13.49, 13.49 Hz, 2H), 2.05 (q, 2H), 1.30 (s, 3H), 1.16 (t, J = 6.99 Hz, 3H). HPLC (Chiralcel OJ-H, 254 nm, 10% IPA/Hexanes) Rt_1 = 6.48, Rt_2 = 7.95

General Cinchona Catalyst Syntheses (PTC_1-PTC_5)[15]



Scheme 8. General reaction scheme of PTCs from cinchonine.

Entry	*Catalyst*	*R_1*	*R_2*	*R_3*	*R_4*	*R_5*
PTC_1	*N*-(4-Trifluoromethylbenzyl)cinchoninium bromide	H	H	CF_3	H	H
PTC_2	*N*-(2,3,4,5,6-Pentafluorobenzyl)cinchoninium bromide	F	F	F	F	F
PTC_3	*N*-(4-Methylbenzyl)cinchoninium bromide	H	H	CH_3	H	H
PTC_4	*N*-benzylcinchoninium bromide	H	H	H	H	H
PTC_5	*N*-(2-cyanobenzyl)cinchoninium bromide	CN	H	H	H	H

Table 1. Summary of cinchona-derived phase transfer catalyst R-groups.

To a flame-dried single-neck round-bottom flask equipped with a stir bar, reflux condenser, and drying tube were added equimolar amounts of cinchonine dissolved in 50 mL anhydrous THF and alkylating agent. The solvent was allowed to reflux for 48 hours. Reaction completion was monitored via TLC with a solvent system of 9:1 dichloromethane (DCM) and methanol and iodine stain. The reaction mixture was poured over diethyl ether and allowed to stir overnight. The precipitated solids were then isolated

via vacuum filtration and recrystallized with methanol and chilled diethyl ether. ^{1}H-NMR and melting point were used for confirmation of product formation and purity. **PTC_4 & PTC_5** were synthesized by Allyson Bullock.

***N*-(4-Trifluoromethylbenzyl)cinchoninium bromide (PTC_1)**

PTC_1 was synthesized using the general procedure for PTC synthesis with 1.78 g (6.05 mmol) cinchonine and 1.4432 g (6.04 mmol) 4-(trifluoromethyl)benzyl bromide. Approximate yield: 55.5 mg, 6.04 mmol, 61% yield. R_f =0.31 (9:1 DCM:MeOH) MP = 226 ºC

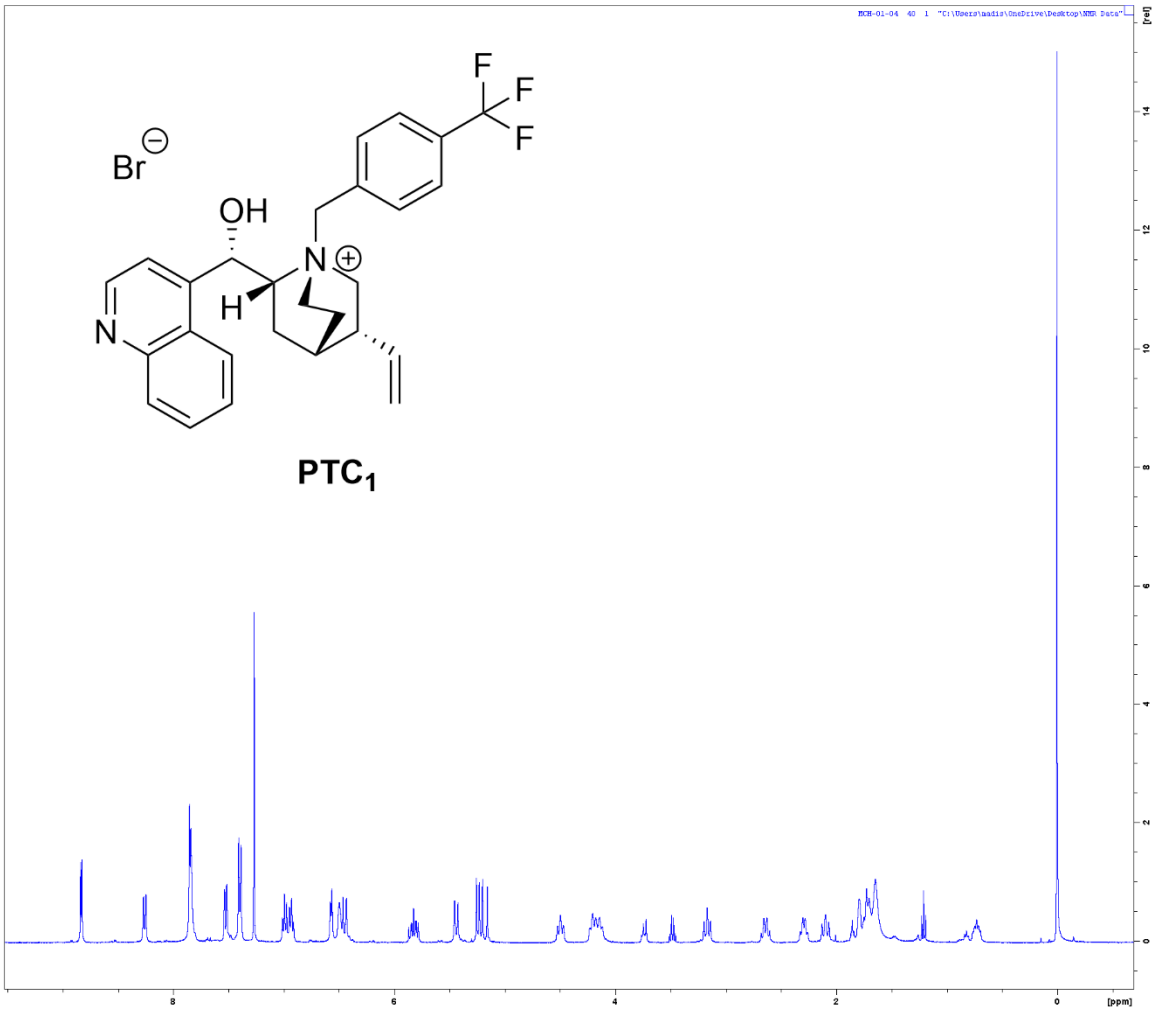


*Figure 10. [1]H-NMR of **PTC1***

***N*-(2,3,4,5,6-Pentafluorobenzyl)cinchoninium bromide (PTC2)**

PTC2 was synthesized using the general procedure for PTC synthesis with 1.95 g (6.62 mmol) cinchonine and 1 mL (6.62 mmol) 2,3,4,5,6-pentafluorobenzyl bromide. Approximate yield: 3.0047 g, 6.63 mmol, 81% yield. MP = 192-194 ºC

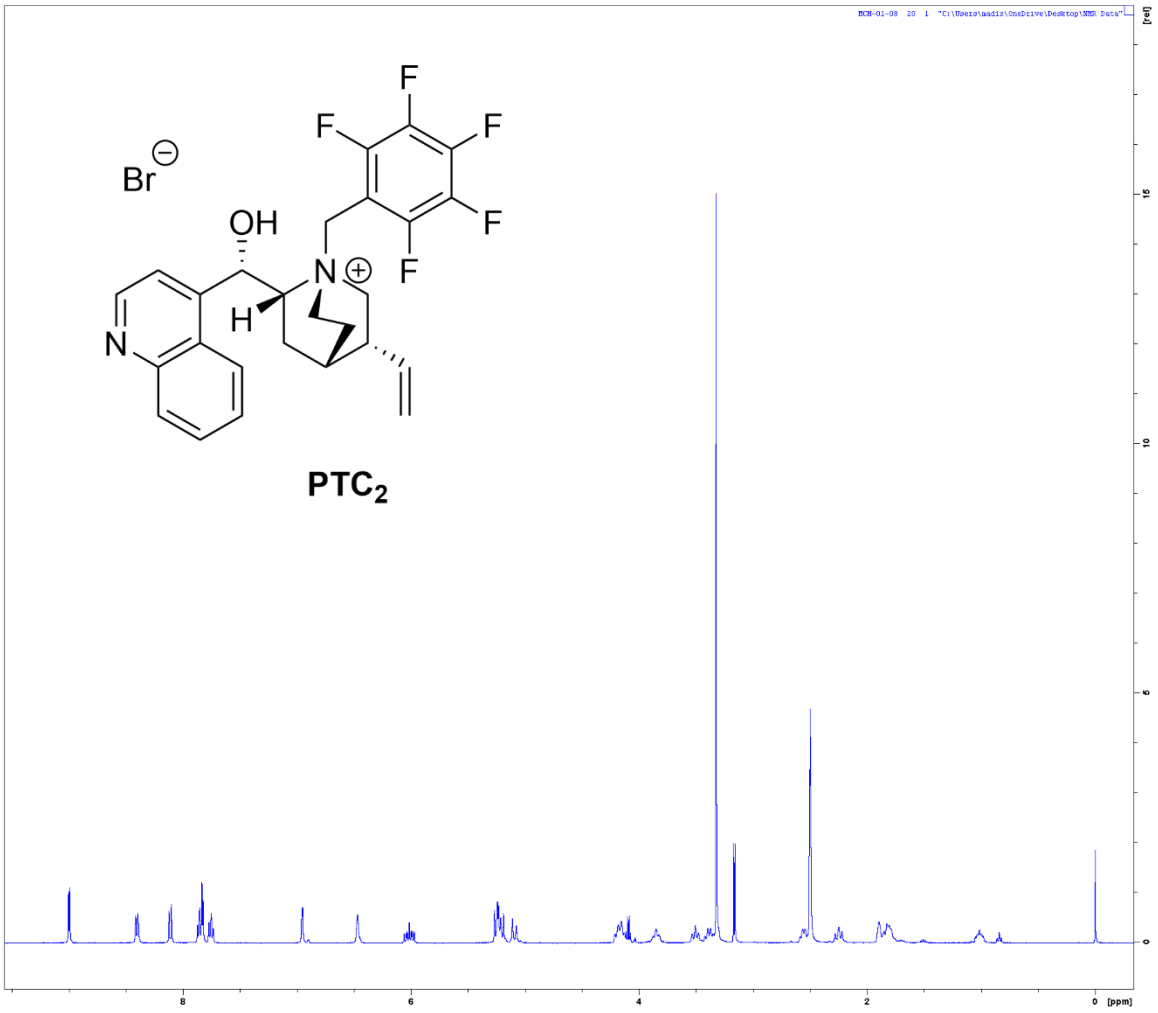


Figure 11. [1]H-NMR of ***PTC₂***

_N_-(4-Methylbenzyl)cinchoninium bromide (PTC₃)

PTC₃ was synthesized using the general procedure for PTC synthesis with 2.00 g (6.79 mmol) cinchonine and 1.26 g (6.81 mmol) 4-methylbenzyl bromide. Approximate yield: 2.1233 g, 4.43 mmol, 65% yield. MP = 233-234 ºC

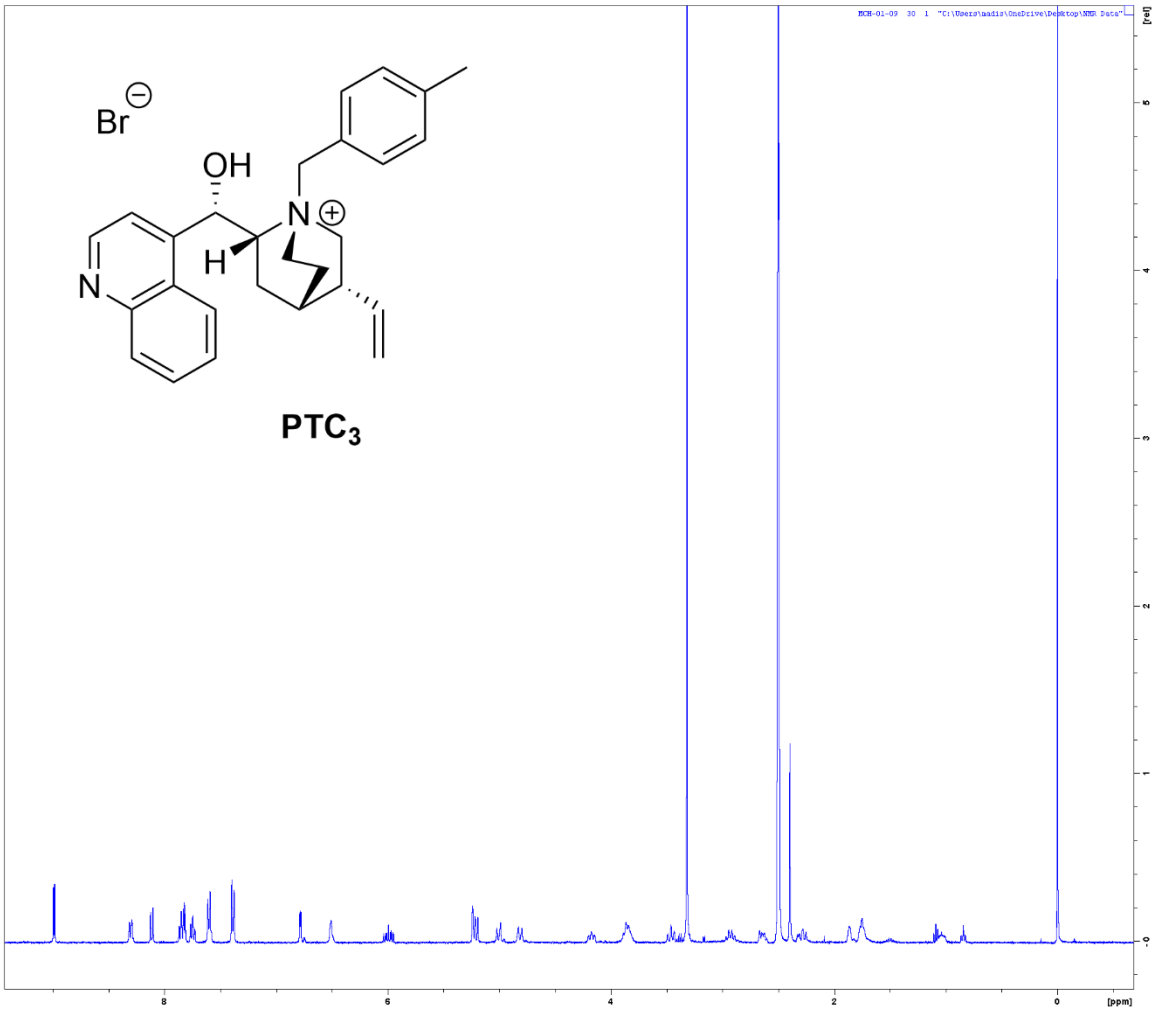
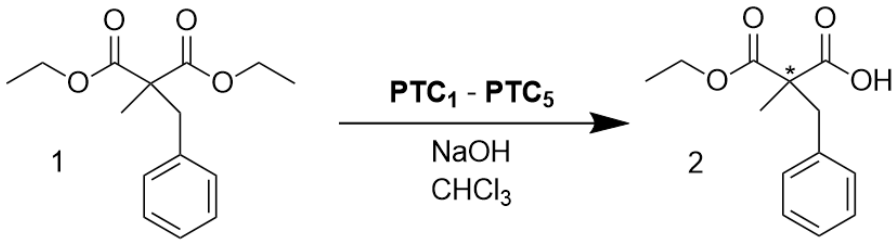


*Figure 12. [1]H-NMR of **PTC3***

General Catalytic Hydrolyses



*Scheme 9. General catalytic hydrolyses with **PTC1-PTC5**.*

To a conical vial equipped with a stir bar on ice was added a catalytic amount (10 mol %) of catalyst dissolved in chloroform ($CHCl_3$) and 10 M NaOH. After stirring for 10 minutes, **1** dissolved in chloroform was added and allowed to stir for the listed time. TLC with a solvent system of 1:1 ethyl acetate and hexanes was used to monitor completion. The reaction mixture was washed with ethyl acetate three times. The aqueous layer was acidified with 5 M hydrochloric acid (HCl) until a pH of 2 was obtained. The product was then extracted with ethyl acetate three times and dried with $MgSO_4$. The solvent was evaporated under vacuum before examination with ^{1}H-NMR for evaluation of product formation. Specifications for each reaction are summarized in Table 2.

PTC Used	*Amount **1***	*Amount PTC*	*Reaction Time*	*Yield*
PTC₁	0.1091 g, 0.41 mmol	0.0200 g, 0.04 mmol	4 days	NR
PTC₂	0.1017 g, 0.38 mmol	0.0214 g, 0.05 mmol	5 days	NR
PTC₃	0.1083 g, 0.41 mmol	0.0186 g, 0.05 mmol	2 days	NR
PTC₄	0.1089 g, 0.41 mmol	0.0180 g, 0.04 mmol	2 days	NR
PTC₅	0.1043 g, 0.39 mmol	0.0156 g, 0.04 mmol	2 days	NR

Table 2. Specifications for catalytic hydrolyses at 10 mol%.

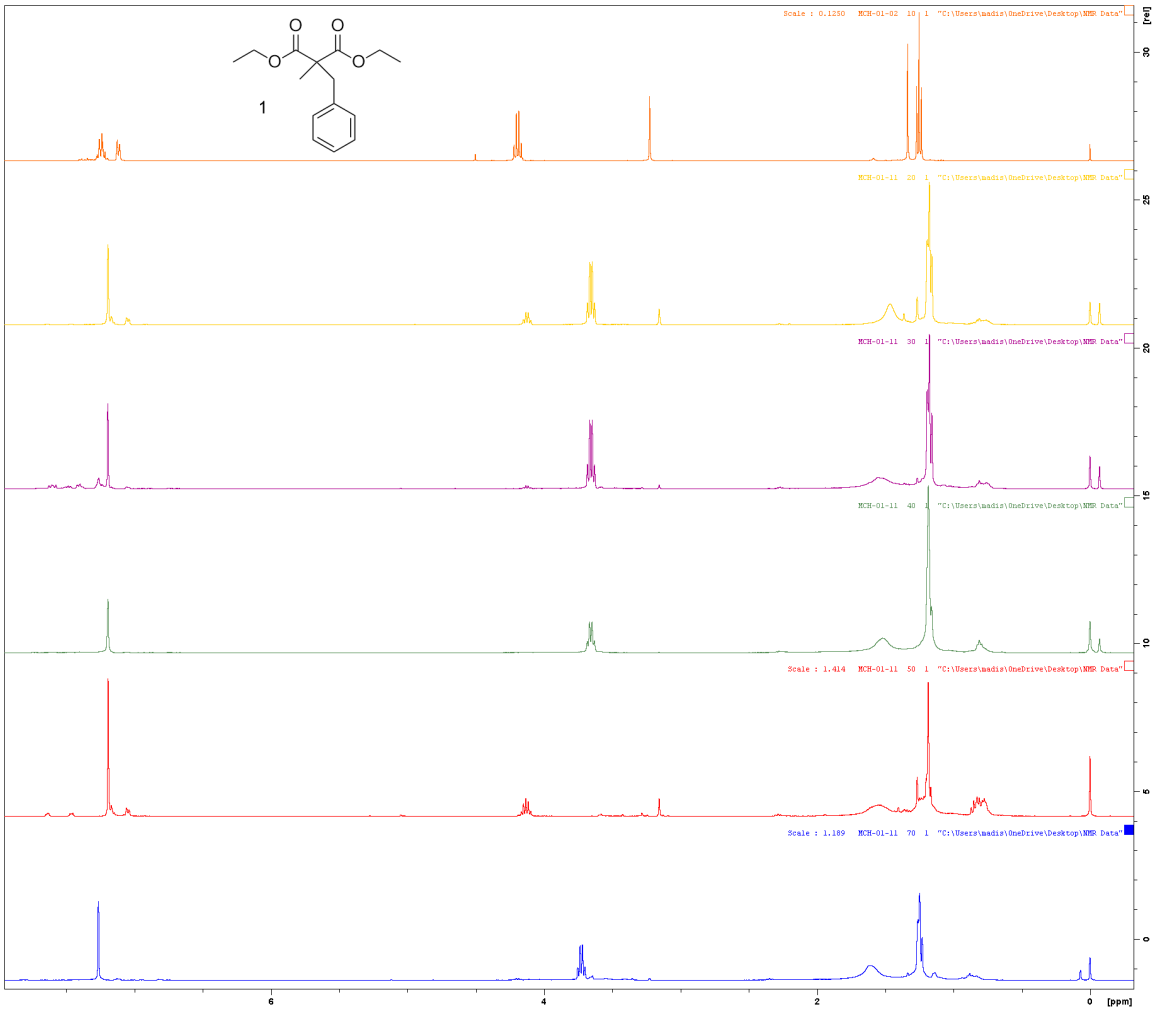


*Figure 13. [1]H-NMR of substrate (orange) followed by hydrolyses with 10 mol% **PTC**$_1$-**PTC**$_5$ (yellow-blue, respectively) showing recovery of starting material.*

Hydrolysis with the catalysts was repeated using a catalytic amount of 25 mol % and extracted with chloroform instead of ethyl acetate due to the catalysts' insolubility in chloroform. Product formation was confirmed via [1]H-NMR and analyzed via APCI-MS. Specifications for each reaction are summarized in Table 3.

PTC Used	*Amount **1***	*Amount PTC*	*Reaction Time*	*Yield*
PTC₁	0.1000 g, 0.38 mmol	0.0431 g, 0.09 mmol	4 days	8%
PTC₂	0.1000 g, 0.38 mmol	0.0451 g, 0.09 mmol	4 days	32%
PTC₃	0.1000 g, 0.38 mmol	0.0379 g, 0.09 mmol	4 days	15%

Table 3. Specifications for catalytic hydrolyses at 25 mol%.

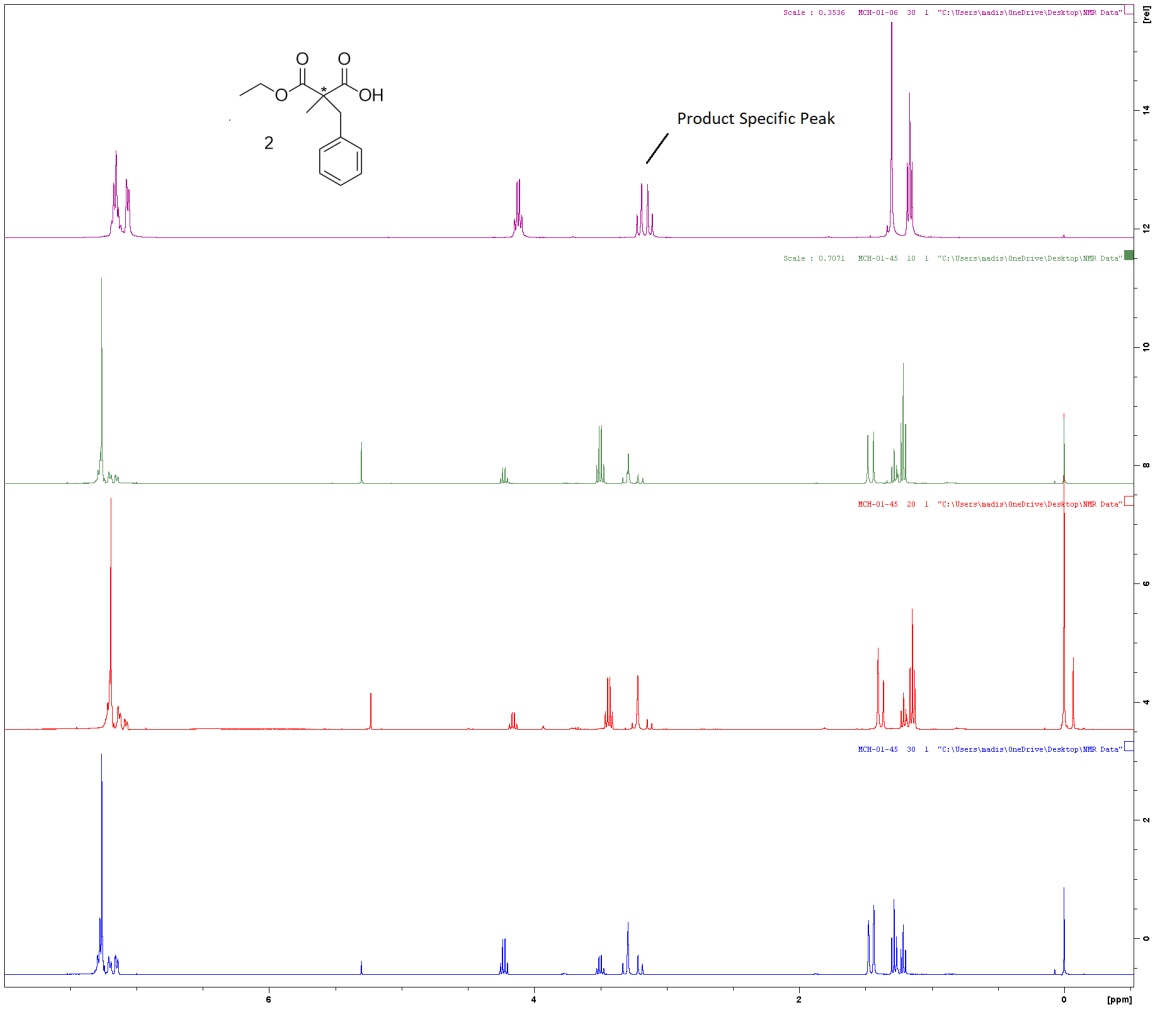


*Figure 14. ^{1}H-NMR of racemic hydrolysis followed by hydrolyses with 25 mol% **PTC₁-PTC₃** showing partial conversion to hydrolyzed product.*

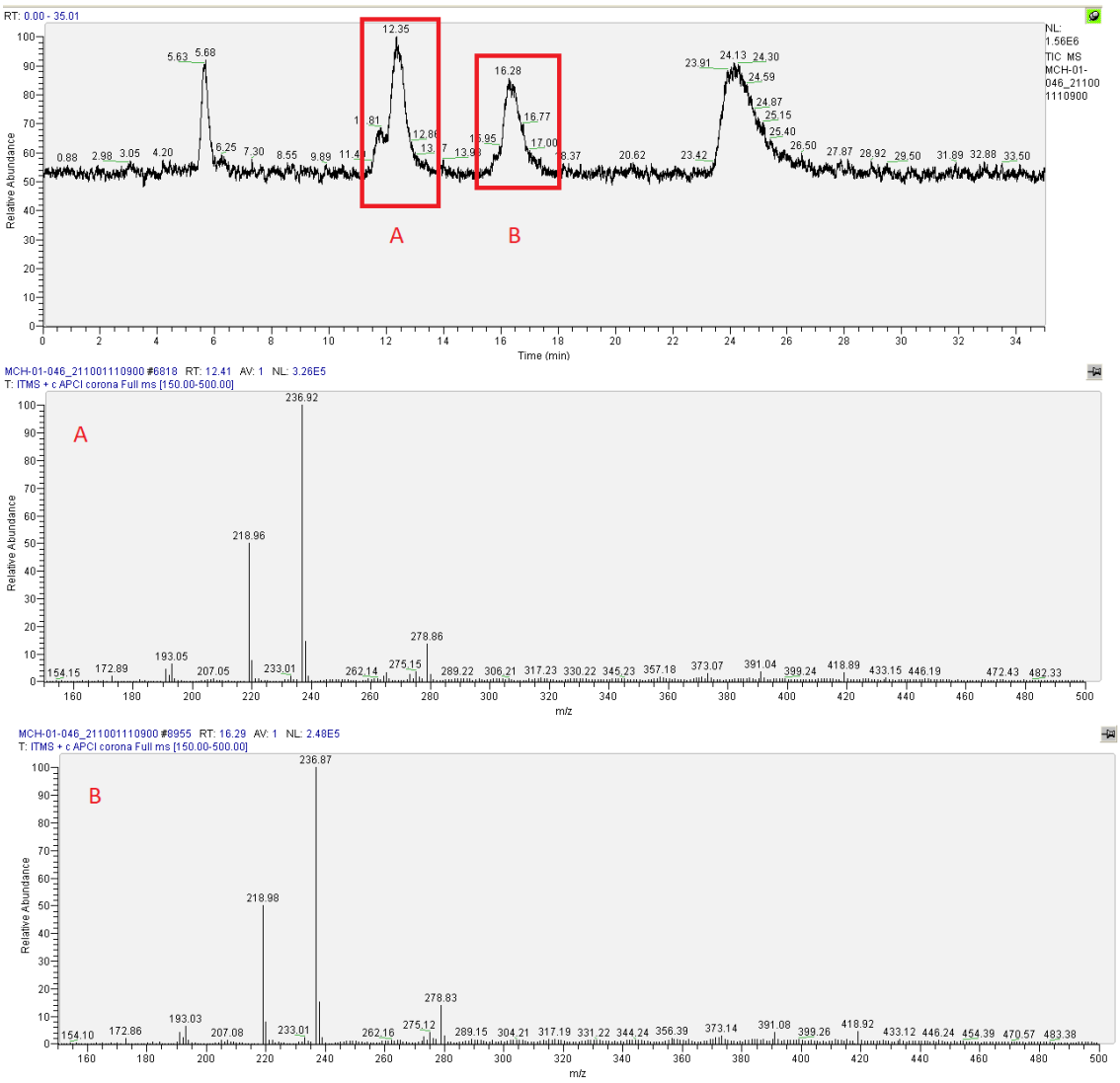


Figure 15. ***PTC$_1$*** *hydrolysis APCI-MS: [$C_{13}H_{16}O_4H^+$] calculated = 237.10, found = 236.92, 236.87.*

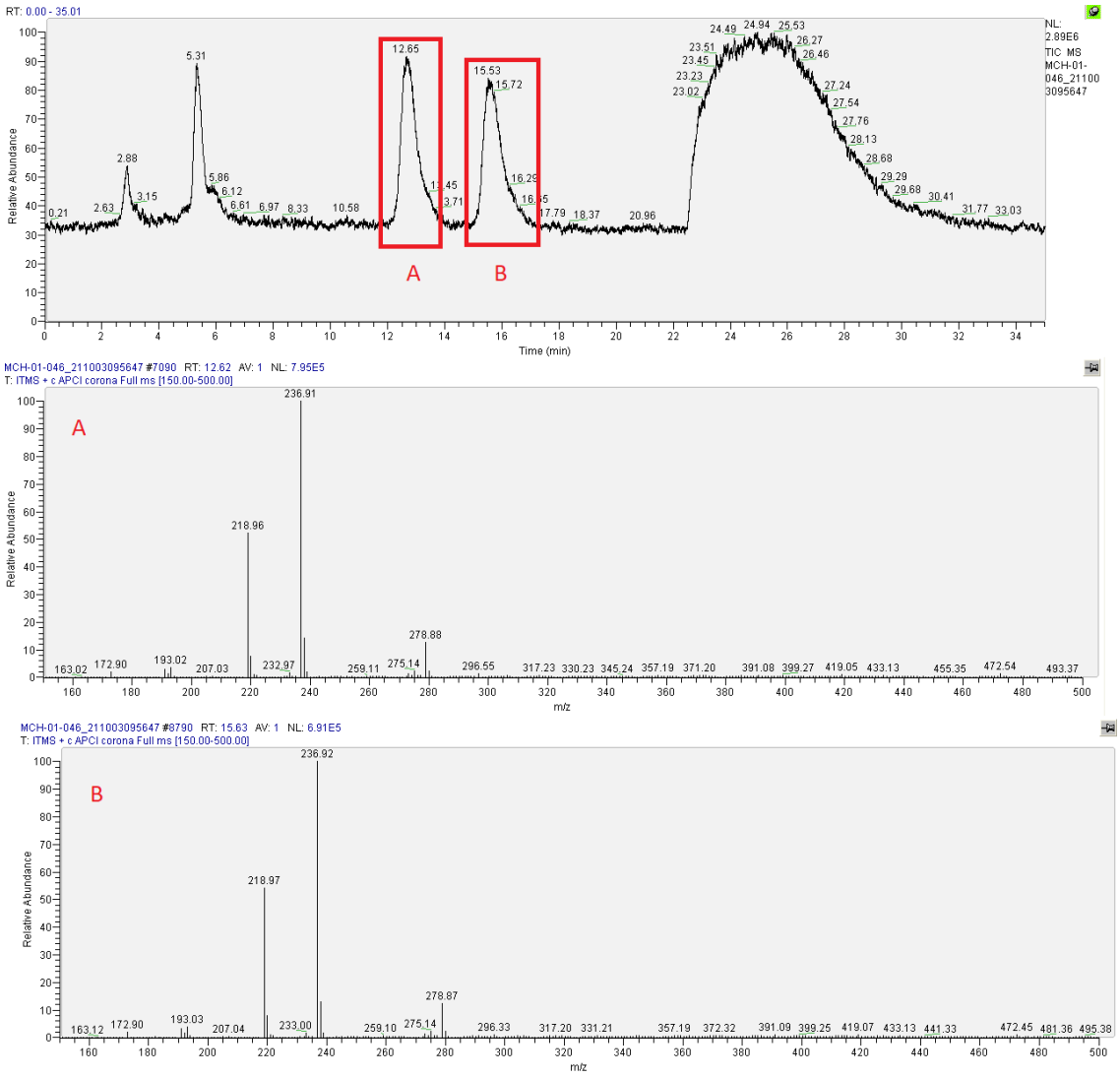


Figure 16. ***PTC₂*** *hydrolysis APCI-MS: [$C_{13}H_{16}O_4H^+$] calculated = 237.10, found = 236.91, 236.92.*

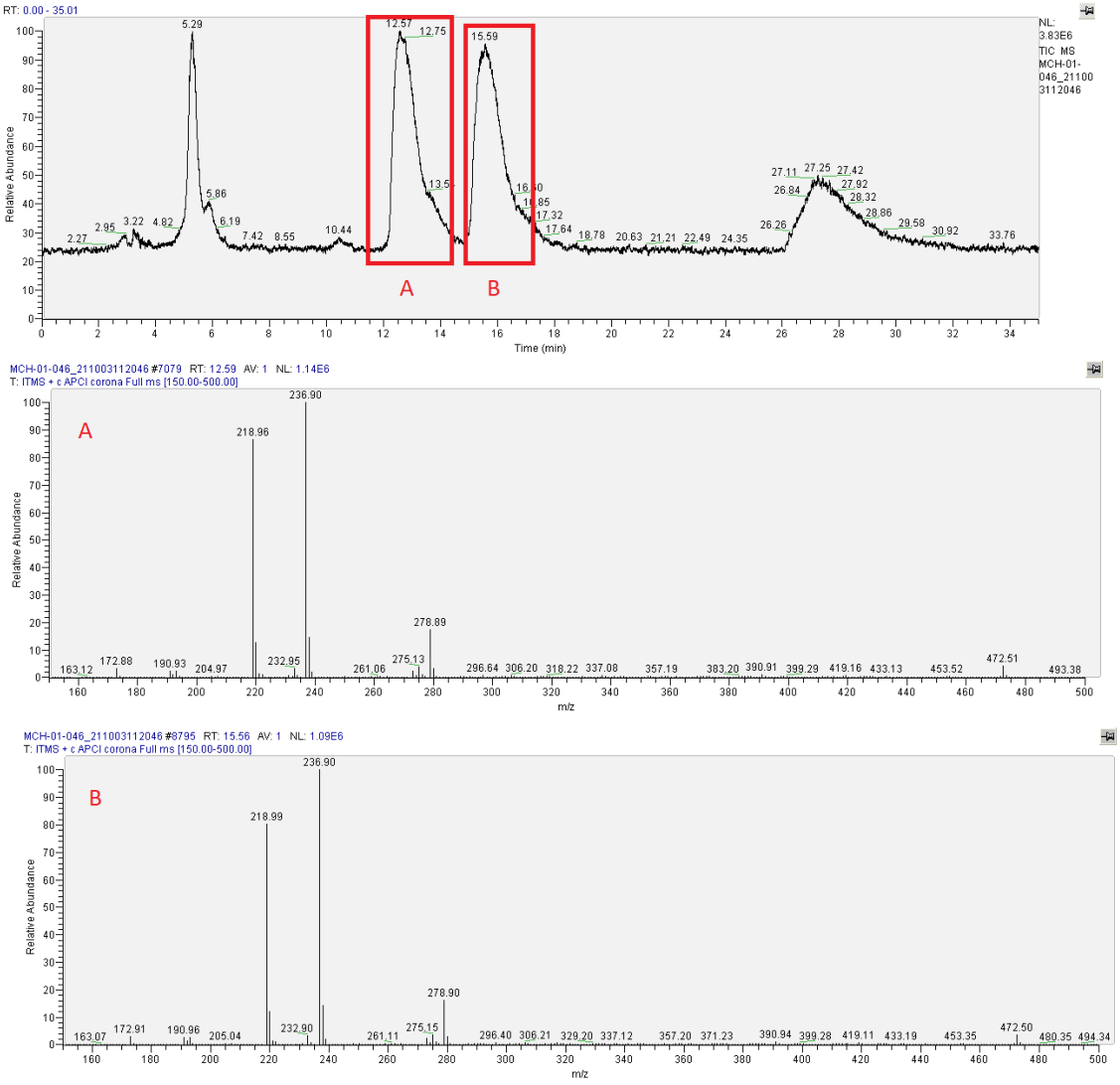
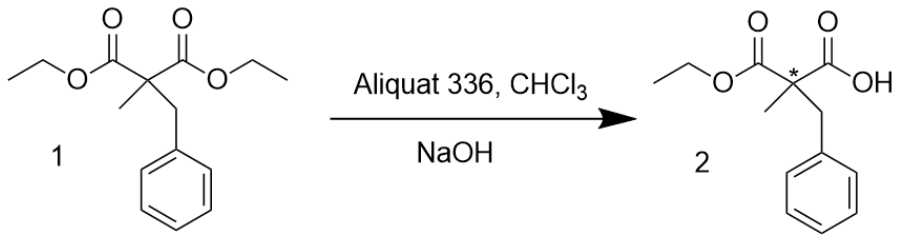


Figure 17. ***PTC₃*** *hydrolysis APCI-MS: [$C_{13}H_{16}O_4H^+$] calculated = 237.10, found = 236.90.*

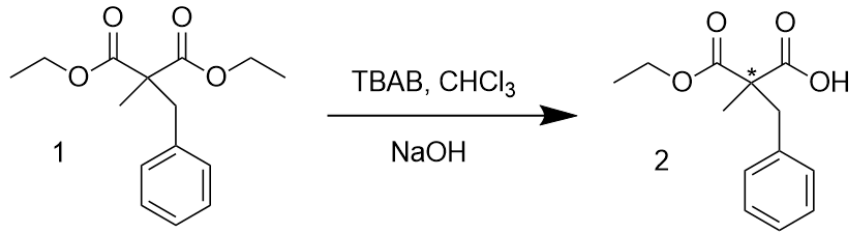
Aliquat® 336 Hydrolysis



Scheme 10. Control hydrolysis with chiral catalyst Aliquat® 336.

To a conical vial equipped with a stir bar on ice was added a catalytic amount (10 mol %) of Aliquat® 336 (12.1 mg, 0.03 mmol) dissolved in chloroform and 10 M NaOH. After stirring for 10 minutes, **1** (82.0 mg, 0.31 mmol) dissolved in chloroform was added and allowed to stir for 24 hours. TLC with a solvent system of 1:1 ethyl acetate and hexanes was used to monitor completion. The reaction mixture was washed with ethyl acetate three times. The aqueous layer was acidified with 5 M HCl until a pH of 2 was obtained. The product was then extracted with ethyl acetate three times and dried with $MgSO_4$. The solvent was evaporated under vacuum before examination with ^{1}H-NMR for evaluation of product formation. It was determined that no product was formed.

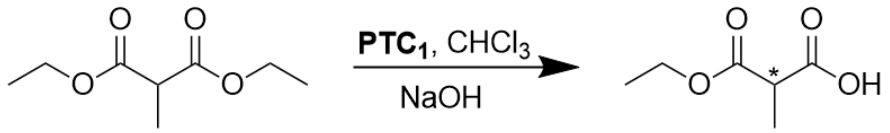
Tetrabutylammonium Bromide (TBAB) Hydrolysis



Scheme 11. Control hydrolysis with chiral catalyst TBAB.

To a conical vial equipped with a stir bar on ice was added a catalytic amount (10 mol %) of tetrabutylammonium bromide (TBAB) (10.0 mg, 0.03 mmol) dissolved in chloroform and 10 M NaOH. After stirring for 10 minutes, **1** (87.1 mg, 0.32 mmol) dissolved in chloroform was added and allowed to stir for 24 hours. TLC with a solvent system of 1:1 ethyl acetate and hexanes was used to monitor completion. The reaction mixture was washed with ethyl acetate three times. The aqueous layer was then acidified with 5 M hydrochloric acid (HCl) until a pH of 2 was obtained. The product was extracted with ethyl acetate three times and dried with $MgSO_4$. The solvent was evaporated under vacuum before examination with ^{1}H-NMR for evaluation of product formation. It was determined that no product was formed.

Diethyl Methylmalonate Hydrolysis



Diethyl 2-methylmalonate

Scheme 12. Control hydrolysis of diethyl 2-methylmalonate with cinchona-based catalyst ***PTC****1.*

To a conical vial equipped with a stir bar on ice was added a catalytic amount (10 mol %) of **PTC1** (10.7 mg, 0.02 mmol) dissolved in chloroform and 10 M NaOH. After stirring for 10 minutes, diethyl 2-methylmalonate (84.1 mg, 0.32 mmol) dissolved in chloroform was added and allowed to stir for 24 hours. TLC with a solvent system of 1:1 ethyl acetate and hexanes was used to monitor completion. The reaction mixture was washed with ethyl acetate three times. The aqueous layer was acidified with 5 M HCl

until a pH of 2 was obtained. The product was then extracted with ethyl acetate three times and dried with $MgSO_4$. The solvent was evaporated under vacuum before examination with ^{1}H-NMR for evaluation of product formation. It was determined that no product was formed.

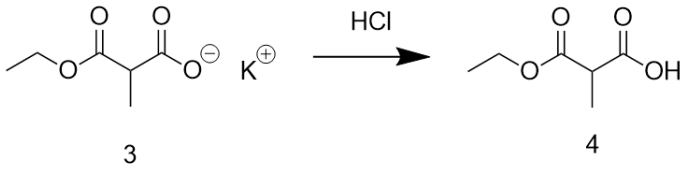
General Chiral HPLC Procedure

A Lab Alliance PeakSimple Chromatography Data System HPLC equipped with a 0.46 cm by 25 cm Chiralcel OJ-H Chiral column was used to examine retention times and determine enantiomeric excess of the hydrolyzed products. The sample was dissolved in a solvent system of 10:1 HPLC-grade hexanes and isopropanol and filtered. Peak detection was performed via UV/Vis Spectroscopy at 254 nm for 60 minutes per sample with a flow rate of 1 mL per minute.

General APCI-MS Procedure

Atmospheric-Pressure Chemical Ionization Mass Spectrometry (APCI-MS) was utilized in the determination of enantiomeric excess for hydrolyses performed with cinchona catalysts at 25 mol %. Samples were prepared at approximately 2.0 mg per mL of 10:1 HPLC-grade hexanes and isopropanol and filtered. 100 μL of sample was injected onto a 0.46 cm by 25 cm Chiralcel OJ-H Chiral column. The mobile phase was 4% isopropanol in hexanes at a flow rate of 1.0 mL/min. Data was collected in full scan mode. Enantiomeric excess was then calculated by comparing the peak areas of the two enantiomers using the reconstructed ion chromatograms (RIC) for the products of interest.

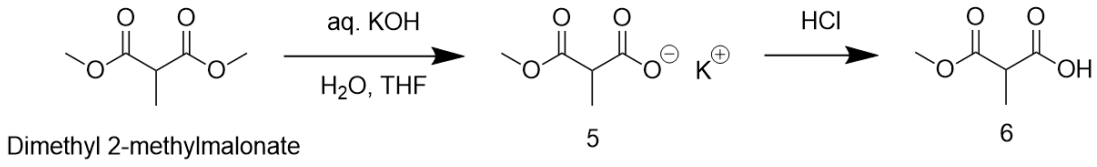
Ethyl 2-methylmalonate Potassium Salt Acidification



Scheme 13. Acidification of ethyl 2-methylmalonat potassium salt.

The ethyl malonate half ester was prepared by dissolving ethyl malonate potassium salt (6.33 g, 34.4 mmol) in DI water and acidifying with 5 M HCl until a pH of 2 was obtained. The product was extracted three times with diethyl ether and dried with $MgSO_4$. The solvent was then evaporated under vacuum before examination with ^{1}H-NMR for confirmation of product formation (4.15 g, 28.4 mmol, 83% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.87 (br, 1H), 4.22 (q, J = 6.48 Hz, 2H), 3.50 (q, J = 6.92 Hz, 1H), 1.44 (d, 3H), 1.29 (t, J = 5.89 Hz, 3H).

Methyl 2-methylmalonate Potassium Salt Synthesis and Acidification

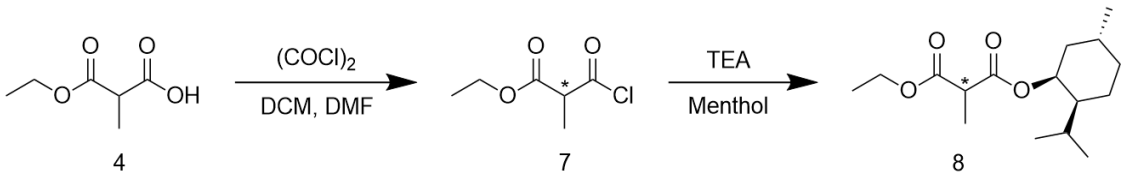


Scheme 14. Synthesis and acidification of methyl 2-methylmalonate potassium salt.

To a single-neck round-bottom flask equipped with a stir bar was added dimethyl 2-methylmalonate (5.00 g, 34.2 mmol) in a solvent of 10:1 DI water and THF at a concentration of 0.05 M. The reaction was then cooled to 0 °C in an ice bath before addition of 1.2 molar equivalents of aqueous potassium hydroxide (KOH) (2.3 g, 41.0

mmol) via a dropping funnel. The mixture was allowed to stir for two hours, and reaction completion was monitored via TLC with a solvent system of 1:1 hexanes and ethyl acetate. Upon completion, the solution was acidified with 5 M HCl until a pH of 2 was obtained. The product was extracted twice with diethyl ether and dried with $MgSO_4$. The solvent was then evaporated under vacuum before examination with ^{1}H-NMR for confirmation of product formation (4.02g, 23.4 mmol, 90% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.99 (br, 1H), 3.77 (s, 3H), 3.51 (q, J = 7.51 Hz, 1H), 1.46 (d, J = 6.54 Hz, 3H).

Coupling of Menthol Chiral Auxiliary



Scheme 15. Coupling of menthol chiral auxiliary to ethyl 2-methylmalonate acid ester.

To a flame-dried three-neck round-bottom flask under an inert atmosphere of nitrogen equipped with a stir bar were added **4** (0.4994 g, 3.4 mmol) dissolved in DCM and two molar equivalents of oxalyl chloride ($(COCl)_2$) (0.6 mL, 7.0 mmol) in a single drop of dimethylformamide (DMF). The reaction was allowed to stir for 48 hours, and completion was monitored via TLC with a solvent system of 4:1 hexanes and ethyl acetate with phosphomolybdic acid (PMA) stain. Solvent was then evaporated under vacuum and the product was diluted with DCM. Slightly more than one molar equivalent of triethanolamine (TEA) (0.5mL, 3.6 mmol) was added to quench any HCl produced in the formation of the acid chloride before addition of two molar equivalents of menthol (1.060 g, 6.8 mmol). The reaction mixture was allowed to stir overnight with repeated TLC monitoring the following day. Upon completion, the product was diluted with

diethyl ether before extracting once with saturated ammonium chloride (NH_4Cl), once with saturated sodium bicarbonate ($NaHCO_3$), and once with brine. The organic layer was then dried with $MgSO_4$, and the solvent was evaporated under vacuum. Examination of the crude product with ^{1}H-NMR revealed impurities, so flash column chromatography was performed with a gradient solvent system of hexanes and increasing ethyl acetate concentration on a 7.5 cm column for isolation of pure product. The isolation of pure product was confirmed via ^{1}H-NMR and further characterization was obtained through Distortionless Enhancement by Polarization Transfer (DEPT) ^{13}C-NMR (0.1723 g, 0.6 mmol, 18% yield). R_f = 0.73 (4:1 Hexanes:EtOAc) ^{13}C-NMR (100 MHz): δ = 13.8 (CH_3), 16.1 (CH_3), 20.75 (CH_3), 22.0 (CH_3), 23.3 (CH_2), 26.0 (CH_3), 31.4 (CH_3), 34.2 (CH_2), 40.6 (CH_2), 46.5 (CH), 46.9 (CH), 61.3 (CH_2), 75.3 (CH).

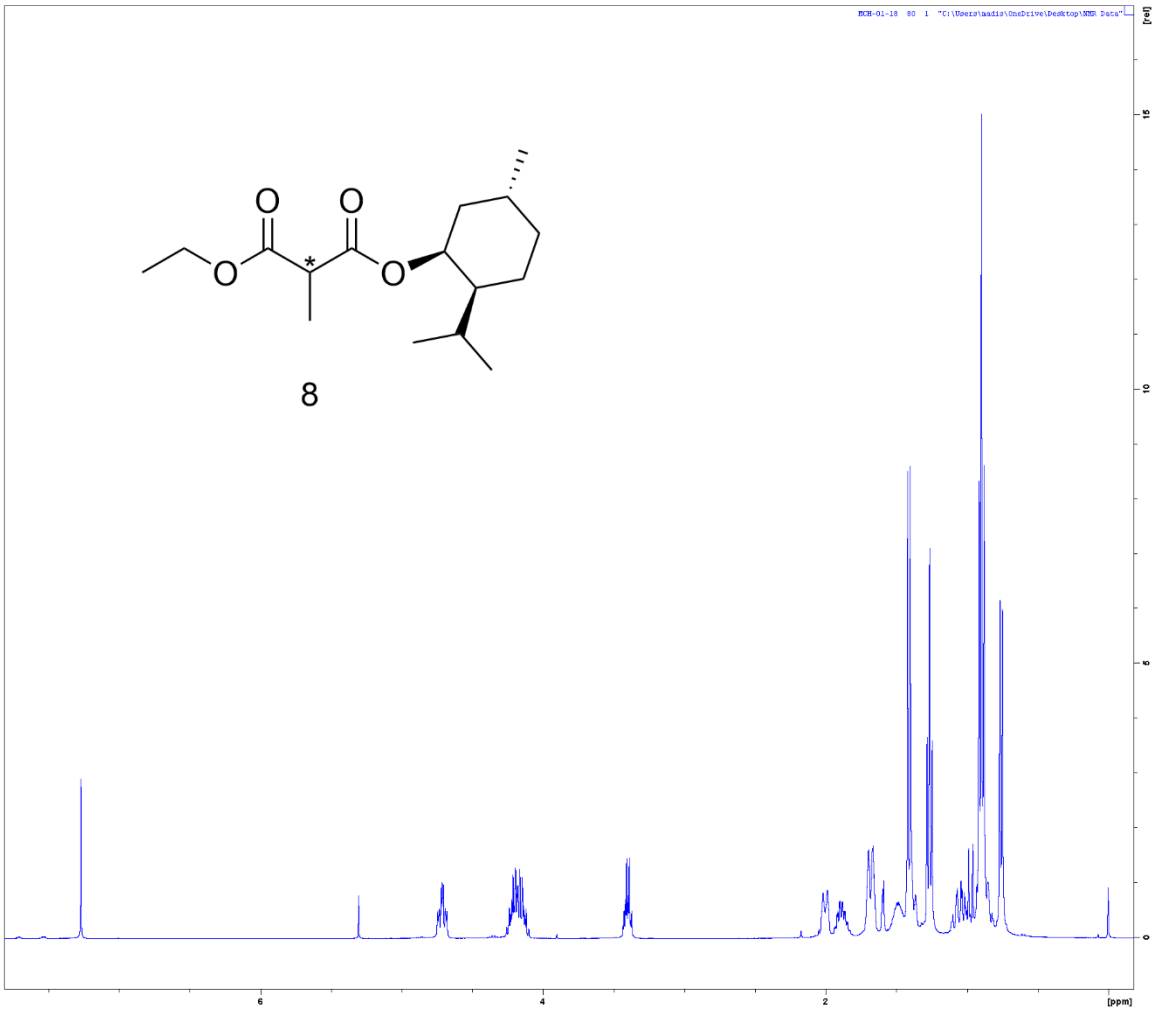
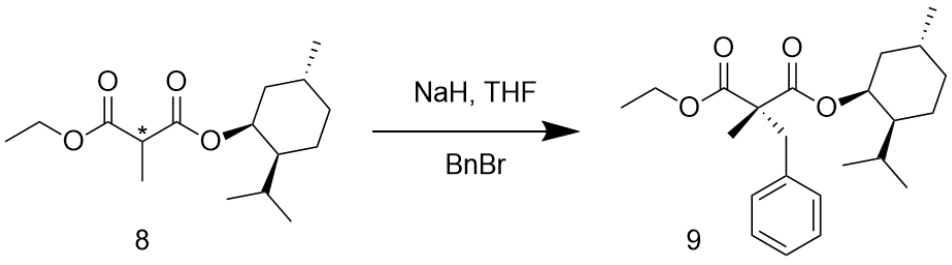


*Figure 18. [1]H-NMR of **8***

Benzylation of Menthol Coupled Ethyl Malonate Ester



Scheme 16. Benzylation of menthol coupled ethyl 2-methylmalonate ester.

To a three-neck round-bottom flask equipped with a stir bar were added 1.2 molar equivalents of sodium hydride (NaH) dispersion in mineral oil (16.8 mg, 0.7 mmol) and pentane. The mineral oil and pentane were then decanted, and the remaining NaH was suspended in anhydrous THF. The reaction was cooled to 0 °C in an ice bath before addition of **8** (0.1723 g, 0.6 mmol) and allowed to stir for one hour. One molar equivalent of benzyl bromide (71.7 μL, 0.6 mmol) was added, and the reaction was allowed to stir for 48 hours. The mixture was then diluted in ice water and transferred to a separation funnel. The product was extracted with ether three times, and the organic layer was washed twice with DI water and once with brine before drying with $MgSO_4$. The solvent was then evaporated under vacuum. Examination of the crude product with ^{1}H-NMR revealed impurities, so flash column chromatography was performed with a solvent system of 4:1 hexanes and ethyl acetate on a 5.7 cm column for isolation of pure product. The isolation of pure product was confirmed via ^{1}H-NMR and further characterization was obtained via DEPT ^{13}C-NMR (33.5 mg, 0.09 mmol, 15% yield). R_f =0.60 (4:1 Hexanes:EtOAc) ^{13}C-NMR (100 MHz): δ = 14.0 (CH_3), 15.9 (CH_3), 19.8 (CH_3), 20.8 (CH_3), 22.0 (CH_3), 23.0 (CH_2), 23.7 (CH), 31.3 (CH), 34.2 (CH_2), 40.4 (CH_2), 41.1 (CH_2), 46.9 (CH), 61.3 (CH_2), 75.4 (CH), 126.8 (CH), 128.2 (CH), 130.3 (CH).

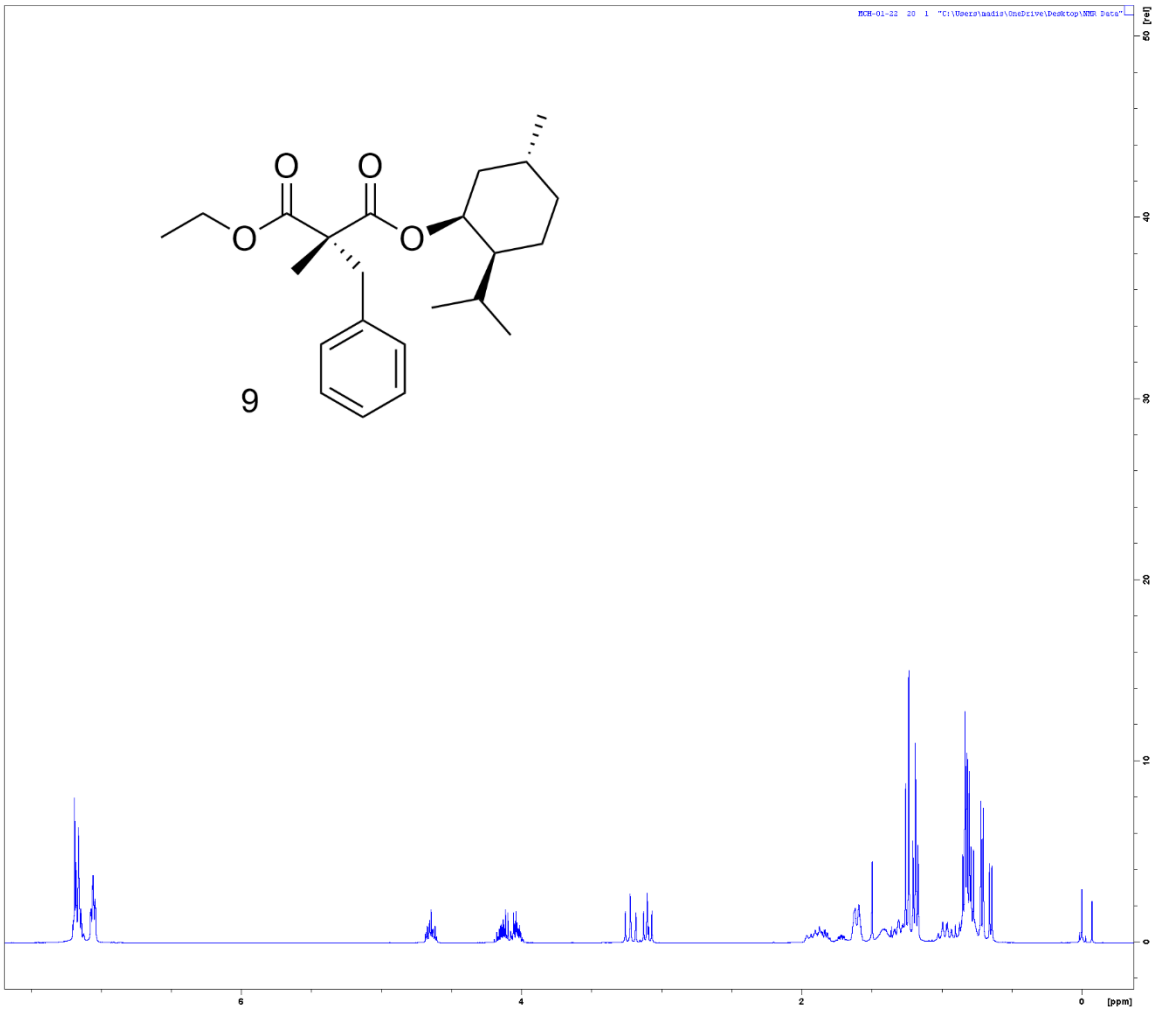
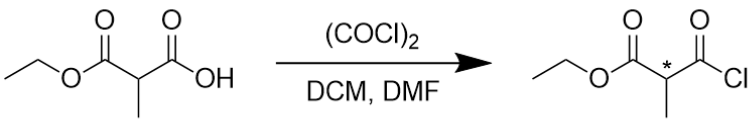


*Figure 19. [1]H-NMR of **9***

Ethyl Acyl Chloride Synthesis via Oxalyl Chloride



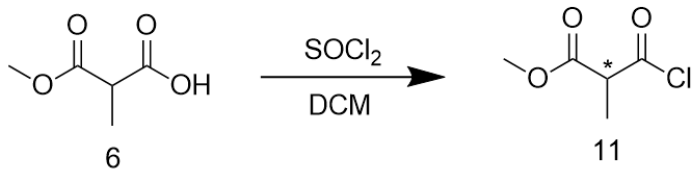
4 10

Scheme 17. Ethyl acyl chloride synthesis via oxalyl chloride.

For subsequent reactions with oxazolidinone chiral auxiliaries, acid chloride intermediates were prepared independently. To a flame-dried three-neck round-bottom

flask equipped with a stir bar were added **4** (1.0299g, 7.0 mmol) and two molar equivalents of oxalyl chloride (1.2 mL, 14.0 mmol) in a single drop of dimethylformamide (DMF) under an inert atmosphere of nitrogen. The reaction was allowed to stir for 24 hours, and completion was monitored via TLC with a solvent system of 4:1 hexanes and ethyl acetate with phosphomolybdic acid (PMA) stain. Solvent was then evaporated under vacuum. TEA was not added in this preparation due to the basicity of the later reactions. Crude product was used directly in the subsequent reaction.

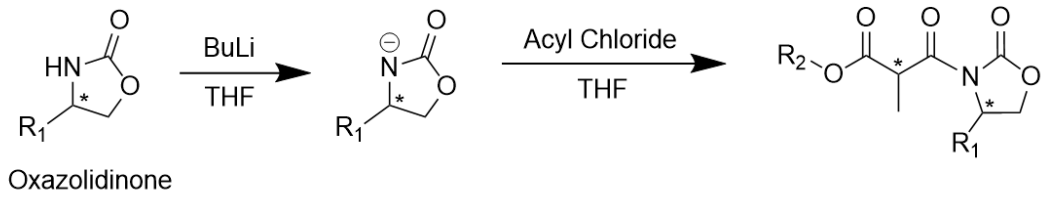
Methyl Acyl Chloride Synthesis via Thionyl Chloride[16]



Scheme 18. Methyl acyl chloride synthesis via thionyl chloride.

To a flame-dried single-neck round-bottom flask equipped with a stir bar and reflux condenser were added **6** (1.7115 g, 12.96 mmol) in anhydrous DCM and an excess of thionyl chloride ($SOCl_2$) (14 mL, 191.2 mmol) under an inert atmosphere of nitrogen. The reaction was allowed to reflux overnight. Solvent was then evaporated under vacuum and under N_2 for 20 minutes before examination with ^{1}H-NMR for confirmation of product formation (1.62g, 10.8 mmol, 83% yield). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.88 (q, J = 7.23 Hz, 1H), 3.81 (s, 3H), 1.54 (d, J = 7.94 Hz, 3H).

General Oxazolidinone Coupling to Acyl Chlorides



Scheme 19. General reaction scheme of oxazolidinone coupling to acyl chlorides.

Entry	*Oxazolidinone*	*Acyl Chloride*	*R_1*	*R_2*	*Coupled Ester*
O_1	*(S)*-(-)-4-isopropyl-2-oxazolidinone	**10**	iPr	Et	**12**
O_2	*(R)*-(-)-4-phenyl-2-oxazolidinone	**11**	Ph	Me	**13**

Table 4. Summary of oxazolidinone R groups.

To an oven-dried three-neck round-bottom flask equipped with a stir bar, two stoppers, and a septum were added 0.5 M oxazolidinone in anhydrous THF via cannula needle at -20 °C under an inert atmosphere of nitrogen. Slightly less than one molar equivalent of BuLi was then added, followed by one molar equivalent of acyl chloride. Concentration of *n*-BuLi was previously determined to be 2.725 M via Gilman Titration.[31] The reaction was allowed to stir for one hour before being diluted with NH_4Cl and ethyl acetate. The mixture was then poured into ice water and transferred to a separatory funnel. The product was extracted from the aqueous phase three times with diethyl ether before drying with $MgSO_4$. Solvent was then evaporated under vacuum. Examination of both products with ^{1}H-NMR revealed impurities, requiring further purification.

***(S)*-(-)-4-isopropyl-2-oxazolidinone Coupled Ester (12)**

12 was prepared via the general procedure for oxazolidinone coupling to acyl chlorides with 0.9053 g (7.0 mmol) *(S)*-(-)-4-isopropyl-2-oxazolidinone, 14 mL anhydrous THF, 2.66 mL (6.6 mmol) BuLi, and 1.1591 g (7.0 mmol) **10**. Flash column chromatography was performed with a solvent system of 1:1 hexanes and ether on a 7.3 cm column for isolation of pure product (0.1231g, 0.5 mmol, 12% yield). R_f=0.17 (1:1 Hexanes:Et_2O) ESI MS: [$C_{12}H_{19}NO_5H^+$] calculated = 258.13, found = 258.08.

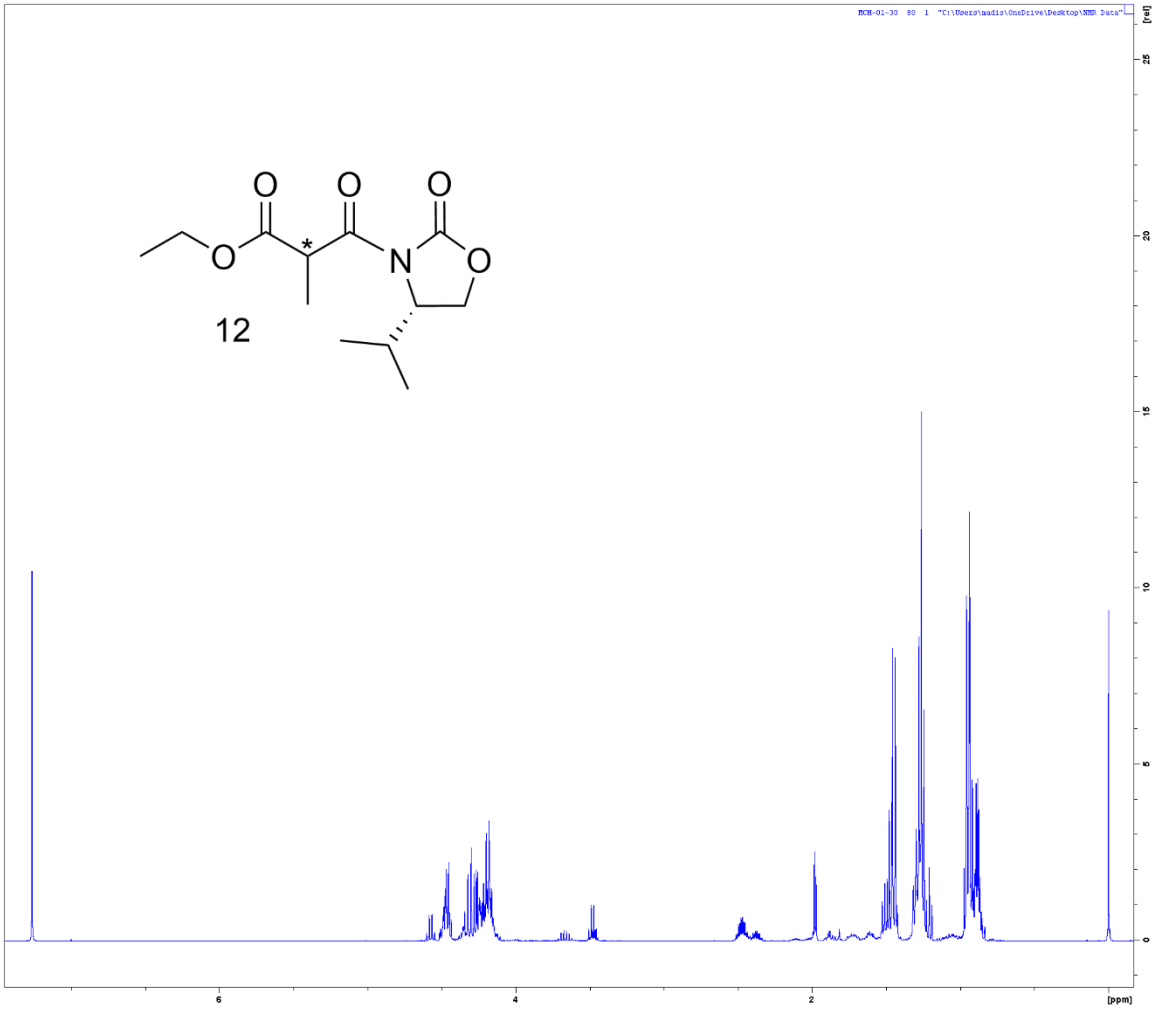


*Figure 20. ^{1}H-NMR of **12***

***(R)*-(-)-4-phenyl-2-oxazolidinone Coupled Ester (13)**

13 was prepared via the general procedure for oxazolidinone coupling to acyl chlorides with 1.6665 g (10.2 mmol) *(R)*-(-)-4-phenyl-2-oxazolidinone, 20 mL anhydrous THF, 3.5 mL (9.7 mmol) BuLi, and 1.62 g (10.8 mmol) **11**. The crude product was purified via Reverse Phase HPLC. The isolation of pure product was confirmed via ^{1}H-NMR and Mass Spectrometry (0.46 g, 1.7 mmol, 18% yield). R_f=0.20 (1:1 Hexanes:Et_2O) ESI MS: [$C_{14}H_{15}NO_5Na^+$] calculated = 300.09, found = 300.07.

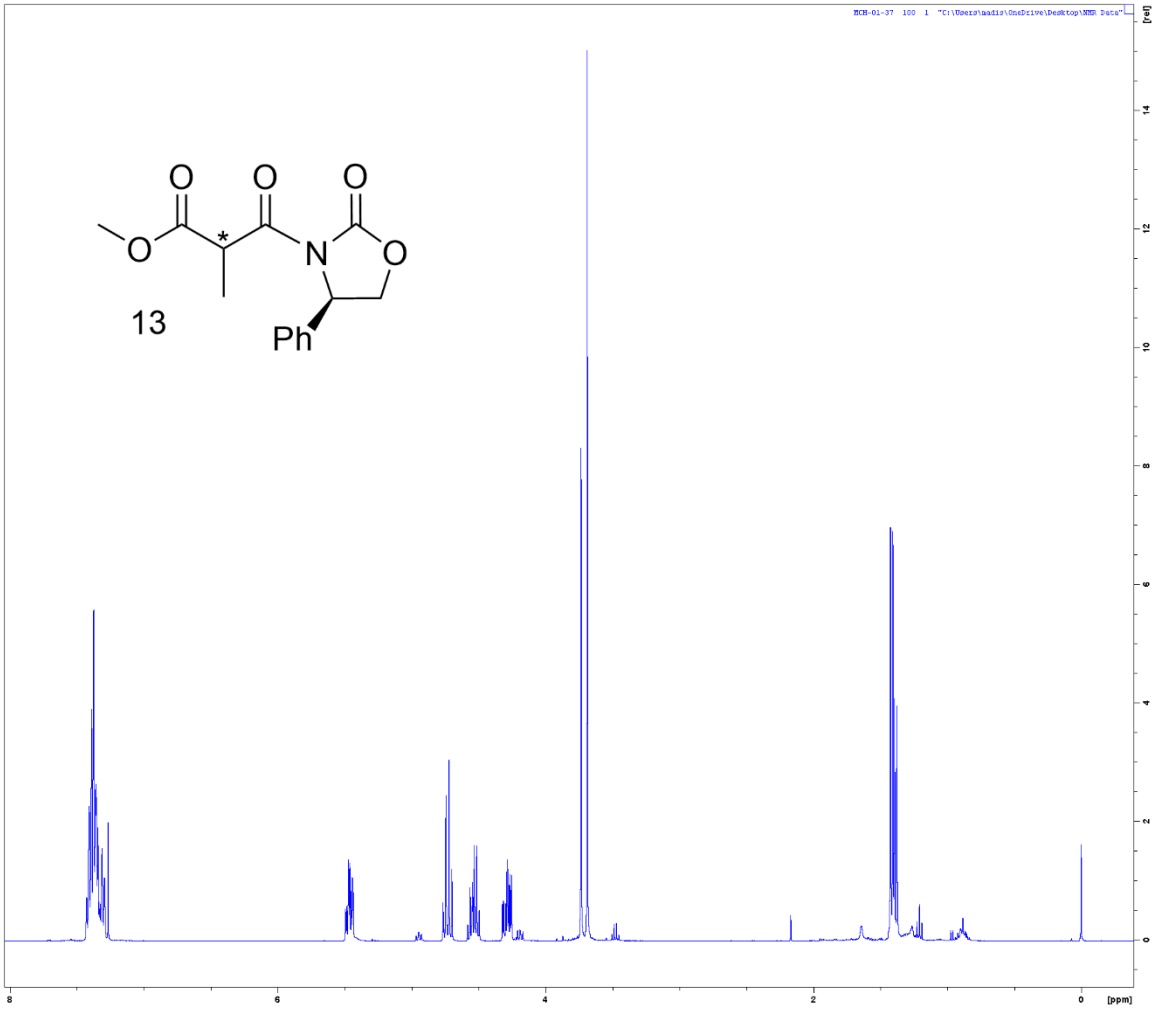


*Figure 21. ^{1}H-NMR of **13***

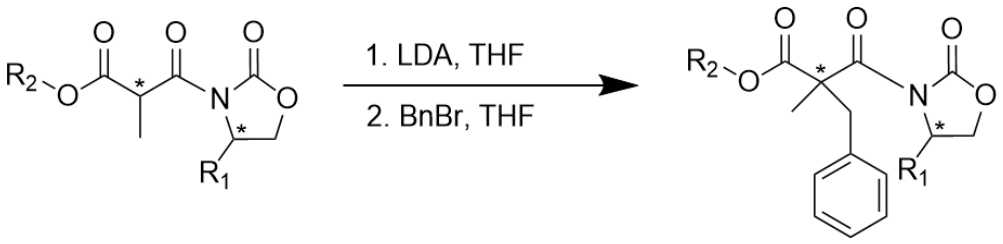
Reverse-phase HPLC of 13

A Lab Alliance PeakSimple Chromatography Data System HPLC equipped with a Rigel C18 column (10 x 250 mm) was used to purify **13**. The sample was dissolved in a solvent system of 1:1 HPLC-grade water and acetonitrile at a concentration of 50 mg per mL and filtered. Peak detection was performed via UV/Vis Spectroscopy at 254 nm for 60 minutes per sample with a flow rate of 1 mL per minute. A gradient solvent system was used and is summarized below.

Time Elapsed (min)	*% Water*	*% Acetonitrile*
0	50	50
15	25	75
45	50	50

Table 5. Reverse-phase HPLC method.

Benzylation of Oxazolidinone Coupled Esters



Scheme 20. Generic benzylation of oxazolidinone coupled esters.

Entry	*R_1*	*R_2*	*Coupled Ester*	*Product*
O_1	iPr	Et	**12**	**14**
O_2	Ph	Me	**13**	**15**

Table 6. Summary of R-groups in oxazolidinone coupled benzylation.

To an oven-dried three-neck round-bottom flask equipped with a stir bar, a stopper, and two septa were added 1.2 molar equivalents of dry diisopropylamine (DIPA) in anhydrous THF via cannula needle at -20 °C under an inert atmosphere of nitrogen. 1.2 molar equivalents of *n*-butyl lithium (*n*-BuLi) were then added dropwise, instantaneously generating lithium diisopropylamide (LDA) before addition of purified oxazolidinone coupled ester dissolved in anhydrous THF. After stirring for 15 minutes, one molar equivalent of benzyl bromide was added and left to stir overnight. The reaction mixture was then diluted with saturated ammonium chloride and extracted three times with ethyl acetate. The organic layer was then washed twice with DI water and once with brine before drying with $MgSO_4$. The solvent was then evaporated under vacuum before examination with ^{1}H-NMR and Mass Spectrometry for detection of product formation.

Benzylation of 12

14 was synthesized using procedures from the general benzylation of oxazolidinone coupled esters with 140.4 µL dry DIPA (1.0 mmol), 3 mL anhydrous THF, 378.1 µL *n*-BuLi (0.9 mmol), 0.2131 g **12** (0.8 mmol), and 98.4 µL benzyl bromide (0.8 mmol). Upon examination with ^{1}H-NMR and ESI-MS, it was determined that no product was formed.

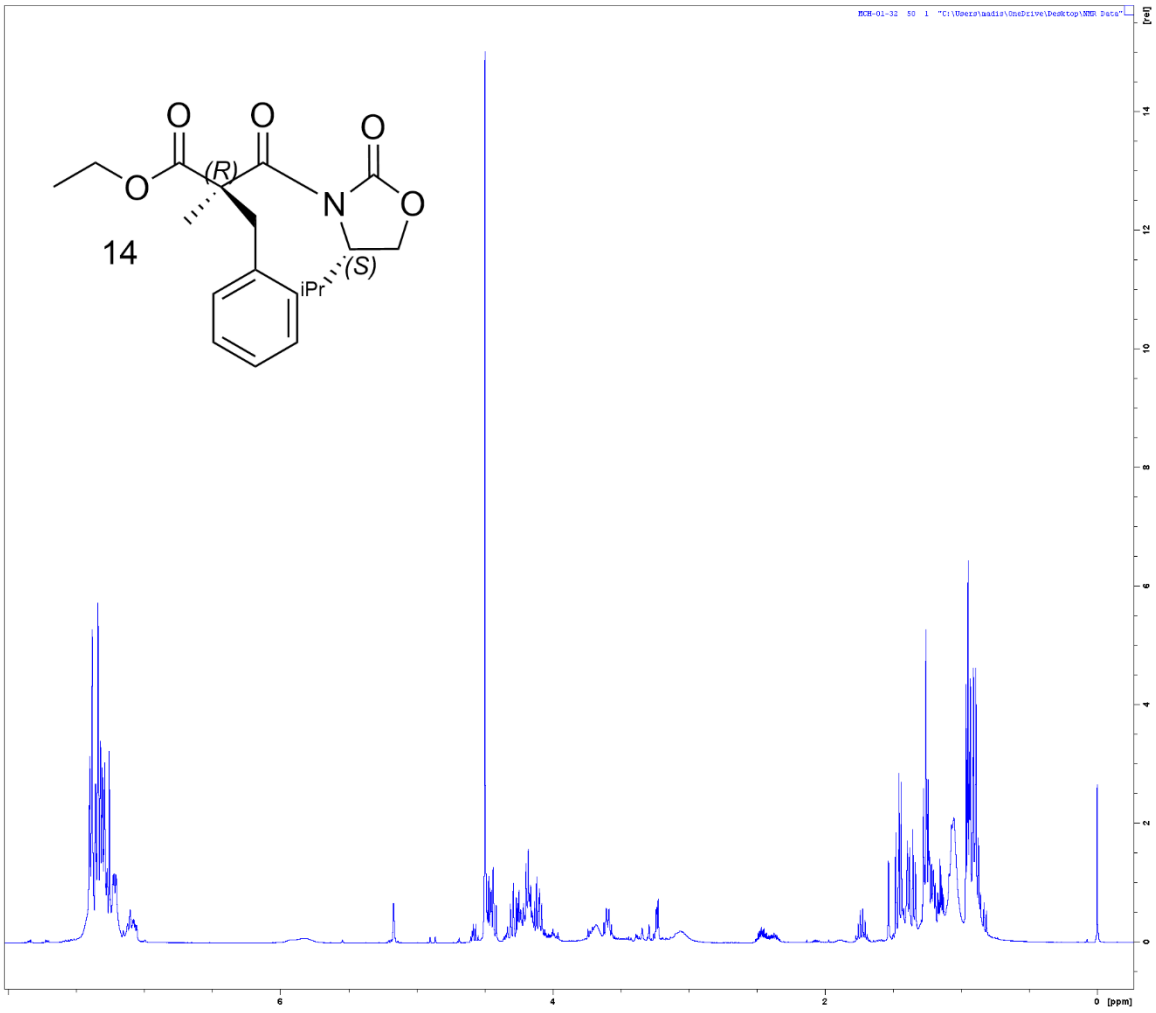


*Figure 22. [1]H-NMR of **14** with trace product formation.*

Benzylation of 13

15 was synthesized using procedures from the general benzylation of oxazolidinone coupled esters with 285.0 µL dry DIPA (2.0 mmol), 6 mL anhydrous THF, 703.0 µL *n*-BuLi (1.6 mmol), 0.46 g **13** (1.7 mmol), and 200.0 µL benzyl bromide (1.7 mmol).The crude product was further purified via Reverse Phase HPLC. ESI MS: $[C_{21}H_{21}NO_5Na^+]$ calculated = 390.13, found = 388.08

Synthesis of **15** from **13** was repeated by adding under N_2 1.2 molar equivalents of NaH dispersion in mineral oil (20.6 mg, 0.9 mmol) and 1 mL of pentane to a conical vial equipped with a stir bar, Claisen adapter, microscale reflux condenser, septum caps. The mineral oil and pentane were then decanted with a needle, and the remaining NaH was suspended in anhydrous THF. The reaction was cooled to 0°C in an ice bath before addition of **13** (117.4 mg, 0.4 mmol) and allowed to stir for one hour. One molar equivalent of benzyl bromide (50.3 μL, 0.4 mmol) was added via syringe, and the solvent was allowed to reflux for 4 hours in a sand bath until the formation of white precipitate. The mixture was then diluted in ice water. The product was extracted with ether three times, and the organic layer was washed twice with DI water and once with brine before drying with $MgSO_4$. The solvent was then evaporated under vacuum before examination of the crude product with ^{1}H-NMR to detect product formation (15.2 mg, 0.04 mmol, 10% yield).

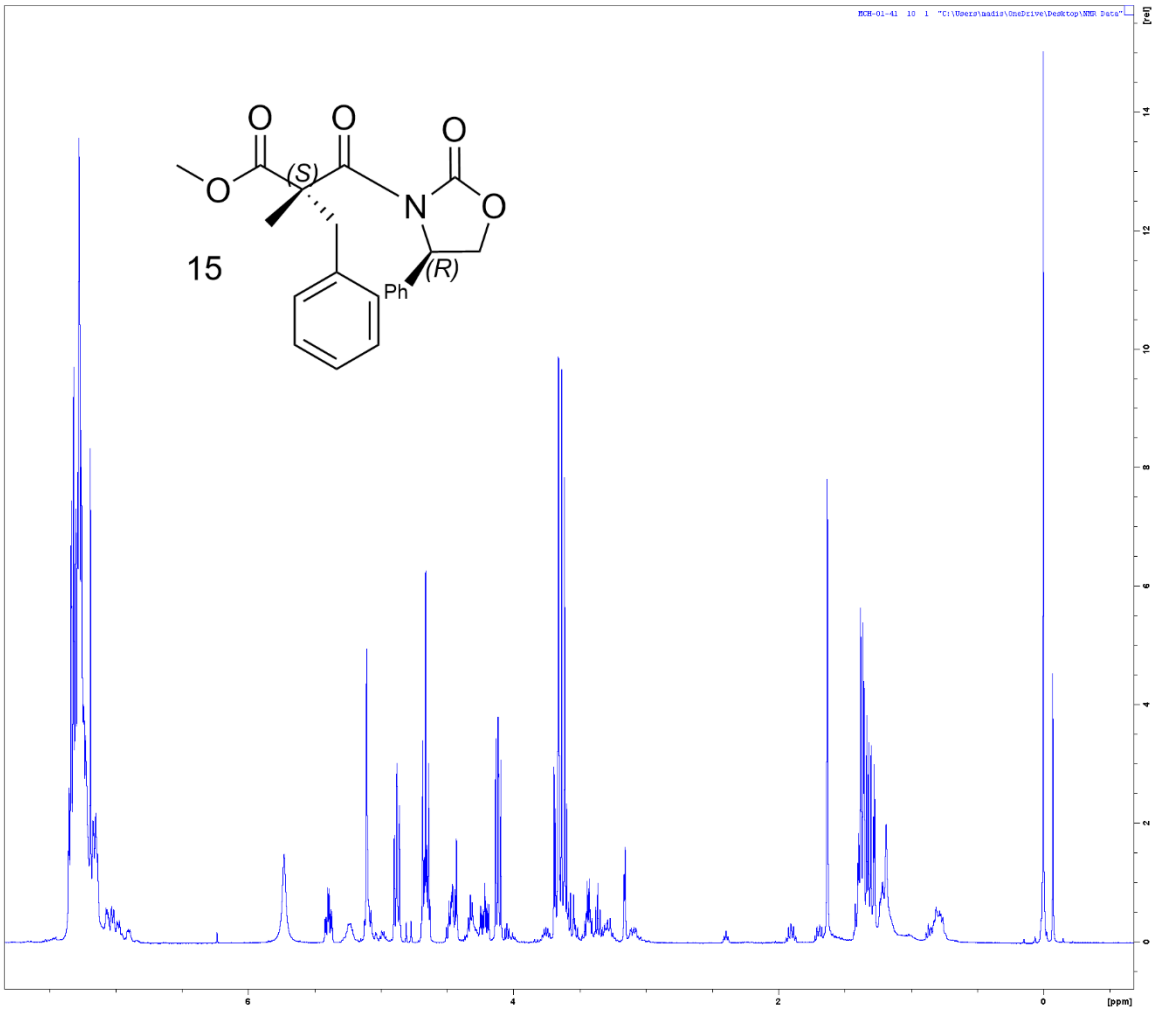


*Figure 23. [1]H-NMR of **15** with trace product formation.*

CHAPTER IV: RESULTS

Substrate Synthesis and Racemic Hydrolysis

Obtaining an accurate mass of the substrate synthesis product **(1)** and analysis via ^{1}H-NMR revealed full conversion of starting material resulting in an 82% isolated yield. A racemic hydrolysis was then performed on **1** (32% yield) to serve as a standard for subsequent hydrolyses. Observation with ^{1}H-NMR depicted in Figure 24 showed the conversion of the singlet at ~3.226 ppm in starting material to two doublets at ~3.164 ppm in the hydrolyzed product due to the topicity of the methylene hydrogens on the benzyl group in the now chiral product.

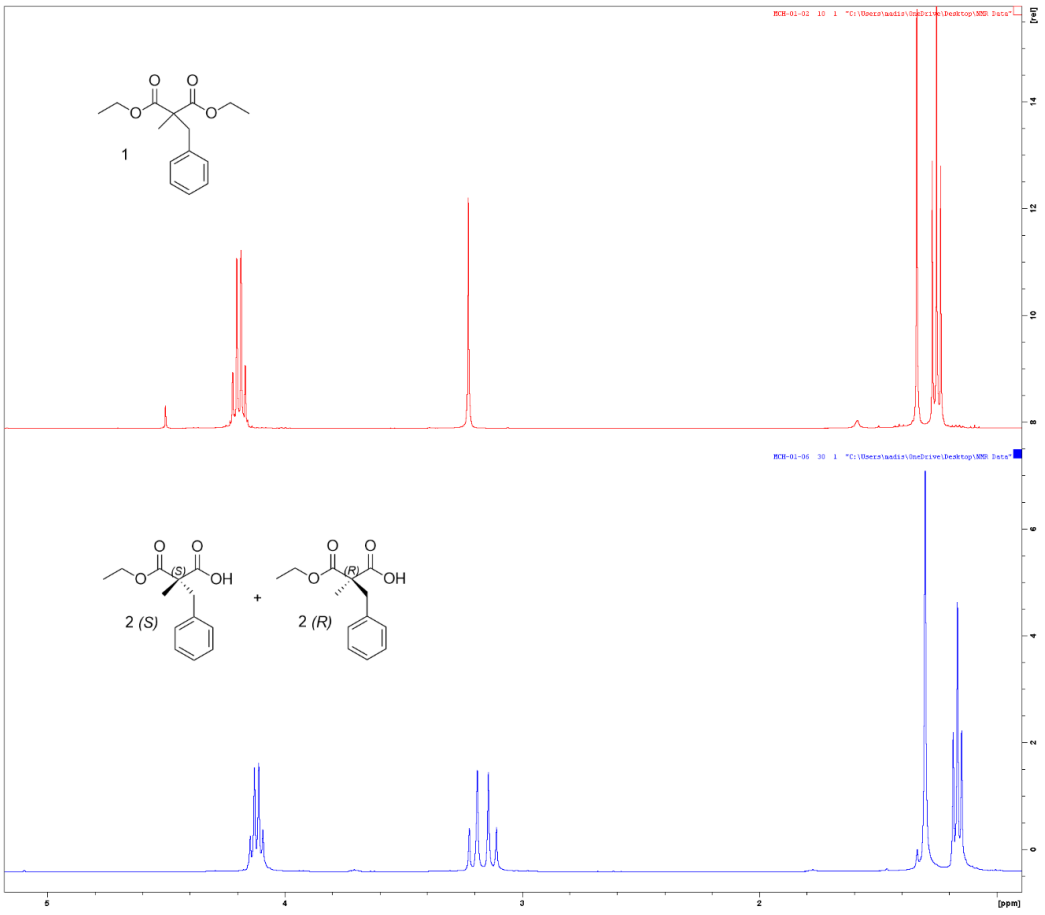


Figure 24. ^{1}H-NMR of substrate (red) and racemic hydrolysis of product (blue).

The hydrolyzed product was then analyzed via chiral HPLC and APCI-MS, in Figures 25 and 26, respectively, according to the procedures described, providing a standard for later catalytic hydrolyses.

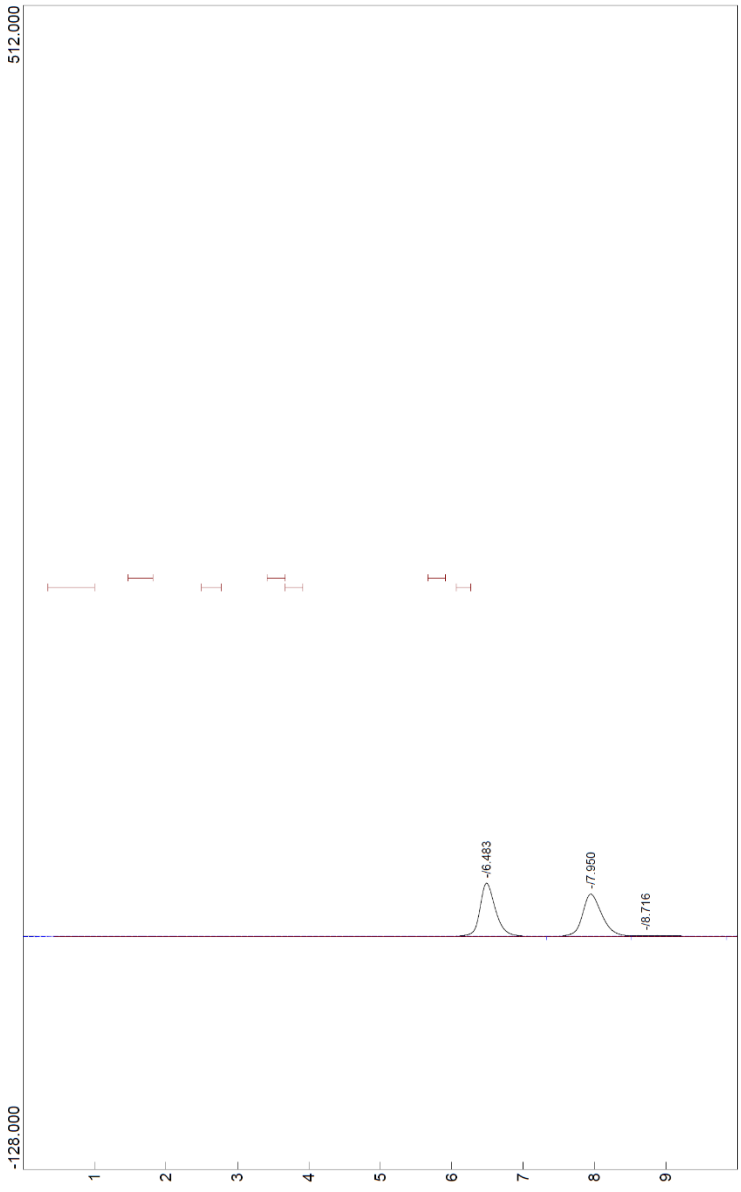


Figure 25. Chiral HPLC (mV vs. min) of racemic hydrolysis with marked retention times.

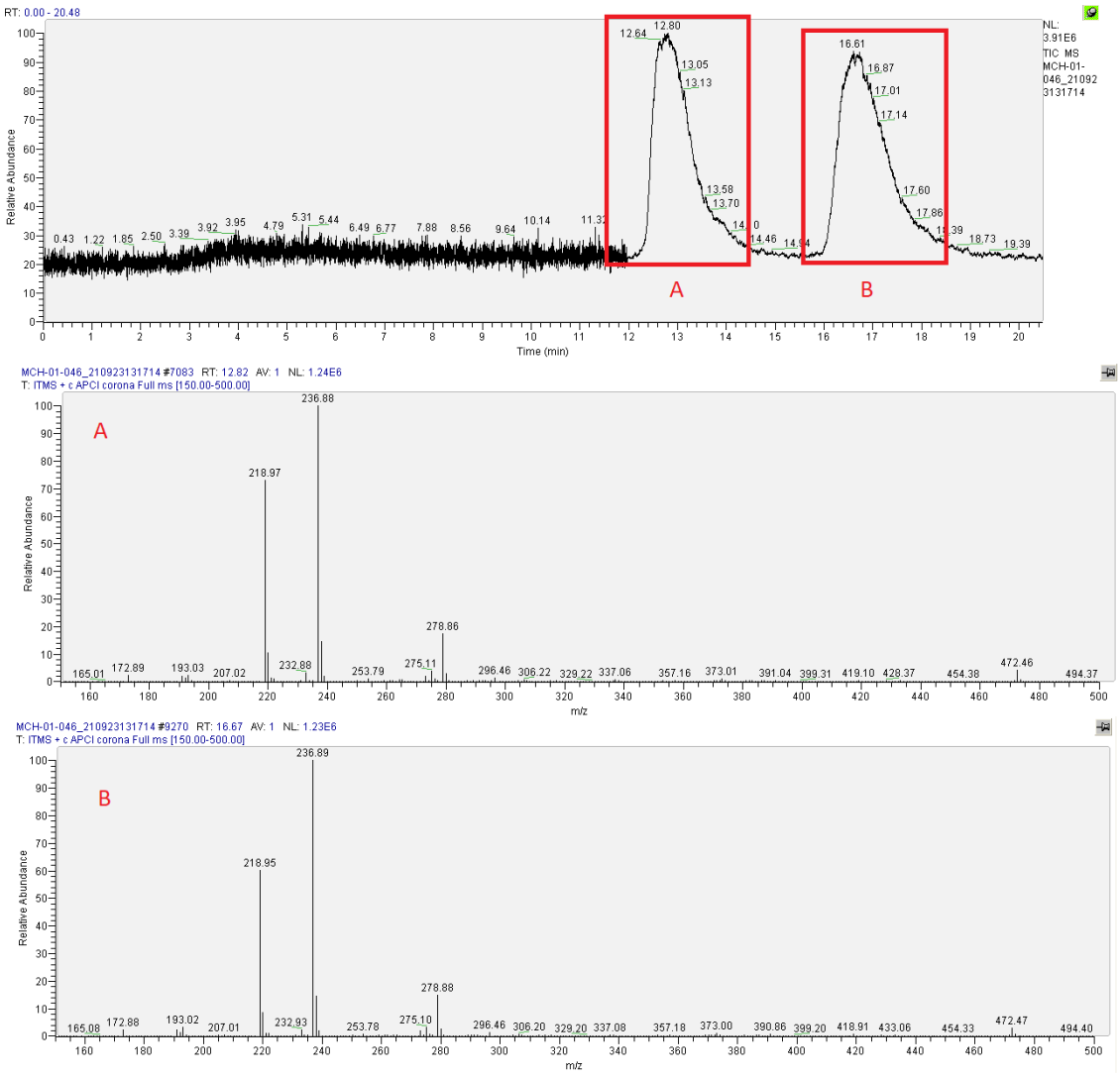


Figure 26. Racemic hydrolysis APCI-MS: [$C_{13}H_{16}O_4H^+$] calculated = 237.10, found = 236.88, 236.89.

N-Benzyl Cinchona-Derived Catalyst Syntheses and Hydrolyses

Catalysts **PTC$_1$**- **PTC$_3$** were then synthesized from cinchonine and each substituted benzyl bromide, yielding each quaternary ammonium salt. **PTC$_4$** & **PTC$_5$** were provided by Allyson Bullock (Yields: **PTC$_1$** 61%, **PTC$_2$** 81%, **PTC$_3$** 65%, **PTC$_4$** & **PTC$_5$** as reported by Allyson Bullock). These were then employed in hydrolysis reactions at 10 mol % and 25 mol %. Yields of these reactions are summarized in Table 7.

	***PTC*$_1$**	***PTC*$_2$**	***PTC*$_3$**	***PTC*$_4$**	***PTC*$_5$**
10 mol %	NR	NR	NR	NR	NR
25 mol %	8%	32%	15%	NA	NA

Table 7. Yields of catalytic hydrolyses.

Reactions yielding product formation were analyzed via APCI-MS, showing nearly racemic hydrolysis.

Control Hydrolyses

To verify the effectiveness of quaternary ammonium salt catalyzed hydrolysis of malonates, controls with less sterically hindered reagents were performed. The first two employed the use of **(1)** hydrolyzed via similar procedures to the cinchona-derived catalyst hydrolyses but substituting the catalyst with Aliquat® 336 and TBAB, producing no reaction for each. This was determined via examination with ^{1}H-NMR, as shown in Figure 27, and the absence of the conversion of the benzyl methylene hydrogens from a singlet to two doublets at ~3.23 ppm.

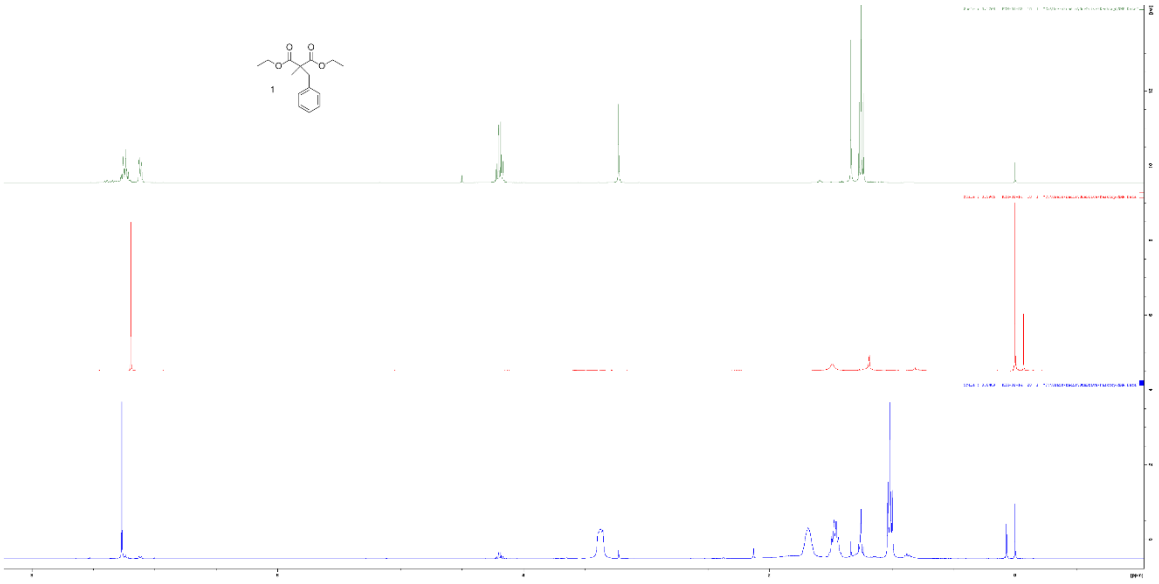


Figure 27. ^{1}H-NMR of substrate (green), Aliquat® 336 hydrolysis (red), and TBAB hydrolysis (blue).

A third control reaction was performed with a less sterically hindered starting material, diethyl methylmalonate, and **PTC$_1$**, also producing no reaction.

Chiral Auxiliary Directed Benzylations

The second investigation in this project employed the coupling of chiral auxiliaries to the prochiral malonates followed by subsequent benzylation reactions. Starting materials were prepared according to the aforementioned procedures, which were then coupled with the selected chiral auxiliaries via acyl chloride formation. Installation of the chiral auxiliaries required the formation of an acyl chloride and subsequent coupling via LDA, which was generated from dry, distilled DIPA and *n*-BuLi whose concentration was determined via Gilman Titration.[31] The menthol coupled ester was used directly in the subsequent benzylation reaction, while the oxazolidinone coupled esters required characterization and purification before further use. Benzylation

of the coupled esters were carried out in similar fashion to synthesis of the substrate **(1)** with yields reported in Table 8.

Menthol	O_1	O_2
15%	NR	Trace

Table 8. Yields of chiral auxiliary directed benzylations.

CHAPTER V: DISCUSSION

Phase-Transfer Catalyzed Hydrolysis

The phase-transfer catalyzed hydrolysis of 2-benzyl 2-methyl malonic acid diethyl ester proved to be a relatively inefficient method for the synthesis of an enantiopure benzyl-substituted malonate half ester as evident in its low yields and lack of stereoselectivity. Initial use at 10 mol % showed no conversion with slight improvement upon increase of catalyst concentration. Still, only one catalyst, **PTC_2**, produced a yield comparable to the racemic hydrolysis. However, examination with APCI-MS showed that this product was nearly racemic. It was hypothesized that these undesirable results were due to steric hinderance between the bulky catalysts and the substrate, prohibiting the ion exchange responsible for the hydrolysis at the interface between the aqueous and organic phases, and inspiring the subsequent control reactions.

Control Hydrolyses

Control hydrolyses were performed using less sterically hindered reagents to explore the lack of product formation in the cinchona-derived catalyzed hydrolyses. Of the three reactions, none produced product, reinforcing the theory that steric hinderance between the benzyl group of the substrate and the catalysts was likely the cause of low yield.

Chiral Auxiliary Directed Benzylation

Chiral auxiliary directed benzylation of malonic esters also proved unsuccessful as evident in the low yields obtained in each reaction. Due to the recovery of uncoupled chiral auxiliary in the benzylated products and report of this phenomenon in literature, it

is hypothesized that the chiral auxiliaries separated from the esters in the benzylation reaction via an unknown mechanism.[14]

CHAPTER VI: CONCLUSION

Hydrolysis of the phenylalanine precursor 2-benzyl-2-methyl-malonic acid diethyl ester with PLE produces only a maximum enantiomeric excess of 17%, inspiring the investigations presented here.[4] Several methods explored for more efficient enantioselective asymmetric synthesis of benzyl-substituted malonic half ester, included phase-transfer catalyzed hydrolysis and chiral auxiliary directed benzylation.

Unfortunately, neither of these methods produced an improvement over the hydrolysis with PLE, but they offered insight into future methods that may be explored. Only one class of cinchona-derived catalysts was employed here, so more remain for further investigation including *N*-Benzyl, *N*-9-Anthracenylmethyl, polymeric, electronic factor-based, and solid-supported cinchona-derived PTCs.[27] Additionally, alteration of the procedures used, like lowering reaction temperature to increase the rate difference between each enantiomer or alteration of stirring strength to increase or decrease the surface area for interaction of the phases, may increase reaction yields.

There are also more chiral auxiliaries to be explored, like the imidazolidinones, which were intended to be used in this project but were not due to supply chain bottlenecks resulting from the COVID-19 pandemic.[14] Though an effective method for the enantioselective asymmetric synthesis of benzyl-substituted malonic acid esters still remains to be found, this research provided valuable groundwork in the investigation.

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