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Michael J. E. Collins Date

Cu- and Pd-Catalyzed α-Hydroxycyclopropanol Ring Opening Reactions: Electrophilic Trappings to 3-Furanones, and Carbonylation to 4-Ketovalerolactones.

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Michael Collins
B.S., Chemistry, Rowan University, 2019

Advisor: Mingji Dai, Ph.D.

A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of
Master of Science
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2023

Abstract

Cu- and Pd-catalyzed α-hydroxycyclopropanol ring opening reactions: electrophilic trappings to 3-furanones, and carbonylation to 4-ketovalerolactones.

By Michael Collins

Cyclopropanols are a useful tool in synthetic organic chemistry, due to their intrinsic ring strain within the cyclopropane ring. For cyclopropanols, they can undergo two distinct reactivity modes. One of which is heterolytic cleavage to form a metal-homoenolate species, and the other being a β-keto radical species. Both reactive intermediates have interesting reactivity, and both can be formed selectively by careful choice of the reaction conditions applied. Hydroxycyclopropanols have been studied in recent years to access various useful synthetic motifs that are present in different natural products, and medicinally relevant compounds. The Dai group has been a pioneer in this area chemistry, synthesizing an array of scaffolds from these hydroxycyclopropanols. The Dai group managed to synthesize these scaffolds from the generated metal-homoenolate species with or without the presence of carbon monoxide to synthesize oxaspirolactones, THF and THP-fused bicyclic lactones, and substituted THF and THP heterocycles. Herein, the application of similar concepts to access two new classes of scaffolds, 3-furanones, and 4-ketovalerolactones will be discussed. Notably these two scaffolds can be accessed from the same starting material, where careful reaction optimization will be disclosed for each method. Additionally, the substrate scope for each method, diversification, and mechanistic studies will be discussed.

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
atm	atmosphere
APCI	atmospheric pressure chemical ionization
Ar	aryl
ATR	attenuated total reflectance
BHT	butylated hydroxytoluene
Bn	Benzyl
Bpin	Pinacolborane
BQ	benzoquinone
Bu	Butyl
CO	carbon monoxide
Cy	cyclohexyl
Cp	cyclopentadienyl
δ	delta
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DCBQ	dichlorobenzoquinone
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMBQ	dimethylbenzoquinone
DME	dimethoxyethane

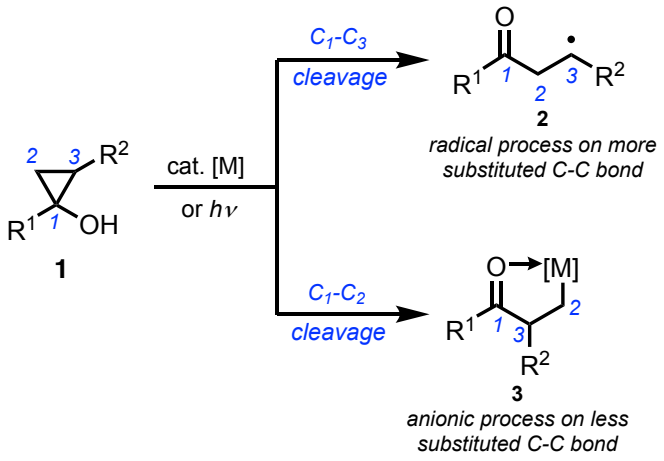
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
Equiv.	equivalents
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
gem	geminal
h	hour
Hex	hexyl
HRMS	high-resolution mass spectrometry
IR	infra-red
M	molar
m-	meta
Me	methyl
MeCN	acetonitrile
MHz	mega hertz
MS	molecular sieves
MTBE	methyl tert-butyl ether
m/z	mass to charge ratio
Naph	Naphthalene
NMR	nuclear magnetic resonance
o-	ortho
OTf	trifluoromethylsulfonyl
p-	para
PGDM	prostaglandin D_2 metabolite

Ph	phenyl
PhMe	toluene
Pr	propyl
PTSA	para-toluenesulfonic acid
r.t.	room temperature
TBS	*tert*-butyldimethylsilyl
TLC	thin layer chromatography
Ts	tosyl
TFA	trifluoroacetic acid
TFBQ	tetrafluorobenzoquinone
TC	thiophene-2-carboxylate
THF	tetrahydrofuran
THP	tetrahydropyran
TBAF	tetrabutylammonium fluoride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
XPhos	[2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl]

CHAPTER 1. CU- AND PD-CATALYZED α-HYDROXYCYCLOPROPANOL RING OPENING REACTIONS: ELECTROPHILIC TRAPPINGS TO 3-FURANONES, AND CARBONYLATION TO 4-KETOVALEROLACTONES.

1.1 Introduction:

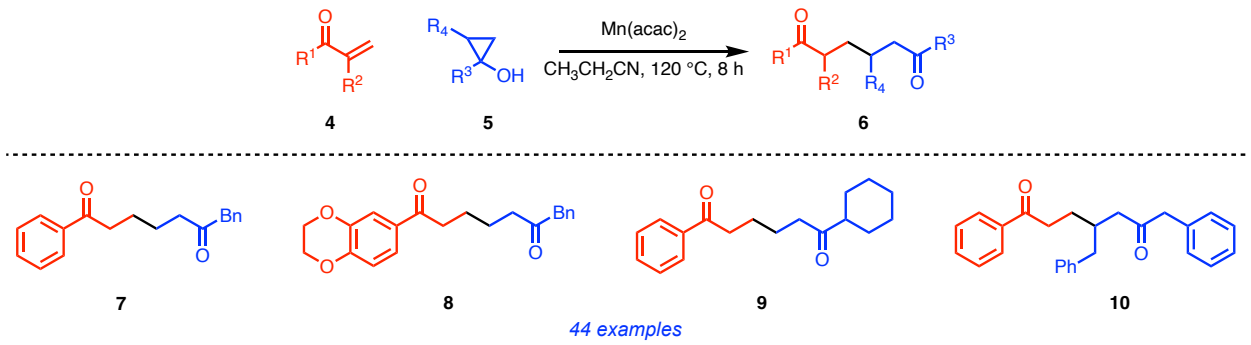
Across various synthetic methods in organic synthesis, one of the most powerful synthetic tools is the release of ring strain. Releasing ring strain is widely used as a tool for further functionalization of sometimes unactivated systems. Cyclopropanols **1** are widely seen as a powerful starting material, due to the intrinsic ring strain that these compounds possess.[1] Much like other modes of releasing ring strain, cyclopropanols can undergo two distinct modes of ring opening. Envisioning ring opening of the cyclopropanol through an anionic process, which typically happens in the presence of transition metal catalysts, a C_1-C_2 cleavage at the lesser substituted carbon occurs as seen in Scheme 1.1. This specific intermediate **3** is often referred as a metal-homoenolate, which has seen various modifications due to the high reactivity of this intermediate. Taking the same cyclopropanol **1**, if a single-electron process occurs, then cleavage would then occur at C_1-C_2 where the generated β-keto radical species would lie on the more substituted carbon. For this specific process if heterolytic cleavage occurred at the less substituted carbon, the resulting β-keto radical species would be a primary radical species, which is not thermodynamically favored in comparison to a secondary radical species. Lastly, from either intermediate **2** or **3**, various oxidations, reductions, and electrophilic couplings could occur (Scheme 1.1).[2,3]



Scheme 1.1 Traditional modes of opening cyclopropanols.

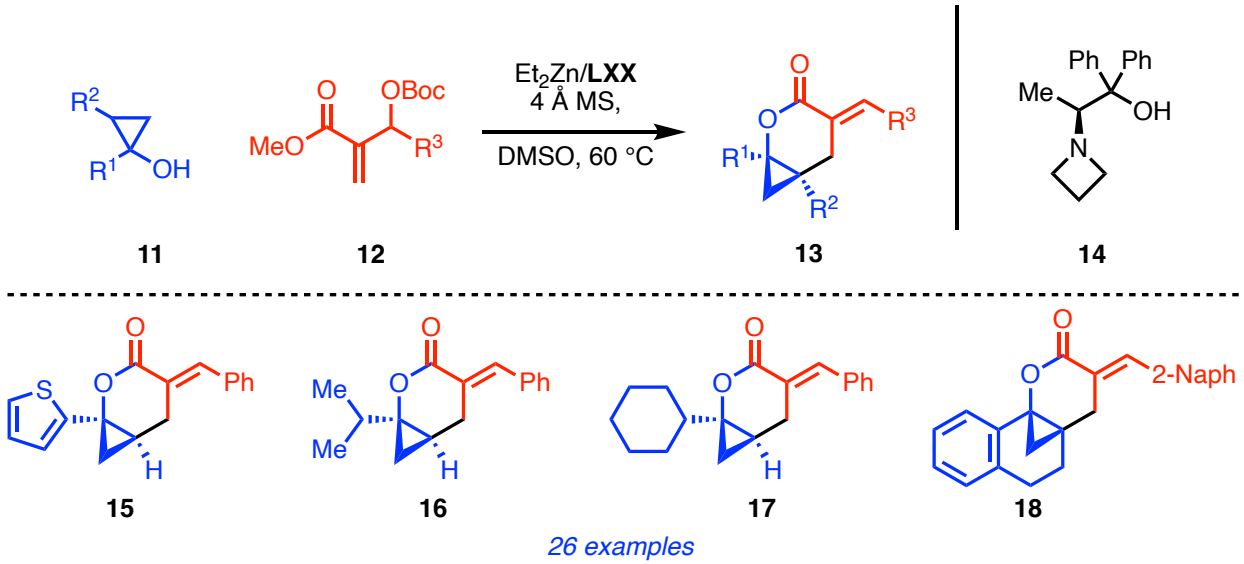
In 2019 Loh and co-workers developed an efficient protocol for the coupling of enones with cyclopropanols with the use of a manganese catalyst. Their optimal reaction conditions were mild with low catalytic loading of $Mn(acac)_2$ at 10 mol%, in propiononitrile at 120 °C for 8 hours.[4] After various mechanistic studies it was elucidated that the reaction goes through a single electron process, generating a β-keto radical species which is further coupled with the enone used for this system. Notably for their catalytic cycle it is proposed that the manganese (II) catalyst generates a O-centered radical species through a proton coupled electron transfer reaction (PCET), which then generates a manganese (I) catalyst.[5] The following ring opening reaction would generate the β-keto radical, which is then coupled to the enone, generating a new β-keto radical species. This new radical intermediate would then be reduced by manganese (I) to form a carbanion, and the active manganese (II) catalyst, where lastly this carbanion would further be quenched upon work-up. This coupling between readily available enones, and cyclopropanols demonstrated a wide substrate scope with good functional group tolerability for both the cyclopropanol and enone. Various electron donating, and electron withdrawing substituents for the enone were tolerated. As well as

electron donating, withdrawing, and trisubstituted cyclopropanols were all tolerated under the optimized reaction conditions.



Scheme 1.2 Loh's coupling reaction of cyclopropanols and enones.

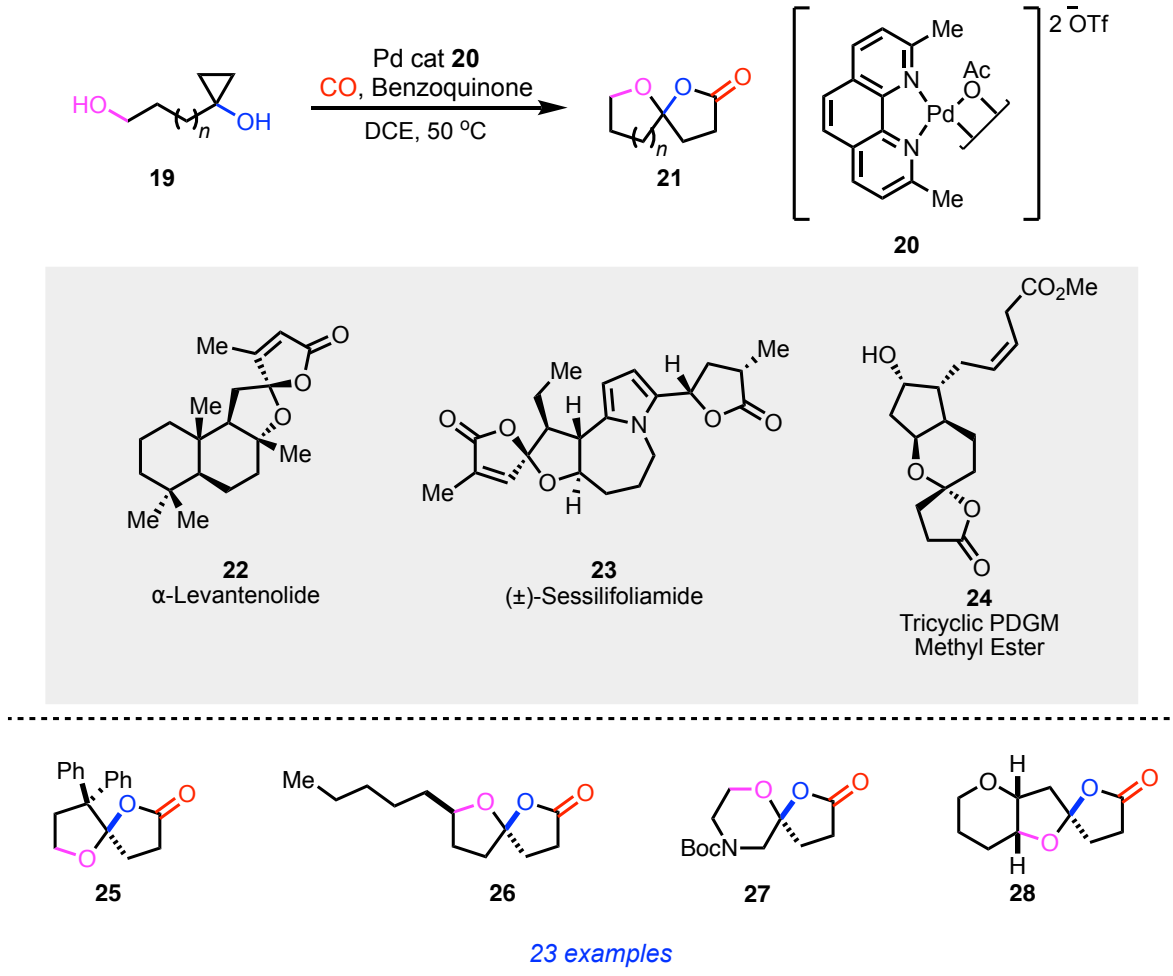
More recently in 2021, Yoshikai and co-workers envisioned a new transformation of cyclopropanols via an enolized metal-homoenolate intermediate. This method was successful with retention of the cyclopropane ring, which is often opened in chemistry related to cyclopropanols. This method looks at this highly reactive intermediate in a new light, where the metal-homoenolate can be intercepted as an intermediate and be further functionalized. This method was successful for the conversion of various cyclopropanols **11**. In the presence of 10 mol% $ZnEt_2$ and 15 mol% of chiral ligand **14**, coupling with Mortia-Baylis-Hillman (MBH) carbonates **12**, in DMSO with gentle heating to 60 °C to generate cyclic lactones with a cyclopropane ring, with high diastereoselectivity.[6] This powerful method utilizes the high reactivity of these cyclopropanols, while still maintaining the cyclopropane ring after functionalization. Inspired by the work of Rousseaux[7, 8] this method had a wide substrate scope for different cyclopropanols, as well as MBH carbonates to generate a wide array of lactones (Scheme1.3).



Scheme 1.3 Yoshikai's β-functionalization of cyclopropanols via enolized homoenolate.

In 2016, Dai and co-workers envisioned a different intramolecular trapping of the resulting metal-homoenolate with a hydroxy nucleophile. Taking different lactones and subjecting them to Kulinkovich conditions could access the necessary cyclopropanol **19** in a single step. Subjecting the hydroxycyclopropanols to the cationic palladium-catalyst **20** in the presence of carbon monoxide, would generate these complex oxaspirolactones.[9] Upon ring opening to generate the metal-homoenolate, subsequent nucleophilic trapping of the distal hydroxy group would generate a hemiacetal. With the pendant metal-homoenolate this then would undergo carbon monoxide insertion to generate an acyl-palladium species, which upon further cyclization and reductive elimination from the resulting hemiacetal would give the corresponding oxaspirolactone **21**. Oxaspirolactones are a privileged scaffold in natural products where access to these compounds in an efficient manner would then give rise to the synthesis of many of these potent natural products.

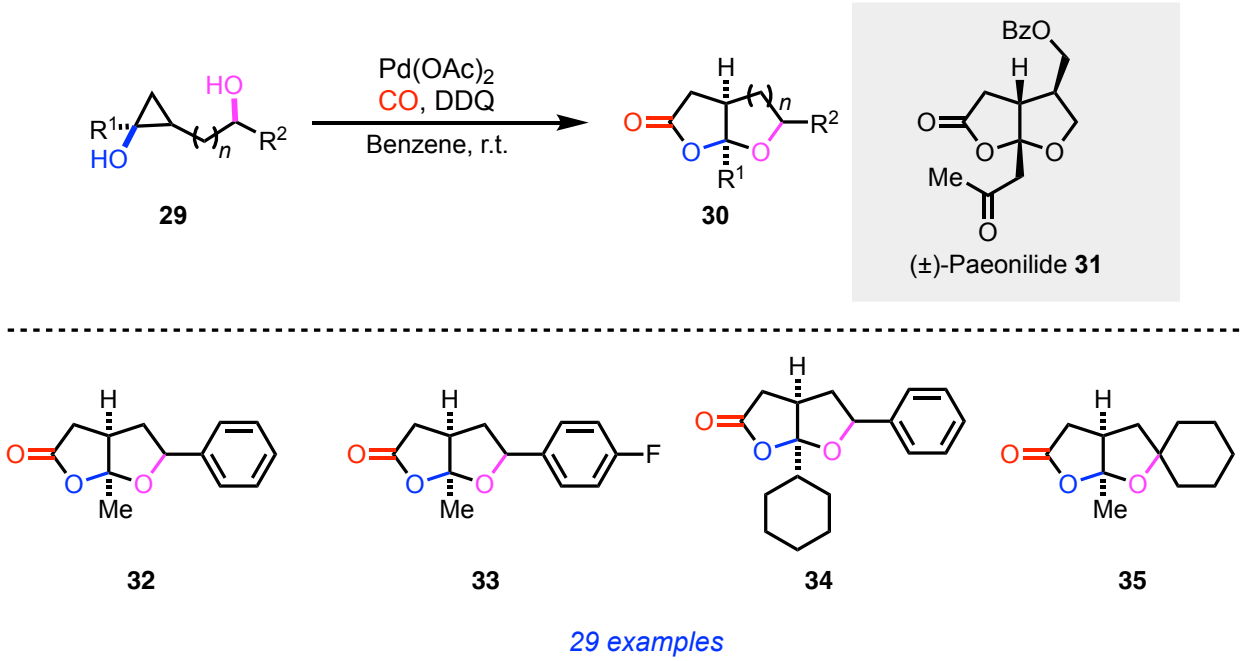
This method was successful for the synthesis of several natural products such as α-Levantenolide **22**,[9] (±)-Sessilifoliamide **23**,[10] and Tricyclic PDGM Methyl Ester **24** (Scheme 1.4).[11]



Scheme 1.4 Dai's palladium-catalyzed carbonylative oxaspirolactonization of cyclopropanols.

Several years later, in 2020, Dai and co-workers developed a new palladium-catalyzed hydroxycyclopropanol carbonylation reaction, but instead to make fused bicyclic lactones. It was envisioned that changing the location of the nucleophilic trapping alcohol to the 2-position on the cyclopropane ring backbone could lead to cyclopropanol **29**, and upon cyclopropanol ring opening and carbonylative lactonization could lead to different fused lactones **30**.[12] Much like oxaspirolactones, these fused lactones are also present in many natural products, where an efficient

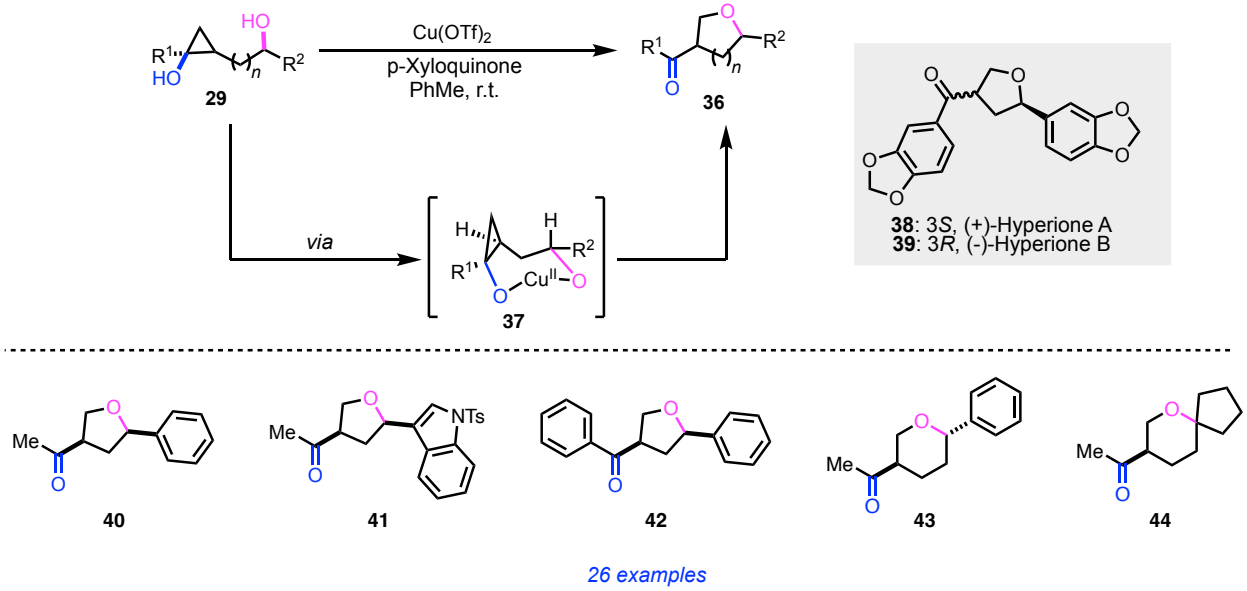
method to access this scaffold could then streamline the synthesis for such complex natural products. Again, this method proved useful for having a wide substrate scope and good functional group tolerability, and was also successful in synthesizing (±)-Paeonilide **31** (Scheme 1.5).



Scheme 1.5 Dai's palladium-catalyzed carbonylative lactonization for fused bicyclic lactones.

Dai and co-workers have already elaborated on various transformations that are possible with cyclopropanols, having great success in this area of chemistry. Specifically various trapping reactions of electrophilic species were successful, with a copper-catalyst.[13, 14, 15, 16] Following the great success of the previously mentioned hydroxycyclopropanol methods, for making oxaspirolactones, and fused bicyclic lactones, Dai and co-workers elaborated on the scope of transformations that could be possible with hydroxycyclopropanols. Taking the knowledge that they accrued from earlier cyclopropanol chemistry (with copper-catalysis), and the different palladium-catalyzed carbonylative transformations that were successful, a new copper-catalyzed cyclopropanol ring opening was envisioned. Taking the same cyclopropanol starting material from

the aforementioned method to make fused bicyclic lactones (**29**, Scheme 1.5), and subjecting this cyclopropanol to copper-catalysis in the presence of oxidant could accomplish the construction of substituted furans and pyrans.[17] Dai and co-workers have established that copper-catalysts are efficient catalysts for opening cyclopropanols, so extending this knowledge to this system worked quite well. They were able to synthesis (+)-Hyperione A **38** and (-)-Hyperione B **39** in 3 and 4 steps respectively, which are the shortest syntheses to date for these molecules. Much like the previous methods described, this hydroxycyclopropanol ring opening also had a wide substrate scope and good functional group tolerability (Scheme 1.6).

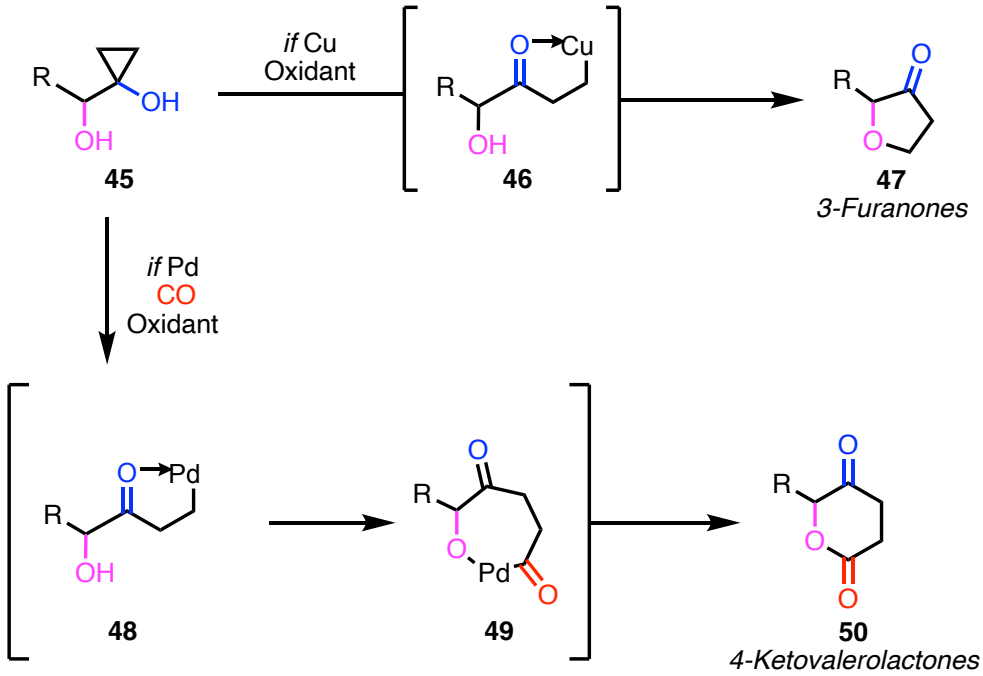


Scheme 1.6 Dai's copper-catalyzed cyclopropanol ring opening and nucleophilic trapping for THF and THP rings.

1.2 Results and Discussion:

With different precedents available for the construction of various scaffolds from hydroxycyclopropanols, a new hydroxycyclopropanol was envisioned. Simple relocation of the pendant nucleophilic trapping alcohol, to the 1-position on the cyclopropanol backbone, and more specifically the α-position of the hydroxy group on the cyclopropane ring would lead to compound

45. Taking the newly designed cyclopropanol and subjecting it to copper-catalysis would then lead to metal-homoenolate **46**, where coordination of the resulting newly oxidized ketone to the metal could occur, before nucleophilic trapping and oxidative C-sp^3-O bond formation, thus resulting in reaction design for 3-furanones **47**. Conversely, with the introduction of palladium catalyst and carbon monoxide, subjecting cyclopropanol **45** to these conditions would generate a new metal-homoenolate **48**, where carbon monoxide insertion would generate acyl-palladium species **49**. Simple nucleophilic trapping of **48** and reductive elimination would then generate 4-ketovalerolactones **50** (Scheme 1.7).

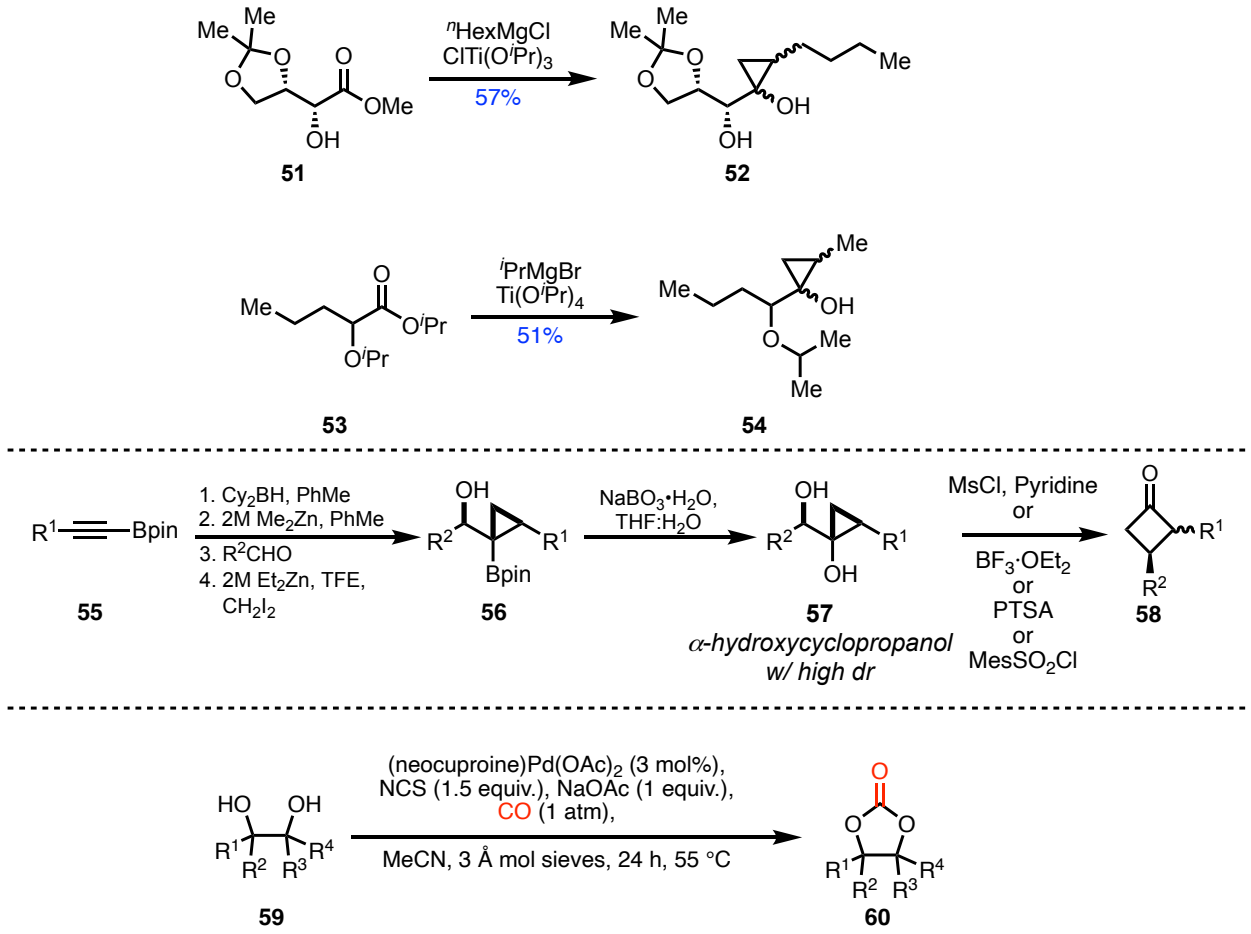


Scheme 1.7 Reaction design for α-hydroxycyclopropanols to 3-Furanones and 4-Ketovalerolactones.

Various challenges accessing these α-hydroxycyclopropanols have already been elucidated in the literature. In 2000, Cha and co-workers encountered various issues when

performing the Kulinkovich reaction on these α-hydroxyesters, such as compounds **51** and **53**. When subjecting either of these compounds to standard Kulinkovich reaction conditions, it generated compounds **52** and **54** (when prepared from compounds **51** and **53** respectively). In both cases all four possible diastereomers were generated which proved extremely challenging to separate these diastereomers.[18] In addition to Kulinkovich reaction conditions to generate these trisubstituted hydroxycyclopropanols, Walsh and coworkers developed an elegant solution to address the challenges encountered by Cha and coworkers. Walsh developed a one-pot protocol for the synthesis of these α-hydroxycyclopropanols with high diastereoselectivity.[19] Taking different borylated alkynes **55** and a series of interesting transformations was accomplished. First, hydroboration of the alkyne, and subsequent transmetallation of the resulting cyclohexylborane with dimethyl zinc would afford a vinyl zinc species which was then trapped with different aldehydes. Simmons-Smith cyclopropanation of the resulting intermediate then affords the resulting α-hydroxycyclopropane, **56**, which could be converted to the desired α-hydroxycyclopropanol with oxidative conditions to afford **57.** Unfortunately, the operational complexity and reproducibility of such methods did not afford our efforts with these highly desirable trisubstituted α-hydroxycyclopropanols. Aside from the operational complexity and poor diastereoselectivity of the previously mentioned methods, additional concerns were present when subjecting the obtained α-hydroxycyclopropanols to different conditions. As explored by both Cha and Walsh, conversion of these α-hydroxycyclopropanols to the corresponding cyclobutanone **58** under basic and acidic conditions is facile and quite easy. Due to the inherent ring strain of these cyclopropanols the addition of Lewis or Brønsted acids, as well as various bases can induce the Pinacol-type rearrangement to generate these cyclobutanones. This challenge would further be encountered during our exploratory studies during the optimization of our envisioned

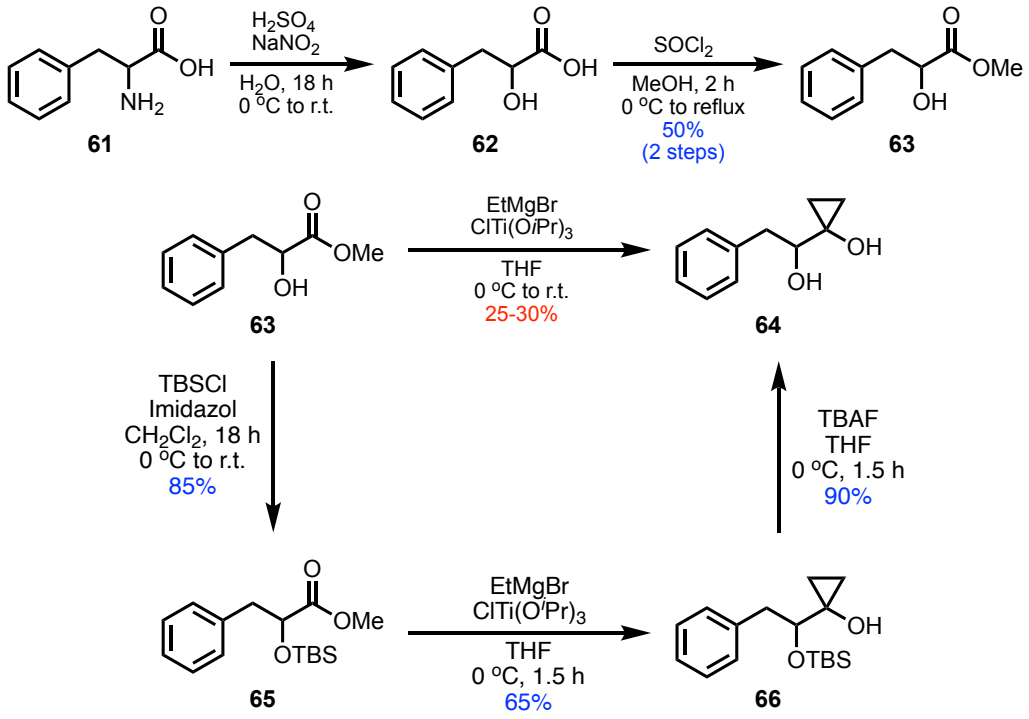
transformations due to the Lewis acidity of some copper-catalysts. Lastly, in 2011 Waymouth and co-workers developed the synthesis of cyclic carbonates **60** from the corresponding 1,2-diol **59**, Using palladium-catalysis and carbon monoxide as the one carbon linchpin.[20] Although this system, and the system for the palladium-catalyzed carbonylation of cyclopropanols is quite different, this challenge must be known because of the similar starting materials used since these α-hydroxycyclopropanols are 1,2-diols (Scheme 1.8).



Scheme 1.8 Challenges associated with 1,1,2-trisubstituted α-hydroxycyclopropanols.

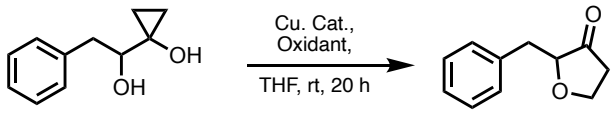
With the previous challenges in mind, we set out to determine a suitable model substrate for the exploration of these newly designed methods. First, commercially available DL-

Phenylalanine **61** was treated with concentrated sulfuric acid, and sodium nitrite in water for 18 hours, from 0 °C to room temperature, and afforded α-hydroxycarboxylic acid **62**. The crude α-hydroxy carboxylic acid was treated thionyl chloride in refluxing methanol for 2 hours to afford the α-hydroxy methyl ester **63** in 50% yield over the first two steps. Subsequent Kulinkovich reaction with various conditions (catalytic or stoichiometric amounts of titanium) and different equivalents of ethyl magnesium bromide only led to poor isolated yields of the desired model substrate **64**. Reaction conditions using 2.4 equivalents of $Ti(OiPr)_3Cl$ and 4.8 equivalents of EtMgBr at 0 °C for 3 hours afforded the model substate in 30% yield. This material supply issue was circumvented with simple protection to the TBS silyl ether **65** in 85% yield. Kulinkovich of the generated protected alcohol to give **66** in 65% yield. Lastly, simple deprotection with TBAF at 0 °C to room temperature then afforded model substrate **64** in 90% yield (Scheme 1.9).



Scheme 1.9 Model substrate 64 synthesis.

Table 1.1 Reaction optimization for Cu-catalyzed α-hydroxycyclopropanol ring opening reaction.



64
(0.1 mmol)

67

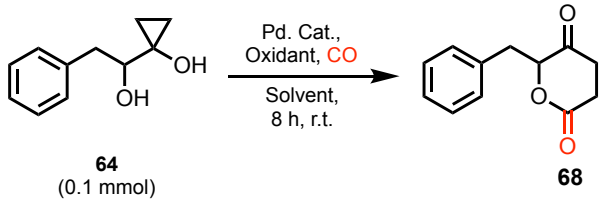
Entry	Cu cat. (x equiv.)	Oxidant (1.0 equiv.)	THF	NMR yield (%)
1	$Cu(OAc)_2$ (0.5)	DDQ	10 mM	90[a]
2	$Cu(OAc)_2$ (0.5)	DDQ	20 mM	90[a]
3	$Cu(OAc)_2$ (0.5)	DDQ	30 mM	83
4	None	DDQ	10 mM	NR
5	$Cu(OAc)_2$ (0.1)	DDQ	10 mM	93[a]
6	$Cu(OAc)_2$ (0.075)	DDQ	10 mM	79[a]
7	$Cu(OAc)_2$ (0.05)	DDQ	10 mM	84[a]
8	$Cu(OAc)_2$ (0.01)	DDQ	10 mM	58[b]
9	$Cu(OAc)_2$ (0.1)	None	10 mM	7[a]
10	$Cu(OAc)_2$ (1.0)	DDQ	10 mM	79[a]
11	$Cu(OAc)_2$ (0.1)	TFBQ	10 mM	74
12	$Cu(OAc)_2$ (0.1)	Chloranil	10 mM	69
13	$Cu(OAc)_2$ (0.1)	2,5-DCBQ	10 mM	37
14	$Cu(OAc)_2$ (0.1)	2,6-DCBQ	10 mM	19
15	$Cu(OTf)_2$ (0.1)	DDQ	10 mM	74[a]
16	$CuCl_2$ (0.1)	DDQ	10 mM	66
17	$CuBr_2$ (0.1)	DDQ	10 mM	49
18	$CuSO_4$ (0.1)	DDQ	10 mM	NR
19	CuTC (0.1)	DDQ	10 mM	82

NMR yield taken with 1,2 dibromoethane as internal standard
[a]Isolated yield. [b]SM not fully consumed.

With the model substrate in hand, we started evaluating the reaction conditions. In this study, parameters such as copper-catalyst, oxidant, and concentration were evaluated. The yields were assessed by NMR using, 1,2-dibromoethane as internal standard and using the methylene hydrogens as product reference. Reaction optimization for the copper-catalyzed ring opening reaction began with promising results from the palladium-catalyzed carbonylation reaction that was screened in-tandem. Reaction optimization first began with screening of copper-catalyst $Cu(OAc)_2$ with low catalytic loading to prevent the cyclobutanone byproduct from forming, since this copper-catalyst did not show high Lewis acidic character. Introducing 1.0 equivalent of DDQ as oxidant, THF as solvent which provided good yields for the palladium-carbonylation reaction

optimization (Table 1.2) with low concentration, provided the desired furanone **67** in great yield (Table 1.1, entry 1). Further increasing of the concentration for the reaction proved to give depreciable yields (entries 2 and 3). Copper proved to be necessary to carry out this transformation, as no copper introduced for the system gave no conversion (entry 4). Lowering of the catalytic loading to 10 mol% of $Cu(OAc)_2$ proved to be optimal for this transformation, giving an isolated yield of 93%, for the optimal conditions shown (entry 5). Further decreasing of the catalyst to 7.5 mol%, 5 mol%, and 1 mol% did not prove to be as powerful as 10 mol% for catalytic loading (entries 6, 7, and 8). Different electron deficient oxidants were also screened such as TFBQ, Chloranil, 2,5-DCBQ, and 2,6-DCBQ, but only gave low NMR yields of the desired 3-furanone (entries 11, 12, 13, 14). Lastly, different copper-catalysts were also evaluated. $Cu(OTf)_2$ although having high Lewis acidity was effective in converting **64** to the desired 3-furanone with low catalytic loading, in 74% yield (entry 15). Other copper (II) catalysts such as $CuCl_2$, $CuBr_2$, and $CuSO_4$ gave yields of 66% NMR yield, 49% NMR yield, and no reaction (entries 16, 17, and 18). Lastly CuTC, a copper (I) catalyst was evaluated which was successful for this transformation in 82% NMR yield (entry 19). Variation of oxidant and copper-catalyst did not prove to be necessary, where the optimized reaction conditions were 93% isolated yield with 10 mol% $Cu(OAc)_2$, 1.0 equivalent of DDQ, at low concentration 10 mM in THF, for 20 hours (entry 5).

Table 1.2 Reaction optimization for Pd-catalyzed α-hydroxycyclopropanol ring opening carbonylation reaction.



64
(0.1 mmol)

68

Entry	Pd cat. (mol %)	Oxidant (equiv.)	Solvent (M)	NMR yield
1	$Pd(OAc)_2$ (10)	DDQ (2)	Benzene (10 mM)	13[a]
2	$Pd(OAc)_2$ (10)	BQ (2)	Benzene (10 mM)	NR
3	$Pd(OAc)_2$ (10)	2,5-DMBQ (2)	Benzene (10 mM)	NR
4	$Pd(OAc)_2$ (10)	Me-BQ (2)	Benzene (10 mM)	NR
5	$Pd(OAc)_2$ (10)	1,4- Naphthoquin. (2)	Benzene (10 mM)	NR
6	$Pd(OAc)_2$ (10)	$Cu(OTf)_2$ (2)	Benzene (10 mM)	70[b]
7	$Pd(OAc)_2$ (10)	$CuCl_2$ (2)	Benzene (10 mM)	18[c]
8	$Pd(dppf)Cl_2$ (10)	DDQ (2)	Benzene (10 mM)	NR
9	$Pd(PPh_3)_4$ (10)	DDQ (2)	Benzene (10 mM)	18
10	$Pd(PPh_3)_2Cl_2$ (10)	DDQ (2)	Benzene (10 mM)	19
11	$Pd(TFA)_2$ (10)	DDQ (2)	Benzene (10 mM)	11[a]
12	$Pd(PPh_3)_2Cl_2$ (10)	DDQ (2)	DCE (10 mM)	12
13	$Pd(PPh_3)_2Cl_2$ (10)	DDQ (2)	DMF (10 mM)	NR
14	$Pd(PPh_3)_2Cl_2$ (10)	DDQ (2)	PhMe (10 mM)	23
15	$Pd(PPh_3)_2Cl_2$ (10)	DDQ (2)	MeCN (10 mM)	NR
16	$Pd(PPh_3)_2Cl_2$ (10)	DDQ (2)	THF (10 mM)	28
17	$Pd(OAc)_2$ (10)	DDQ (2)	THF (10 mM)	55
18	$Pd(PPh_3)_4$ (10)	DDQ (2)	THF (10 mM)	54
19	$Pd(OAc)_2$ (10)	DDQ (3)	THF (10 mM)	56
20	$Pd(OAc)_2$ (10)	DDQ (1.1)	THF (10 mM)	54
21	$Pd(OAc)_2$ (10)	DDQ (1.2)	THF (10 mM)	72 (59%)[d]
22	$Pd(OAc)_2$ (10)	DDQ (1.3)	THF (10 mM)	59
23	$Pd(OAc)_2$ (10)	DDQ (1.2)	MTBE (10 mM)	25
24	$Pd(OAc)_2$ (10)	DDQ (1.2)	DMSO (10 mM)	0
25	$Pd(OAc)_2$ (10)	DDQ (1.2)	Dioxane (10 mM)	35

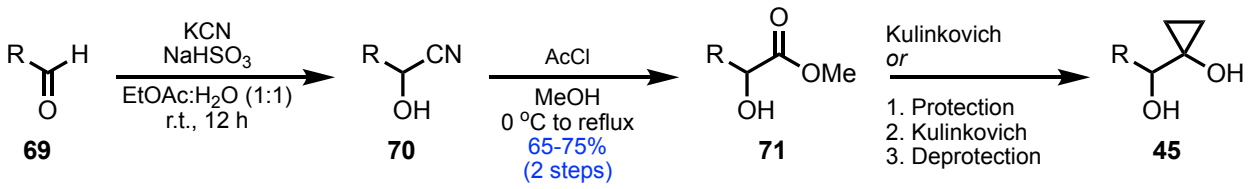
[a]SM not fully consumed. [b]Cyclobutanone pinacol by-product formed. [c]3-furanone product obtained. [d]Isolated yield.

For reaction optimization for the palladium-catalyzed carbonylation reaction, palladium-catalyst, oxidant, solvent, concentration, and temperature were evaluated. The yields were assessed by NMR using, 1,2-dibromoethane as internal standard and using the methylene hydrogens as product reference. The condition screening started with the known conditions for the synthesis of THF-fused bicyclic lactones, with the use of 10 mol% $Pd(OAc)_2$, 2.0 equivalents of DDQ as oxidant, benzene as solvent with low concentration, only afforded desired 4-ketovalerolactone **68**

in low NMR yield 13%, where not all the starting material was consumed (Table 1.2 entry 1). Different benzoquinone derivatives were also evaluated. 1,4-Benzoquinone, 2,5-dimethylbenzoquinone, methylbenzoquinone, and 1,4-naphthoquinone did not give any of the desired 4-ketovalerolactone (entries 2, 3, 4, and 5). Introduction of $Cu(OTf)_2$ as oxidant only gave 70% yield of the undesired cyclobutanone product (entry 6). Changing the copper-catalyst to $CuCl_2$ as oxidant gave 18% yield of the 3-furanone product (entry 7). Different palladium-catalysts were then screened, where $Pd(dppf)Cl_2$ did not afford the desired product (entry 8). $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $Pd(TFA)_2$ gave similar yields compared to $Pd(OAc)_2$ (entry 9-11). Additionally, changing the solvent to toluene, DCE, DMF, or MeCN gave slight increase to the reaction yield, or inhibited the reaction altogether (entries 12, 13, 14, and 15). Gratifyingly, when THF was used the yield increased to 28% (entry 16). Both $Pd(OAc)_2$ and $Pd(PPh_3)_4$ gave significantly higher yields with 55% and 54% when screened in THF, respectively (entries 17 and 18). Due to the stability of using $Pd(OAc)_2$ compared to $Pd(PPh_3)_4$, $Pd(OAc)_2$ was chosen as catalyst moving forward. Changing the loading of optimal oxidant DDQ from 1.0 equivalent up to 3.0 equivalents (entries 19, 20, 21, and 22) indicated that 1.2 equivalents of DDQ was most optimal (entry 21) giving the optimized reaction conditions. Various ethereal solvents such as MTBE and Dioxane proved to decrease the reaction yields, while DMSO did not provide any of the desired product (entries 23, 24, and 25).

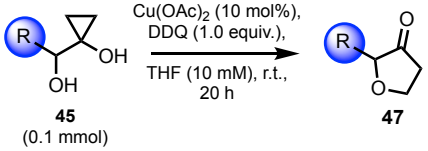
After reaction optimization for both the copper-catalyzed and palladium-catalyzed transformations was achieved, expansion of the substrate scope was investigated. The previously described method in Scheme 1.9 can be applied to different amino acid precursors since simple diazotization and substitution of the resulting compounds would generate the desired α-hydroxy moiety necessary for have the nucleophilic alcohol for the reaction design. The synthesis of other

α-hydroxycyclopropanols was successful though commercially available aldehydes as shown in Scheme 1.10. Taking different commercially available aldehydes **69** can be successful for the synthesis of these highly desired α-hydroxycyclopropanols **45**. Conversion of **69** to **70** with potassium cyanide in the presence of sodium bisulfite, in a 1:1 mixture of water and ethyl acetate gave sufficiently pure cyanohydrins for further modification. Generation of dry HCl was required for conversion of cyanohydrins directly to the corresponding methyl ester **71** through a Pinner reaction. Generation of a Pinner salt from the *in-situ* generation of dry HCl through mixing acetyl chloride in methanol at 0 °C, and subsequent refluxing would afford a quaternary ammonium salt which would precipitate out in solution, which upon basic aqueous work-up provided methyl ester **71** in moderate yields over the first two steps (65-75% yield). As previously described in Scheme 1.9 direct Kulinkovich reaction could then be accomplished. Or the three-step procedure of protection, Kulinkovich, and deprotection was implemented to access an array of different α-hydroxycyclopropanols **45** (Scheme 1.10).

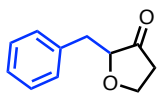


Scheme 1.10 Substrate synthesis for additional α-hydroxycyclopropanols.

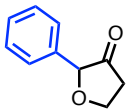
Table 1.3 Substrate scope for copper-catalyzed a-hydroxycyclopropanol ring opening to 3-furanones.



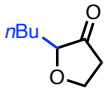
45 (0.1 mmol) → **47**



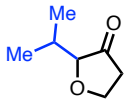
67: 93%



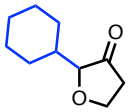
72: 80%



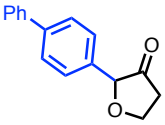
73: 35%



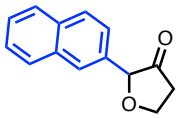
74: Decomposition under column



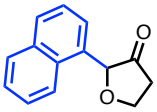
75: 81%



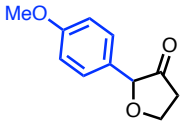
76: 81%



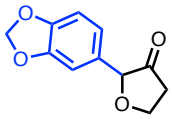
77: 81%



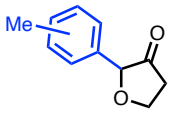
78: 63%



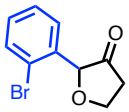
79: 59%



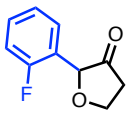
80: 93%



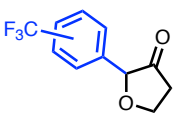
81 (*o*): 75%
82 (*m*): 83%
83 (*p*): 70%



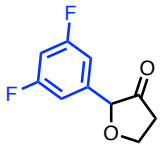
84: 78%



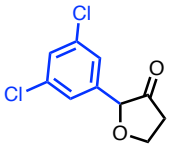
85: 67%



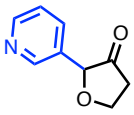
86 (*o*): 72%[a]
87 (*m*): 74%[a]
88 (*p*): 57%[a]



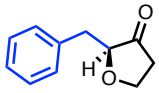
89: 73%[a]



90: 58%[a]



91: No Reaction



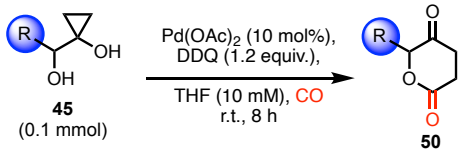
67': 80%[b]

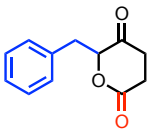
[a]Reaction time 36 h [b]SM: 97% ee to Product 96% ee
Isolated yields

With optimized reaction conditions in hand for each method, and the synthetic scheme for various cyclopropanols was established, 22 different α-hydroxycyclopropanols were synthesized

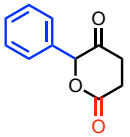
and subjected to the optimized reaction conditions. For the case of the copper-catalyzed α-hydroxycyclopropanol ring opening reaction to 3-furanones benzyl and phenyl substituents were tolerated well with the optimized reaction conditions (Table 1.3, **67** and **72**). Aliphatic substituents such as *n*-Butyl, isopropyl, and cyclohexyl were also investigated. For the case of *n*-Butyl the desired 3-furanone was isolated in a moderate yield of 35% (**73**), whereas isopropyl gave complete conversion via crude NMR, but upon column chromatography led to decomposition (**74**). Cyclohexyl was used as a suitable substrate to probe this transformation if it would give appreciable amounts of the desired product, due to the similar disubstitution pattern. Gratifyingly, when subjected to optimized reaction conditions the cyclohexyl substituted 3-furanone was isolated in 81% yield (**75**). Different electron neutral substituents, and sterically encumbered substituents were successful such as 4-phenyl, and 1 and 2-naphthalene all showed good to moderate yields (**76**, **77**, and **78**). In the case of 1-naphthalene the lower yield is presumably due to the steric interaction of the large biaryl ring. Different electron donating groups were also tolerated well, such as *p*-methoxy (**79**) and 2,3-dioxomethylene (**80**). Various substitution pattern was also tolerated with mild electron donating groups such as methyl (**81**, **82**, and **83**), *o*-Bromo (**84**) also gave good yields. Thus far it is apparent that more suitable substrates for this transformation may be aryl rings, where the electronics on the aryl ring play a vital role in the reaction yield. Various electron withdrawing substrates were synthesized to test this hypothesis. Substrates with *o*-fluoro (**85**), *o*-, *m*-, *p*-trifluoromethyl (**86**, **87**, and **88**), 3,5-difluoro (**89**), and 3,5-dichloro (**90**) also gave moderate to good yields for these transformations. When enantioenriched cyclopropanol derived from enantiopure L-phenylalanine was subjected to the optimized reaction conditions it led to a slight drop-off in yield, and only a slight depreciation in *ee* (**67'**) (Table 1.3).

Table 1.4 Substrate scope for palladium-catalyzed a-hydroxycyclopropanol ring opening to 4-ketovalerolactones.

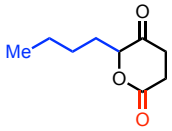




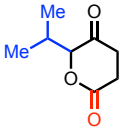
68: 59%



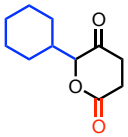
92: 52%



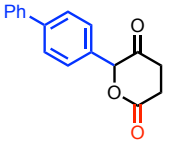
93: 38%



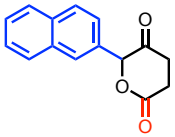
94: 34%



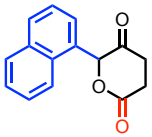
95: 36%



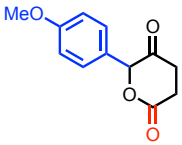
96: 53%



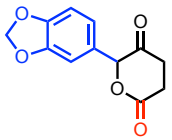
97: 64%



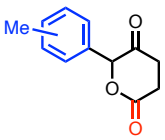
98: 38%



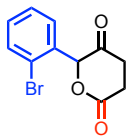
99: 44%



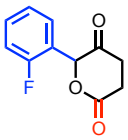
100: 44%



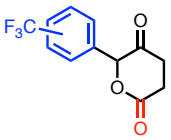
101 (*o*): 65%
102 (*m*): 56%
103 (*p*): 49%



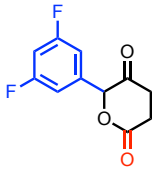
104: 60%



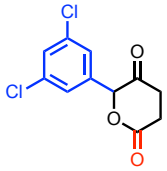
105: 48%



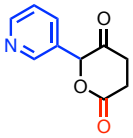
106 (*o*): 64%
107 (*m*): 42%
108 (*p*): 70%



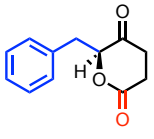
109: 63%



110: 48%



111: No reaction



91': 55%[a]

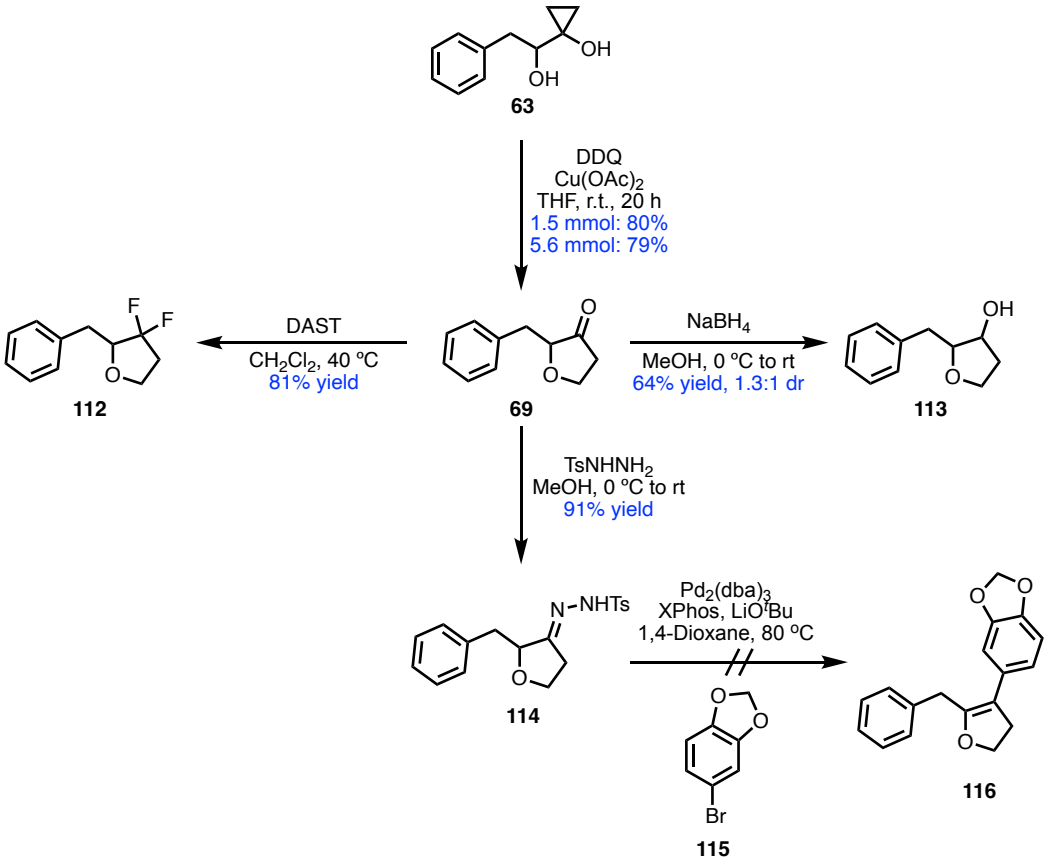
[a]SM: 97% ee to Product: 94% ee.
Isolated yields.

For the carbonylative lactonization benzyl and phenyl substituents were tolerated well with the optimized reaction conditions as to be expected (Table 1.4, **68** and **92**). Aliphatic substituents

such as *n*-Butyl, isopropyl, and cyclohexyl were also investigated. Aliphatic substituents were not tolerated well in the case of *n*-Butyl, isopropyl, and cyclohexyl only having isolated yields ranging from 34-38% yield (**93**, **94**, and **95**). Different electron neutral substituents, and sterically encumbered substituents were again successful. Such as 4-phenyl, 1 and 2-naphthalene all showing moderate yields (**96**, **97**, and **98**). Different electron donating groups were also tolerated well, such as *p*-methoxy (**99**) and 2,3-dioxomethylene (**100**). Various substitution pattern was also tolerated with mild electron donating groups such as methyl (**101**, **102**, and **103**), and *o*-Bromo (**104**) gave good yields. Substrates with *o*-fluoro (**105**), *o*-, *m*-, *p*-trifluoromethyl (**106**, **107**, and **108**), 3,5-difluoro (**109**), and 3,5-dichloro (**110**) also gave moderate to good yields for these transformations. When enantioenriched cyclopropanol derived from enantiopure L-phenylalanine was subjected to the optimized reaction conditions there was again only a slight loss in *ee* for this substrate, from 97% to 94% *ee* **91'** (Table 1.4).

After expansion of the substrate scope was achieved it was investigated if this transformation was scalable and if these 3-furanones could be diversified. On 1.5 mmol (267 mg) and 5.6 mmol (1.0 gram) scale the 3-furanone was isolated in 80% and 79% respectively. Although a decrease in yield was observed from the 93% yield obtained on 0.1 mmol scale, it was shown to be scalable. Conversion of the resulting ketone was successful to the *gem*-difluoro compound (**112**) with DAST in DCM at 40 °C with an isolated yield of 81%. Tetrahydrofuran derivatives are privileged scaffolds in medicinal chemistry, where the ability to introduce fluorine atoms can sometimes prove to be quite challenging, where this method could prove to be useful to access such compounds. Additionally, conversion to the resulting 3-furanol (**113**) proceeded in moderate yield, with a 1.3:1 mixture of inseparable diastereomers, where the major diastereomer was ambiguous after extensive NMR analysis. These compounds are prevalent in natural products

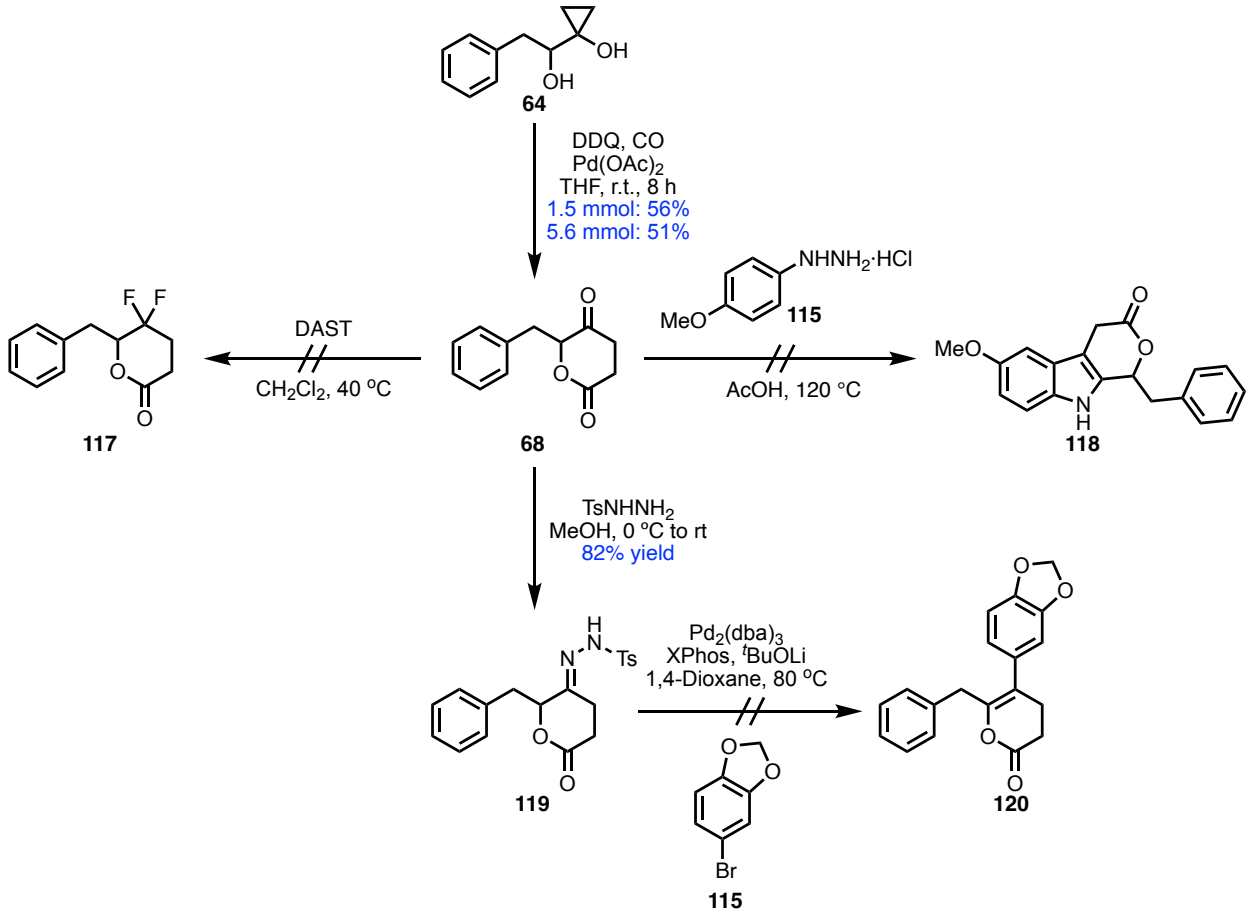
where similar oxidation patterns of these tetrahydrofurans can be seen across natural products. Conversion to the tosyl-hydrazone **114** with *N*-tosylhydriazine in methanol proceeded in 91% yield. Unfortunately, attempts to further functionalize the hydrazone under Barluenga coupling conditions were unsuccessful (Scheme 1.11).[21]



Scheme 1.11 Scale up and diversification of 3-furanones.

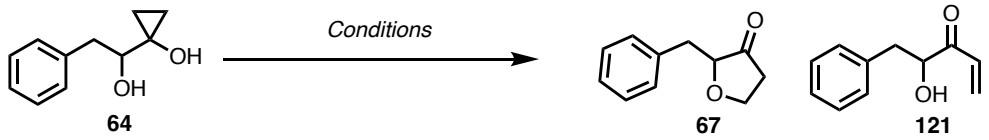
In the case of 4-ketovalerolactones, the scalability of the reaction was also assessed. At 1.5 mmol scale (267 mg) the yield decreased only slightly with a yield of 56%. At larger scale of 5.6 mmol (1.0 gram) the desired product was obtained in 51% yield. These 4-ketovalerolactones proved to be much more scalable without suffering a drop-off in yield as compared to what was observed with the 3-furanones. As for diversifying these lactones, it proved challenging.

Conversion to the gem-difluoro **117** was unsuccessful using DAST in DCM at 40 °C, leading to decomposition of the starting material. Treatment of **68** with 4-methoxyphenylhydrazine hydrochloride, in acetic acid under reflux only afforded degradation and only the hydrazine was recovered. Conversion to the corresponding tosyl-hydrazone **119** was successful in 82% yield. However, again Barluenga coupling was also unsuccessful. In the case of these 4-ketovalerolactones it proved challenging to diversify this scaffold due to the inherent instability under highly basic, or acidic conditions that were screened. It is useful to note that more mild and neutral conditions gave conversion to the desired product (Scheme 1.12).



Scheme 1.12 Scale up and diversification of 4-ketovalerolactones.

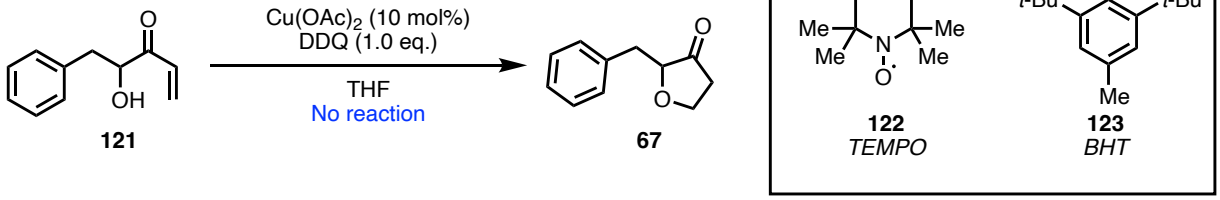
Table 1.5 Mechanistic studies for the copper-catalyzed ring opening reaction.



64 67 121

Entry	Cu cat. (x equiv.)	Oxidant (1.0 equiv.)	THF	Radical Inhibitor (1.2 equiv.)	**67**, **119**[a]
1	None	DDQ	10 mM	None	NR
2	$Cu(OAc)_2$ (0.1)	None	10 mM	None	7%, 0%
3	$Cu(OAc)_2$ (1.0)	DDQ	10 mM	None	79%, 0%
4	$Cu(OAc)_2$ (0.1)	DDQ	10 mM	120	0%, 43%
5	$Cu(OAc)_2$ (0.1)	DDQ	10 mM	121	51% (61% brsm), 0%

[a]Isolated yields



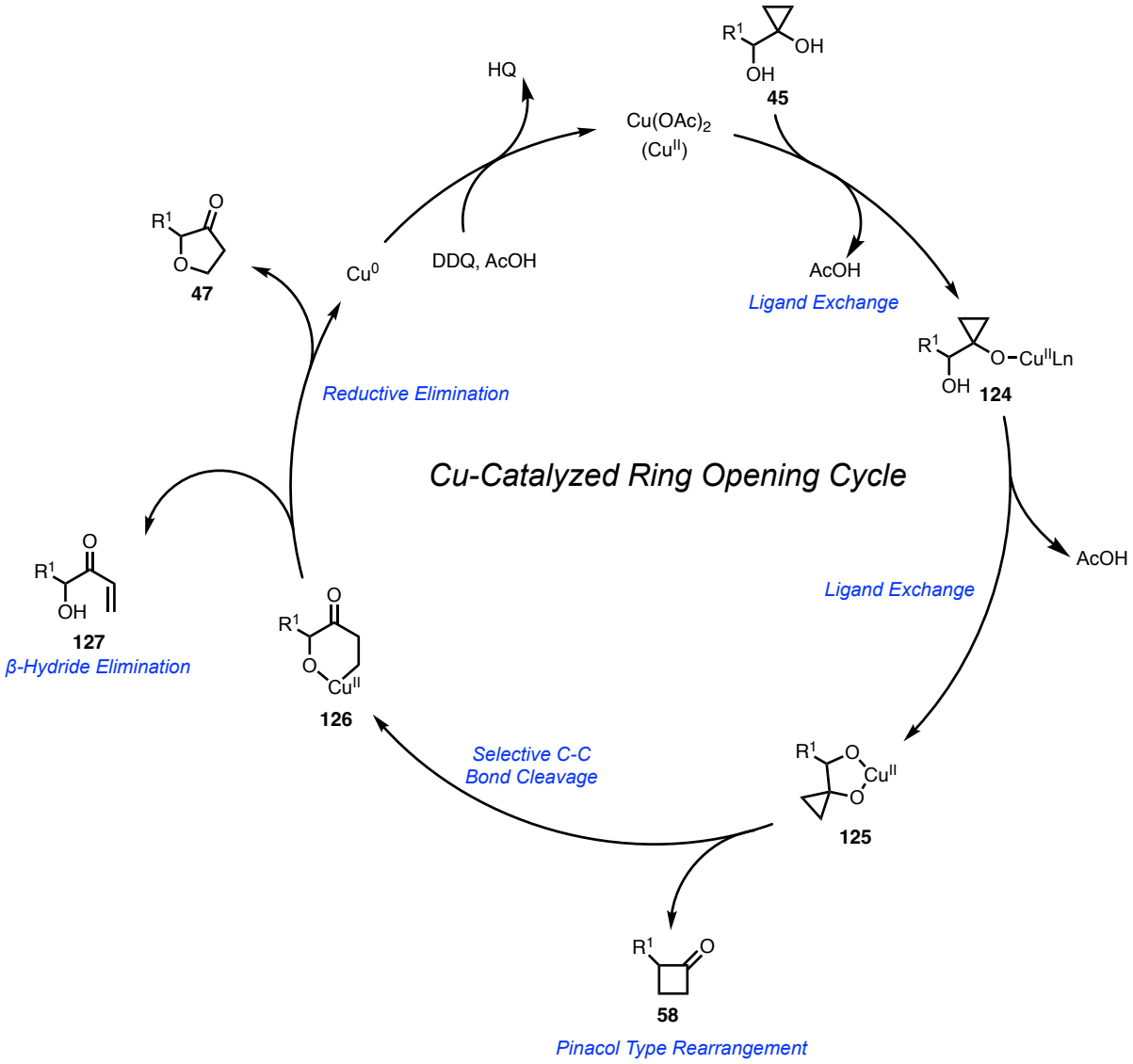
121 67 **122** *TEMPO* **123** *BHT*

To probe the mechanism for the reaction of the copper-catalyzed ring opening transformation to 3-furanones several conditions were screened. It is known that these cyclopropanols can either undergo heterolytic cleavage to form metal-homoenolates, or homolytic cleavage to generate β-keto radical type species. Additionally, copper-catalysts can facilitate different types of transformations in the literature through various heterolytic cleavage and homolytic cleavage, so before proposing a plausible mechanism several experiments were implemented. In Table 1.5 it is shown that the use of copper catalyst is necessary, as well as oxidant is also necessary to ensure catalytic turnover for this transformation (entry 1 and 2). Increasing the catalytic loading to 1.0 equivalent of $Cu(OAc)_2$ gave successful conversion to **67** however a decrease in yield was observed, which was consistent with the previous optimization studies in Table 1.1. Introducing radical inhibitors such as TEMPO and BHT to see if a generated β-keto

radical was generated in this reaction were then screened. For the case of TEMPO (entry 4) it gave no desired furanone product, but a considerable amount of the undesired enone byproduct facilitated by a β-hydride elimination. For this transformation there was no observed β-keto radical type cross-coupled product to TEMPO which is often observed for radical initiated reactions. When BHT was added it gave a considerable decrease in the 3-furanone product which was isolated (entry 5). As BHT is a potent hydrogen atom donor, it is possible that if the reaction would undergo a radical-type process that a generated β-keto radical species could be quenched by BHT as a hydrogen atom donor, which was not observed as an isolated product. Lastly, taking undesired enone **121** and subjecting this compound to the optimized reaction conditions to see if this could be accomplished by a Baldwin's rules disfavored 5-endo-trig cyclization, was not successful. With this experimentally obtained data it is believed that this transformation does not occur though a β-keto radical species, but rather a homolytic cleavage of the cyclopropanol to generate a metal-homoenolate species (Table 1.5).

With the previously obtained experimental data a plausible catalytic cycle for this transformation is proposed. First, $Cu(OAc)_2$ would enter the catalytic cycle as the active Cu(II) catalytic species and undergo a double ligand exchange with a general α-hydroxycyclopropanol **45**, to generate metal-cycle **125**. Species **125** could then undergo a Pinacol-type rearrangement to afford undesired **58** which was observed for highly Lewis acidic copper-catalysts. If C-C bond cleavage was then achieved as the next step in the catalytic cycle it would generate metal-homoenolate species **126**, which could also be susceptible to β-hydride elimination to give rise to the other undesired enone **127**. If intermediate **126** then immediately reductively eliminates to generate the resulting 3-furanone as the desired product it would then give a Cu(0) species, which

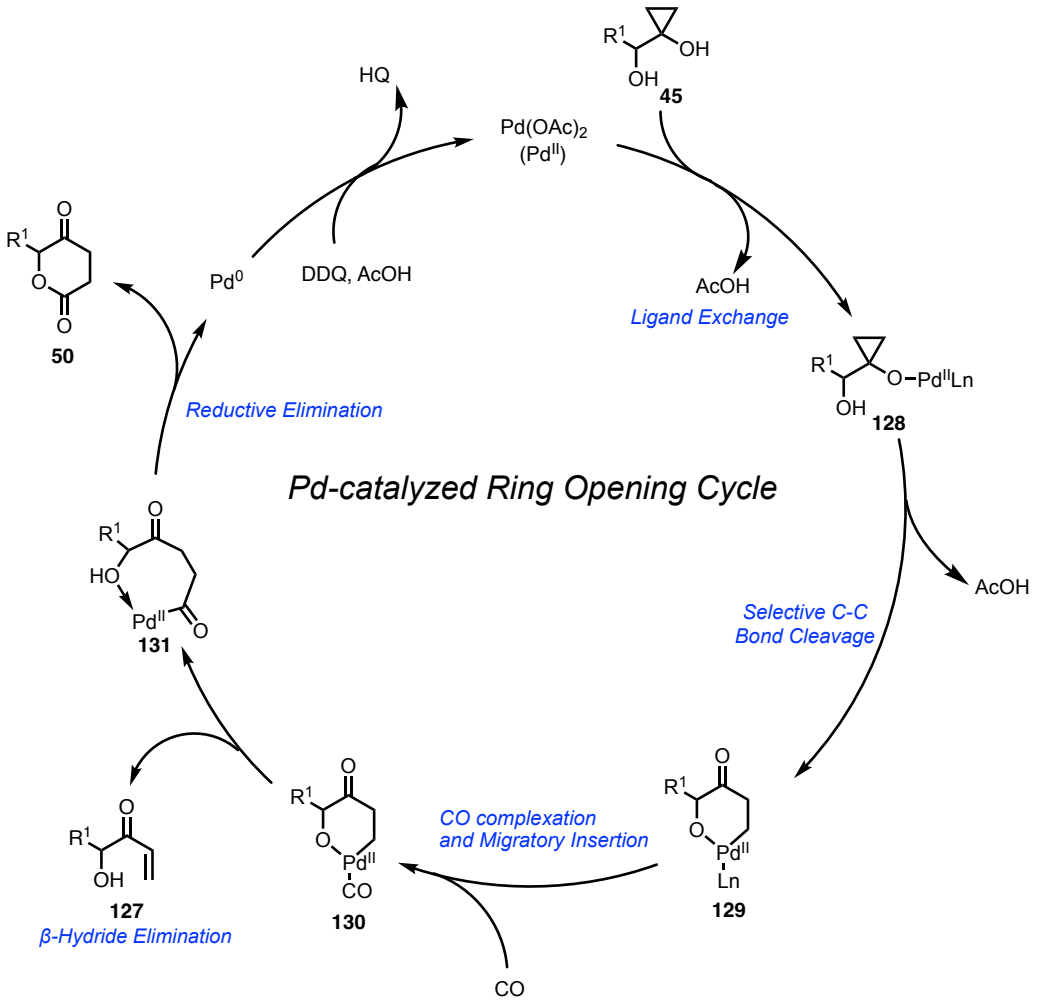
would then be further oxidized by DDQ to give the active Cu(II) species necessary for the reaction (Scheme 1.13).



Scheme 1.13 Proposed catalytic cycle for the copper-catalyzed ring opening reaction.

The palladium-catalyzed carbonylative lactonization reaction has already been investigated previously by Dai and coworkers during the synthesis for oxaspirolactones.[9] From this information a plausible catalytic cycle for the formation of these 4-ketovalerolactones is proposed. First,

$Pd(OAc)_2$ would enter the catalytic cycle as the active Pd(II) catalytic species and undergo a ligand exchange with a general α-hydroxycyclopropanol **45**, to generate **128**. Species **128** could then undergo selective C-C bond cleavage to generate metal-homoenolate **129**. Species **129** could then undergo CO complexation (**130**) followed by migratory insertion to afford the acyl-palladium species **131**. Subsequent cyclization and reductive elimination would then afford the desired 4-ketovalerolactone **50** and Pd(0) which would further be oxidized by DDQ to give the active Pd(II) catalytic species for the reaction.



Scheme 1.14 Proposed catalytic cycle for the palladium-catalyzed carbonylation reaction.

1.3 Conclusions:

In summary, two novel a-hydroxycyclopropanol ring opening reactions were developed. A new copper-catalyzed ring opening reaction to access 3-furanones in high yields was developed. Using $Cu(OAc)_2$ as catalyst, and DDQ as oxidant, an array of twenty 3-furanones was synthesized in moderate to high yields. Scaling up this reaction was also achieved, although a slight drop-off in yield was observed at gram scale, with 80% which is still synthetically useful. Several diversifications of these 3-furanones were explored, most notable to the gem-difluoro compound which could see applications for medicinal chemistry. Additionally, under palladium-catalysis the synthesis of 4-ketovalerolactones was achieved. Using $Pd(OAc)_2$ as catalyst, and DDQ as oxidant, twenty-one saturated lactones were synthesized. The palladium carbonylation reaction was more tolerable when scaled up to gram scale. Diversifying these lactones proved to be very challenging due to the two carbonyls present, as well as the acid and base sensitive proton adjacent to the lactone and ketone moieties. However, using mild conditions, conversion to the corresponding *N*-tosylhydrazone was successful in good yield. These newly developed methodologies should find application on the synthesis of natural products and the synthesis of drug-like molecules containing these two unique motifs.

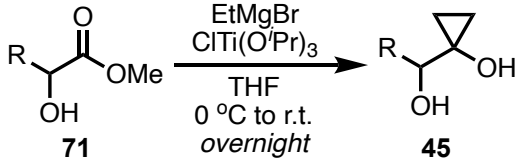
1.4 Experimental Data

1.4.1 General Methods:

NMR spectra were recorded on Bruker spectrometers (^1H at 400 MHz, 500 MHz, ^{13}C at 100 MHz, 125 MHz, and ^{19}F at 376 MHz, 470 MHz). Chemical shifts (δ) were given in ppm with reference to solvent signals [^1H NMR: $CHCl_3$ (7.26), CD_3OD (3.30); ^{13}C NMR: $CDCl_3$ (77.2), CD_3OD (49.0)]. High-resolution mass measurements for compound characterization were carried

out using a Thermo Exact Plus spectrometer using APCI. IR spectra were collected either on a Nicolet iS10 FT-IR or Nicolet iS50 ATR-IR from Thermo Scientific. Column chromatography was performed on silica gel. All reactions requiring heating were heated in an oil bath. All reactions sensitive to air or moisture were conducted under argon atmosphere in dry solvents under anhydrous conditions, unless otherwise noted or in the case of carbon monoxide atmosphere. Anhydrous THF, CH_2Cl_2, DMF, MeCN and toluene were obtained from a Solvent Purification System (Cabinet Mount SPS from Pure Process Technology). All other solvents and reagents were used as obtained from commercial sources without further purification.

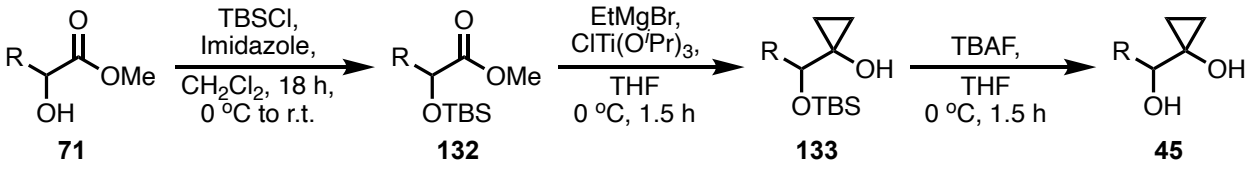
1.4.2 Representative procedure 1 for the synthesis of α-hydroxycyclopropanols:



Scheme 1.1 General procedure 1 for the synthesis of α-hydroxycyclopropanols.

The corresponding α-hydroxy methyl esters were synthesized using known procedures in the literature. The following procedure is adaptation of a known literature procedure. To a solution of α-hydroxy methyl esters **71** (1.0 equiv.) in THF (0.2 M), $ClTi(O^iPr)_3$ (2.0 equiv.) was added in a single portion. The reaction is then cooled to 0 °C. Next, EtMgBr (3.0 M in Et_2O, 4.0 equiv.) was added dropwise over a 10-minute period. The reaction is then let reach room temperature overnight. EtOAc acetate is then added at 0 °C to quench the excess EtMgBr, followed by NH_4Cl. The aqueous phase is then extracted another three times with EtOAc, and the combined organic layers are dried over $MgSO_4$, filter through a short celite pad, and the solvent removed under reduced pressure. Column chromatography afforded the pure α-hydroxycyclopropanols **45**.

1.4.3 Representative procedure 2 for the synthesis of α-hydroxycyclopropanols:



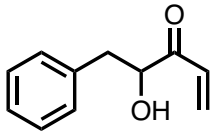
Scheme 1.2 General procedure 2 for the synthesis of α-hydroxycyclopropanols.

To a solution of the α-hydroxy methyl ester **71** (1.0 equiv.) and imidazole (2.4 equiv.) in CH_2Cl_2 or DMF (0.15 M), TBSCl (1.2 equiv.) in one portion at 0 °C. The reaction mixture is let stir for 18 h at room temperature, and then is quenched with a saturated $NaHCO_3$ solution. Layers were separated and the aqueous layer was extracted three more times with CH_2Cl_2. The organic layers are then combined and dried over $MgSO_4$, filtered through a short celite pad and volatiles removed under reduced pressure to give the crude product. Column chromatography afforded the pure α-siloxy methyl esters **132**.

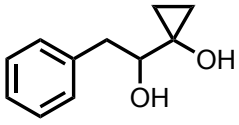
To a solution of α-siloxy methyl esters **132** (1.0 equiv.) in THF (0.1 M), $ClTi(O^iPr)_3$ (2.0 equiv.) was added in a single portion. The reaction is then cooled to 0 °C. Next, EtMgBr (3.0 M in Et_2O, 4.0 equiv.) was added dropwise over a 10-minute period. The reaction is then let at that temperature for 1.5 hours. EtOAc acetate is then added at 0 °C to quench the excess EtMgBr, followed by NH_4Cl. The aqueous phase is then extracted another three times with EtOAc, and the combined organic layers are dried over $MgSO_4$, filter through a short celite pad, and the solvent removed under reduced pressure. Column chromatography afforded the pure α-siloxycyclopropanols **133**.

To a solution of **133** in THF (0.06 M) at 0 °C, TBAF (1 M in THF, 1.2 equiv.) is added dropwise over 5 min. The reaction mixture is then let stir at that temperature for another 1.5 hours.

After the starting material was consumed, the volatiles were removed under reduced pressure and then diluted once again with EtOAc and transferred to a separatory funnel. A saturated NH_4Cl solution was added, and the aqueous layer was extracted two more times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a short celite pad. Volatiles were once again removed under reduced pressure to give the crude product. Column chromatography gave the desired pure α-hydroxycyclopropanols **45**.

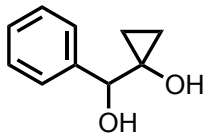


121. (Enone byproduct). Light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 6.57 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.44 (dd, *J* = 17.5, 1.38 Hz, 1H), 5.94 (dd, *J* = 10.44, 1.44 Hz, 1H), 4.71 (dt, *J* = 10.4, 4.9 Hz, 1H), 3.47 (d, *J* = 5.47 Hz, 1H), 3.16 (dd, *J* = 14.4, 4.3 Hz, 1H), 2.93 (dd, 14.5, 6.83 Hz, 1H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 200.2, 136.3, 131.6, 130.7, 129.4, 128.5, 126.9, 75.9, 40.6. **IR** (ATR, cm^{-1}) 3462, 3062, 3029, 2924, 1694, 1499, 1454, 1053, 984, 699. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 177.0916; found 177.09129.

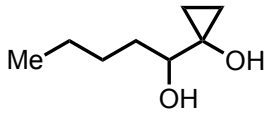


64. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37-7.29 (m, 2H), 7.28-7.22 (m, 3H), 3.37 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.04 (dd, *J* = 13.7, 4.3 Hz, 1H), 2.95 (dd, *J* = 13.8, 9.2, 1H), 1.69 (bs, 2H), 0.93-0.74 (m, 2H), 0.63-0.56 (m, 1H), 0.52-0.45 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 138.3, 129.4, 128.7, 126.6, 77.8, 58.1, 39.8, 13.0, 11.1.

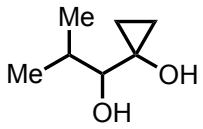
IR (ATR, cm^{-1}) 3349, 3277, 2948, 2925, 2904, 1603, 1496, 1453, 1420, 1217, 1067. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{15}O_2$ $[M+H]^+$ = 179.1066; found 179.1068.



134. Synthesized following general procedure 1. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.40-7.35 (m, 2H), 7.34-7.29 (m, 1H), 4.49 (s, 1H), 0.93-0.87 (m, 1H), 0.86-0.80 (m, 1H), 0.79-0.68 (m 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 140.8, 128.4, 128.0, 126.6, 78.0, 59.4, 12.1, 11.4. **IR** (ATR, cm^{-1}) 3174, 2882, 2360, 1450, 1418, 1280, 1198, 1039, 1024. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{13}O_2$ $[M+H]^+$ = 165.0910; found 165.0913.

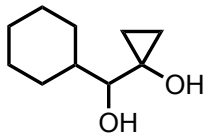


135. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.14 (dd, *J* = 8.2, 5.3 Hz, 1H), 2.06 (bs, 2H), 1.72-1.57 (m, 2H), 1.51-1.42 (m, 1H), 1.42-1.29 (m, 3H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.88-0.84 (m, 1H), 0.81-0.76 (m, 1H), 0.59-0.51 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 77.0 (under $CDCl_3$), 58.7, 32.9, 28.2, 22.8, 14.0, 12.6, 11.3. **IR** (ATR, cm^{-1}) 3236, 2953, 2933, 2871, 2856, 1736, 1464, 1454, 1429, 1284, 1220, 1066, 1006. **HRMS** (APCI+) *m/z* calcd for $C_8H_{17}O_2$ $[M+H]^+$ = 145.1223; found 145.1225.

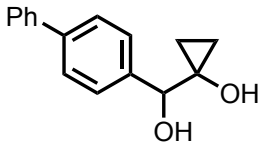


136. Synthesized following general procedure 1. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.65-2.62 (m, 1H), 2.08 (ddt, *J* = 13.5, 6.7, 3.5 Hz, 1H), 1.1-0.88 (m, 7H), 0.72-0.63 (m, 2H), 0.53-0.45 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 83.3, 58.1, 32.0, 20.0, 19.8, 13.7, 11.9. **IR** (ATR,

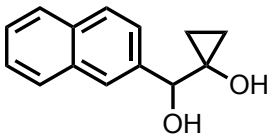
cm^{-1}) 3372, 2958, 2928, 2873, 2357, 1712, 1470, 1383, 1285, 1228, 1026. **HRMS** (APCI+) *m/z* calcd for $C_7H_{15}O_2$ $[M+H]^+$ = 131.1066; found 131.1071.



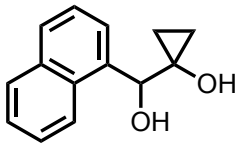
137. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.68 (d, *J* = 8.7 Hz, 1H), 2.14-1.91 (m, 4H), 1.81-1.71 (m, 3H), 1.70-1.63 (m, 1H), 1.35-1.21 (m, 2H), 1.15 (qt, *J* = 12.6, 3.4 Hz, 1H), 1.05-0.93 (m, 3H), 0.73-0.62 (m, 2H), 0.51-0.44 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 81.8, 57.5, 41.0, 29.9, 29.4, 26.5, 26.1, 26.0, 13.1, 11.3. **IR** (ATR, cm^{-1}) 3343, 2918, 2846, 2360, 1738, 1448, 1420, 1285, 1228, 1023, 1012. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{19}O_2$ $[M+H]^+$ = 171.1379; found 171.1381.



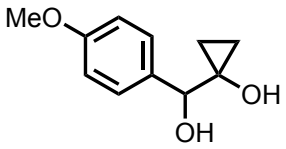
138. Synthesized following general procedure 1. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63-7.57 (m, 4H), 7.54-7.50 (m, 2H), 7.47-7.42 (m, 2H), 7.38-7.33 (m, 1H), 4.53 (s, 1H), 2.46-2.31 (m, 2H), 0.96-0.90 (m, 1H), 0.90-0.84 (m, 1H), 0.83-0.72 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 140.9, 140.8, 139.8, 128.8, 127.4, 127.2, 127.1, 127.1, 77.8, 59.4, 12.2, 11.5. **IR** (ATR, cm^{-1}) 3272, 3032, 2901, 2359, 1737, 1486, 1409, 1203, 1191, 1037, 1018, 1003. **HRMS** (APCI+) *m/z* calcd for $C_{16}H_{17}O_2$ $[M+H]^+$ = 241.1223; found 241.1225.



139. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93-7.89 (m, 1H), 7.87-7.79 (m, 3H), 7.55 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.52-7.46 (m, 2H), 4.65 (s, 1H), 2.36 (bs, 2H), 0.93 (ddd, *J* = 9.7, 6.8, 4.6 Hz, 1H), 0.84 (dddd, *J* = 16.5, 9.9, 6.5, 5.1 Hz, 2H), 0.75 (ddd, *J* = 10.0, 6.9, 4.6 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 138.2, 133.2, 133.1, 128.1, 128.1, 127.7, 126.3, 126.1, 125.5, 124.7, 78.1, 59.5, 12.1, 11.5. **IR** (ATR, cm^{-1}) 3264, 3177, 2359, 1601, 1414, 1281, 1193, 1037. **HRMS** (APCI+) *m/z* calcd for $C_{14}H_{15}O_2$ $[M+H]^+$ = 215.1066; found 215.1068.

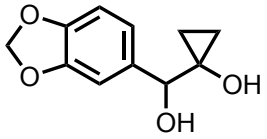


140. Synthesized following general procedure 1. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08-8.01 (m, 1H), 7.88-7.81 (m, 1H), 7.79-7.73 (m, 2H), 7.53-7.39 (m, 3H), 5.60 (s, 1H), 3.49 (bs, 2H), 0.83 (dt, *J* = 11.7, 6.1 Hz, 1H), 0.73 (dt, *J* = 11.1, 6.1 Hz, 1H), 0.63 (dt, *J* = 11.8, 6.2 Hz, 1H), 0.35 (dt, *J* = 11.1, 6.0 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 136.1, 133.6, 131.2, 128.8, 128.4, 126.2, 125.6, 125.3, 124.5, 123.5, 74.0, 59.0, 13.0, 10.5. **IR** (ATR, cm^{-1}) 3343, 3050, 3009, 2923, 1711, 1597, 1414, 1395, 1270, 1199, 1062, 1018, 994, 783. **HRMS** (APCI+) *m/z* calcd for $C_{14}H_{15}O_2$ $[M+H]^+$ = 215.1066; found 215.1068.

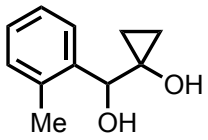


141. Synthesized following general procedure 1. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, 2H), 6.95-6.87 (m, 2H), 4.46 (d, *J* = 3.8 Hz, 1H), 3.81 (s, 3H), 2.30-2.24 (m, 2H), 0.89 (ddd, *J* = 10.1, 5.4, 3.6 Hz, 1H), 0.81 (ddd, *J* = 9.3, 5.6, 4.2 Hz, 1H), 0.75-0.66 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 159.4, 132.9, 127.8, 113.8, 77.5, 59.4, 55.3, 12.0, 11.2. **IR** (ATR, cm^{-}

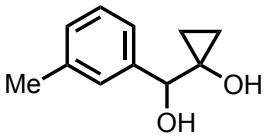
[1]) 3426, 2963, 2935, 2839, 2586, 1778, 1696, 1674, 1600, 1574, 1512, 1246, 1172, 1027. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{11}O_3$ $[M+H]^+$ = 191.0702; found 191.0703.



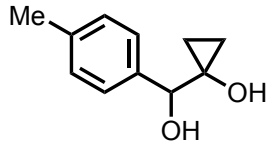
142. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, CD_3OD) δ 6.98 (d, *J* =1.7 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.90 (s, 2H), 4.36 (s, 1H), 0.75-0.66 (m, 3H), 0.65-0.60 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 147.4, 146.8, 136.2, 120.2, 107.3, 107.1, 100.7, 76.8, 57.9, 11.0, 9.8. **IR** (ATR, cm^{-1}) 3310, 2891, 2359, 1737, 1500, 1485, 1434, 1285, 1238, 1216, 1182, 1054, 1037. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_4$ $[M+H]^+$ = 209.0808; found 209.0810.



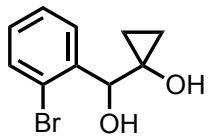
143. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.23-7.15 (m, 2H), 7.13 (dd, *J* = 7.1, 1.9 Hz, 1H), 5.09 (s, 1H), 3.07 (bs, 1H), 2.76 (bs, 1H), 2.34 (s, 3H), 0.83 (ddd, *J* = 10.7, 6.8, 5.1 Hz, 1H), 0.73 (ddd, *J* = 10.6, 6.7, 5.5 Hz, 1H), 0.64 (ddd, *J* = 10.7, 6.8, 5.3 Hz, 1H), 0.38 (ddd, *J* = 10.6, 6.7, 5.1 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 138.5, 135.7, 130.3, 127.7, 126.4, 126.0, 73.9, 58.6, 19.7, 11.9, 9.9. **IR** (ATR, cm^{-1}) 3372, 2248, 1778, 1202, 1025, 905. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 117.0910; found 177.0912.



144. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29-7.19 (m, 3H), 7.14-7.10 (m, 1H), 4.43 (s, 1H), 2.41 (bs, 2H), 2.87 (s, 3H), 0.88 (ddd, *J* = 10.6, 6.2, 4.3 Hz, 1H), 0.81 (ddd, *J* = 10.2, 6.3, 4.9 Hz, 1H), 0.78-0.65 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 140.8, 138.1,128.7, 128.3, 127.3, 123.7, 78.0, 59.3, 21.5, 12.1, 11.4. **IR** (ATR, cm^{-1}) 3239, 3034, 3008, 2917, 1607, 1466, 1424, 1412, 1375, 1291, 1235, 1209, 1149, 1029, 1021. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 177.0910; found 177.0911.

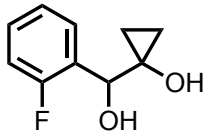


145. Synthesized following general procedure 1. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.23-7.18 (m, 2H), 4.48 (s, 1H), 2.40-2.36 (m, 4H), 2.34 (bs, 1H), 0.93-0.88 (m, 1H), 0.86-0.81 (m, 1H), 0.79-0.68 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 137.8, 137.7, 129.1, 126.5, 77.8, 59.4, 21.1, 12.0, 11.3. **IR** (ATR, cm^{-1}) 3370, 2921, 2648, 1701, 1683, 1605, 1413, 1207, 1177, 1034, 1019. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{15}O_2$ $[M+H]^+$ = 179.1066; found 179.1066.

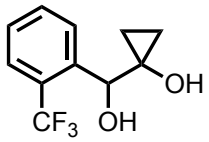


146. Synthesized following general procedure 1. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 (td, *J* = 7.6, 1.3 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.3, 1.8 Hz, 1H), 5.10 (s, 1H), 2.71 (bs, 2H), 0.90 (ddd, *J* = 10.6, 6.7, 5.1 Hz, 1H), 0.82 (ddd, *J* = 10.5, 6.8, 5.5 Hz, 1H), 0.76 (ddd, *J* = 10.6, 6.8, 5.4 Hz, 1H), 0.58 (ddd, *J* = 10.3, 6.8, 5.1 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 139.7, 132.7, 129.4, 129.0, 127.5, 123.2, 76.1, 58.6,

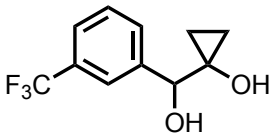
12.8, 10.4. **IR** (ATR, cm^{-1}) 3351, 2958, 2922, 2852, 1716, 1467, 1435, 1275, 1196, 1038, 1017. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{12}O_2{}^{79}Br$ $[M+H]^+$ = 243.0015; found 243.0015.



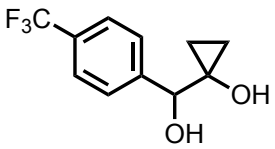
147. Synthesized following general procedure 1. Light yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (td, *J* = 7.5, 1.8 Hz, 1H), 7.32-7.26 (m, 1H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1H), 7.05 (ddd, *J* = 10.5, 8.2, 1.2 Hz, 1H), 4.84 (s, 1H), 2.45 (bs, 1H), 2.36 (bs, 1H), 0.93 (ddd, *J* = 10.5, 7.2, 4.9 Hz, 1H), 0.84-0.74 (m, 2H), 0.70 (ddd, *J* = 10.0, 7.0, 4.9 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ159.6 (d, *J* = 244 Hz), 129.3 (d, *J* = 8.3 Hz), 128.4 (d, *J* = 4.1 Hz), 127.8 (d, *J* = 12.2 Hz), 124.2 (d, *J* = 3.7 Hz), 115.3 (d, *J* = 22.4 Hz), 72.0, 59.0, 12.8, 11.0, 11.0. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -118.9. **IR** (ATR, cm^{-1}) 3347, 2919, 1616, 1587, 1488, 1454, 1274, 1225, 1030. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{12}O_2F$ $[M+H]^+$ = 183.0815; found 183.0819.



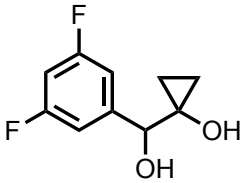
148. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 5.06 (s, 1H), 3.14 (bs, 2H), 0.90-0.80 (m, 1H), 0.77-0.64 (m, 2H), 0.54-0.46 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 139.4, 132.0, 129.1, 128.0, 127.7 (d, *J* = 35 Hz), 125.6 (q, *J* = 6.3 Hz), 124.6 (d, *J* = 275.8 Hz), 72.6, 58.8, 13.3, 10.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -57.2. **IR** (ATR, cm^{-1}) 3358, 1455, 1309, 1202, 1158, 1114, 1063, 1041, 1027. **HRMS** (ESI-) *m/z* calcd for $C_{11}H_{10}O_2F_3$ $[M-H]^-$ = 231.0627; found 231.0630.



149. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74-7.70 (m, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 4.50 (s, 1H), 2.62-2.19 (m, 2H), 0.99-0.84 (m, 2H), 0.81-0.68 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 141.8, 130.6, 130.0, 128.8, 124.7 (d, *J* = 3.3 Hz), 123.5 (d, *J* = 4.2 Hz), 123, 77.6, 59.3, 12.4, 11.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.6. **IR** (ATR, cm^{-1}) 3353, 2886, 1707, 1452, 1327, 1216, 1159, 1111, 1099, 1071, 1042, 1016. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{12}O_2F_3$ $[M+H]^+$ = 233.0783; found 233.0786.

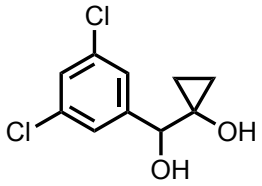


150. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 4.49 (s, 1H), 2.58-2.15 (m, 2H), 0.97-0.84 (m, 2H), 0.82-0.67 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 144.7, 130.1 (d, *J* = 31.2 Hz), 127.0, 125.3 (q, *J* = 3.9 Hz), 123.0, 77.6, 59.4, 12.4, 11.6. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -63.7. **IR** (ATR, cm^{-1}) 3274, 2359, 1618, 1413, 1375, 1257, 1163, 1108, 1064, 1054, 1014. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{12}O_2F_3$ $[M+H]^+$ = 233.0783; found 233.0786.

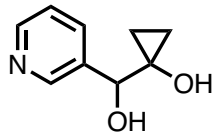


151. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04-6.95 (m, 2H), 6.75 (tt, *J* = 8.9, 2.4 Hz, 1H), 4.38 (s, 1H), 2.49 (bs, 1H), 2.27 (bs, 1H), 0.99-0.86

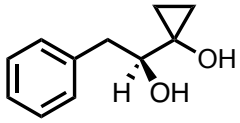
(m, 2H), 0.80-0.76 (m, 1H), 0.75-0.70 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 164 (d, *J* = 12.7 Hz), 162 (d, *J* = 12.7 Hz), 145 (t, *J* = 8.3 Hz), 109.6 (dd, *J* = 19.8, 6.1 Hz), 103.2 (t, *J* = 25.8 Hz), 77.3 (under $CHCl_3$ residual peak), 59.2, 12.4, 11.8. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -110.6 (t, *J* = 7.9 Hz). **IR** (ATR, cm^{-1}) 3340, 1625, 1595, 1453, 1315, 1278, 1222, 1200, 1115, 1059, 1019. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{11}O_2F_2$ $[M+H]^+$ = 201.0721; found 201.0723.



152. Synthesized following general procedure 2. White solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.35 (dd, *J* = 1.88, 0.65 Hz , 2H), 7.31 (t, *J* = 1.99 Hz, 1H), 4.35 (s, 1H), 0.96-0.89 (m, 2H), 0.80-0.71 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 144.3, 135.0, 128.0, 125.2, 59.2, 12.4, 11.8. **IR** (ATR, cm^{-1}) 3342, 3280, 1593, 1572, 1422, 1382, 1215, 1195, 1100, 1046, 1013. **HRMS** (APCI-) *m/z* calcd for $C_{10}H_9O_2{}^{35}Cl_2$ $[M-H]^-$ = 230.9985; found 230.9984.

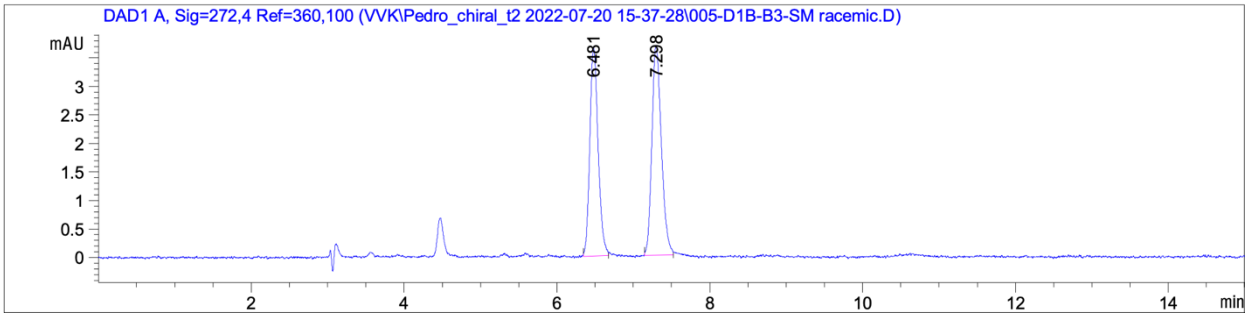


152. Synthesized following general procedure 2. Light yellow solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.61 (d, *J* = 1.72 Hz, 1H), 8.42 (dd, *J* = 6.75, 1.72 Hz, 1H), 7.94 (dt, *J* = 8.0, 1.76 Hz, 1H), 4.42 (s, 1H), 3.3 (p, *J* = 1.61 Hz, 1H), 0.86-0.76 (m, 2H), 0.77-0.73 (m, 1H), 0.70-0.65 (m, 1H). **^{13}C{1H} NMR** (100 MHz, CD_3ODzz) δ 147.6, 147.2, 139.1, 135.8, 123.4, 74.7, 57.7, 10.8, 10.2. **IR** (ATR, cm^{-1}) 3340, 3073, 2697, 1596, 1580, 1481, 1284, 1059, 1042. **HRMS** (APCI-) *m/z* calcd for $C_9H_{12}O_2N$ $[M+H]^+$ = 166.0968; found 166.0852.

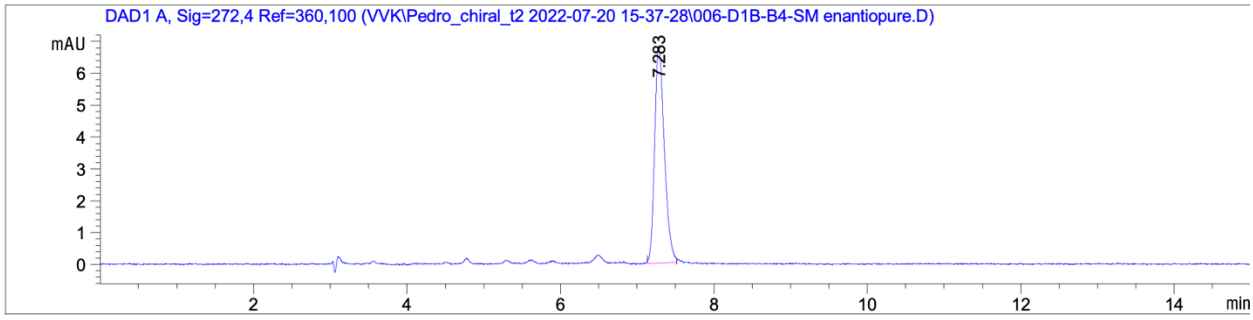


64'. Synthesized following general procedure 2. White solid. 94% *ee*; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.28-7.22 (m, 3H), 3.35 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.03 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.95 (dd, *J* = 13.7, 9.1, 1H), 2.64 (bs, 1H), 1.98 (bs, 1H), 0.91-0.79 (m, 2H), 0.63-0.57 (m, 1H), 0.49-0.45 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 138.4, 129.4, 128.6, 126.6, 78.0, 58.0, 39.8, 12.9, 11.2. **IR** (ATR, cm^{-1}) 3334, 3235, 2954, 2932, 2892, 1604, 1496, 1455, 1432, 1229, 1071. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{15}O_2$ $[M+H]^+$ = 179.1066; found 179.1068. SFC (Chiralpak IA column) 3% MeOH/CO_2 (2.0 mL/min, λ = 210 nm)

Racemic 64			
	RT (min)	Area (mAU*s)	% Area
1	6.481	573.93634	46.2609
2	7.298	575.50488	53.7391

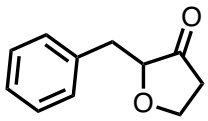


Enantioenriched 64'			
	RT (min)	Area (mAU*s)	% Area
1	15.495	37.39734	3.0239
2	16.766	1056.44800	96.9761



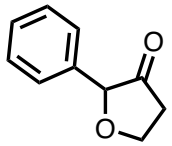
1.4.4 Representative procedure for copper-catalyzed ring opening intramolecular trapping reaction:

To a flame dried vial under argon, is added the α-hydroxycyclopropanol **45** (1.0 equiv., 0.1 mmol), followed by $Cu(OAc)_2$ (0.1 equiv., 0.01 mmol, 1.83 mg) and DDQ (1.0 equiv., 0.1 mmol, 22.7 mg) .The mixture was then dissolved in THF (0.01 M, 10 mL). The reaction is then stirred for 20 hours at room temperature. After completion the mixture was filtered through a short pad of celite, then quenched with DI water (50 mL), and diluted with EtOAc (50 mL). The aqueous phase was washed three times with EtOAc (20 mL), and then the organic phases were combined and washed with brine (50 mL). The organic phase was then dried over Na_2SO_4, then filtered, and the volatiles removed under reduced pressure. The resulting crude residue was then dissolved in $CHCl_3$ and filtered, once again, through a pad of celite to give the crude product. Column chromatography afforded the pure 3-furanones **47**.

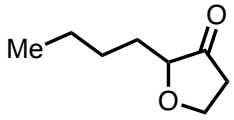


67. 16.4 mg; 93%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.26-7.21 (m, 3H), 4.20 (td, *J* = 9.2, 4.0 Hz, 1H), 4.02 (td, *J* = 9.3, 7.1 Hz, 1H), 3.98 (dd, *J* = 7.8, 3.7 Hz, 1H), 3.08 (dd, *J* = 14.5, 3.8 Hz, 1H), 2.86 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.46 (ddd, *J* = 18.1, 7.1, 4.0

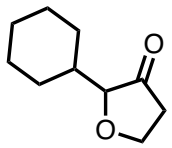
Hz, 1H), 2.33 (dt, *J* = 18.2, 9.1 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 215.5, 137.1, 129.4, 128.4, 126.7, 80.6, 64.5, 37.0, 36.9. **IR** (ATR, cm^{-1}) 3029, 2920, 2874, 1753, 1496, 1454, 1403, 1146, 1075, 994. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 177.0910; found 177.0909.



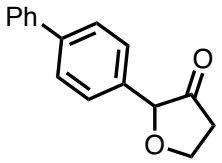
72. 13.0 mg; 80%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 4.75 (s, 1H), 4.50 (ddd, *J* = 9.4, 7.2, 6.3 Hz, 1H), 4.30 (dt, *J* = 9.3, 7.9 Hz, 1H), 2.65-2.61 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 213.0, 135.6, 128.6, 128.2, 126.0, 80.9, 64.8, 36.6. **IR** (ATR, cm^{-1}) 3062, 3032, 2917, 2876, 1755, 1719, 1494, 1452, 1403, 1142, 1055, 987. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{11}O_2$ $[M+H]^+$ = 163.0753; found 163.0756.



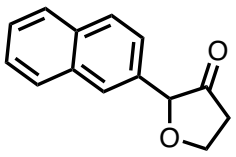
73. 5.0 mg; 35%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.30 (dt, *J* = 9.3, 6.3 Hz, 1H), 4.05 (dt, *J* = 9.3, 8.2 Hz, 1H), 3.69 (dd, *J* = 7.9, 4.2 Hz, 1H), 2.52-2.43 (m, 2H), 1.77-1.67 (m, 1H), 1.61-1.50 (m, 2H), 1.50-1.27 (m, 3H), 0.90 (t, *J* = 7.1 Hz, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 216.4, 80.0, 64.3, 37.1, 30.3, 27.5, 22.5, 13.9. **IR** (ATR, cm^{-1}) 2957, 2930, 2861, 2360, 2341, 1756, 1728, 1466, 1286, 1159, 1128, 1088, 1037. **HRMS** (APCI+) *m/z* calcd for $C_8H_{15}O_2$ $[M+H]^+$ = 143.1066; found 143.1067.



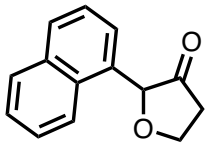
75. 13.5 mg; 80%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.29 (dddd, *J* = 8.9, 8.3, 4.5, 0.6 Hz, 1H), 4.04 (td, *J* = 9.2, 7.3 Hz, 1H), 3.53 (d, *J* = 3.9 Hz, 1H), 2.52-2.37 (m, 2H), 1.80-1.70 (m, 4H), 1.67-1.61 (m, 1H), 1.52-1.46 (m, 1H), 1.32-1.11 (m, 5H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 216.5, 83.7, 64.5, 39.8, 38.0, 29.3, 27.1, 26.3, 26.1, 26.0. **IR** (ATR, cm^{-1}) 2925, 2853, 1753, 1450, 1404, 1158, 1139, 1028. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{17}O_2$ $[M+H]^+$ = 169.1223; found 169.1223.



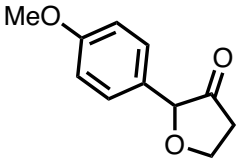
76. 19.3 mg; 81%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62-7.56 (m, 4H), 7.50-7.42 (m, 4H), 7.37-7.33 (m, 1H), 4.80 (s, 1H), 4.56-4.50 (m, 1H), 4.34 (dt, *J* = 9.4, 8.0 Hz, 1H), 2.68-2.64 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 213.1, 141.2, 140.7, 134.6, 128.8, 127.4, 127.4, 127.2, 126.4, 80.8, 64.9, 36.6. **IR** (ATR, cm^{-1}) 3055, 3030, 2918, 2870, 1755, 1487, 1402, 1141, 1050, 1007. **HRMS** (APCI+) *m/z* calcd for $C_{16}H_{15}O_2$ $[M+H]^+$ = 239.1066; found 239.1063.



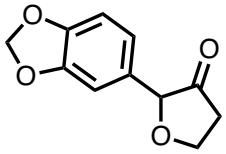
77. 17.2 mg; 81%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89-7.82 (m, 4H), 7.54-7.46 (m, 3H), 4.92 (s, 1H), 4.60-4.54 (m, 1H), 4.38 (dt, *J* = 9.4, 7.9 Hz, 1H), 2.70-2.66 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 213.0, 133.2, 133.0, 128.5, 128.1, 127.7, 126.3, 126.2, 125.1, 123.7, 81.0, 64.9, 36.6. **IR** (ATR, cm^{-1}) 3056, 2919, 2973, 1756, 1507, 1402, 1142, 1123, 1057. **HRMS** (APCI+) *m/z* calcd for $C_{14}H_{13}O_2$ $[M+H]^+$ = 213.0910; found 213.0905



78. 13.4 mg; 63%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12-8.09 (m, 1H), 7.89-7.82 (m, 2H), 7.58-7.44 (m, 4H), 5.51 (s, 1H), 4.62 (td, *J* =9.23, 4.38 Hz, 1H), 4.37 (td, *J* = 9.3, 7.2 Hz, 1H), 2.84 (dt, *J* = 18.2, 9.1 Hz, 1H), 2.72 (ddd, *J* = 18.2, 7.2, 4.1 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 212.9, 134.0, 131.7, 131.2, 129.1, 128.7, 126.4, 125.9, 125.1, 124.3, 124.2, 79.4, 64.9, 37.0. **IR** (ATR, cm^{-1}) 3050, 2921, 1752, 1714, 1595, 1510, 1398, 1243, 1138, 1087. **HRMS** (APCI+) *m/z* calcd for $C_{14}H_{13}O_2$ $[M+H]^+$ = 213.0910; found 213.0909.

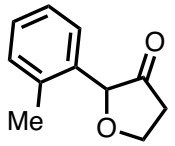


79. 11.3 mg; 59%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 6.93-6.88 (m, 2H), 4.69 (s, 1H), 4.51-4.43 (m, 1H), 4.25 (ddd, *J* = 9.4, 8.4, 7.5 Hz, 1H), 3.80 (s, 3H), 2.71-2.55 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 213.5, 159.6, 127.8, 127.5, 114.1, 80.8, 64.6, 55.3, 36.7 **IR** (ATR, cm^{-1}) 3001, 2958, 2926, 2838, 1779, 1677, 1600, 1577, 1512, 1463, 1247, 1177, 1071, 1031. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ = 193.0859; found 193.0859.

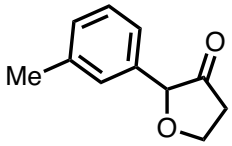


80. 19.2 mg; 93%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.87-6.85 (m, 2H), 6.81-6.79 (m, 1H), 5.95 (d, *J* = 0.7 Hz, 2H), 4.64 (s, 1H), 4.50-4.41 (m, 1H), 4.27-4.21 (m, 1H), 2.64-2.60 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 213.1, 148.0, 147.6, 129.4, 119.8, 108.4, 106.7,

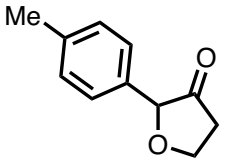
101.2, 80.9, 64.7, 36.5. **IR** (ATR, cm^{-1}) 2916, 2850, 1753, 1503, 1487, 1442, 1402, 1239, 1144, 1099, 1034, 926. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{11}O_4$ $[M+H]^+$ = 207.0651; found 207.0651.



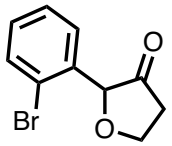
81. 13.2 mg; 75%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.27 (m, 1H), 7.24-7.16 (m, 3H), 4.96 (s, 1H), 4.55 (td, *J* = 9.3, 3.3 Hz, 1H), 4.25 (td, *J* = 9.7, 6.9 Hz, 1H), 2.73 (dt, *J* = 18.9, 9.6 Hz, 1H), 2.62 (ddd, *J* = 18.1, 6.9, 3.3 Hz, 1H), 2.42 (s, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 213.5, 136.6, 134.4, 130.8, 128.3, 126.5, 126.0, 79.9, 64.7, 37.0, 19.6. **IR** (ATR, cm^{-1}) 3023, 2955, 2921, 2871, 1753, 1490, 1462, 1403, 1216, 1140, 1050, 1037, 986. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 177.0910; found 177.0909.



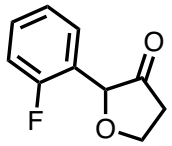
82. 14.6 mg; 83%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.22-7.19 (m, 2H), 7.14-7.12 (m, 1H), 4.71 (s, 1H), 4.52-4.47 (m, 1H), 4.30-4.24 (m, 1H), 2.65-2.61 (m, 2H), 2.36 (s, 3H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 213.2, 138.3, 135.6, 129.0, 128.5, 126.7, 123.2, 81.0, 64.8, 36.6, 21.5. **IR** (ATR, cm^{-1}) 2956, 2923, 2870, 1756, 1720, 1607, 1489, 1461, 1403, 1278, 1140, 1054, 985. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 177.0910; found 177.0909.



83. 12.4 mg; 70%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.20-7.16 (m, 2H), 4.71 (s, 1H), 4.52-4.44 (m, 1H), 4.27 (dt, *J* = 9.3, 8.1 Hz, 1H), 2.65-2.58 (m, 2H), 2.34 (s, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 213.3, 138.0, 132.7, 129.3, 126.0, 81.0, 64.7, 36.6, 21.2. **IR** (ATR, cm^{-1}) 2922, 2879, 2360, 1759, 1449, 1328, 1163, 1121, 1073. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 177.0910; found 177.0910.

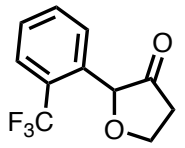


84. 18.8 mg; 78%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62-7.57 (m, 1H), 7.35-7.27 (m, 2H), 7.19 (ddd, *J* = 8.1, 5.9, 3.2 Hz, 1H), 5.13 (s, 1H), 4.57 (td, *J* = 9.4, 3.2 Hz, 1H), 4.27 (td, *J* = 9.7, 7.0 Hz, 1H), 2.77 (dt, *J* = 18.3, 9.6 Hz, 1H), 2.65 (ddd, *J* = 18.3, 7.0, 3.3 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 211.8, 135.5, 133.3, 130.0, 128.9, 127.6, 123.5, 81.5, 64.9, 36.9. **IR** (ATR, cm^{-1}) 3064, 2920, 2874, 2359, 2337, 1757, 1472, 1439, 1402, 1137, 1063, 1023, 988. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{10}O_2{}^{79}Br$ $[M+H]^+$ = 240.9858; found 240.9856.

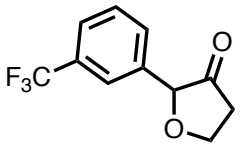


85. 12.1 mg; 67%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H), 7.17-7.06 (m, 2H), 4.90 (s, 1H), 4.87 (td, *J* = 9.3, 3.7 Hz, 1H), 4.54 (td, *J* = 9.5, 7.1 Hz, 1H), 4.26 (td, *J* = 9.34, 7.20 Hz), 2.79 (dt, *J* = 18.4, 9.3 Hz, 1H), 2.65 (ddd, *J* = 18.1, 7.1, 3.7 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ δ 212.8, 160.78 (d, *J* = 248.2 Hz), 130.6 (d, *J* = 8.6 Hz), 129.8 (d, *J* = 4.7 Hz), 124.3 (d, *J* = 3.0 Hz), 123.8 (d, *J* = 13.8 Hz), 115.9 (d, *J* = 21.4 Hz), 77.7, 65.2, 36.7. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -117.31 (dt, *J* = 11.5, 6.2 Hz). **IR** (ATR, cm^{-1}) 2922, 2876, 1758, 1617,

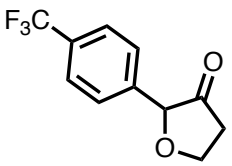
1587, 1492, 1457, 1403, 1233, 1143, 1052, 1030, 986. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_{10}O_2F$ $[M+H]^+$ = 181.0659; found 181.0660.



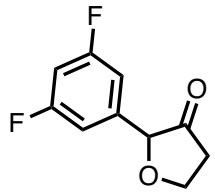
86. 16.6 mg; 72%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 1H), 7.57-7.54 (m, 1H), 7.46-7.42 (m, 2H), 5.03 (s, 1H), 4.56 (td, *J* = 9.1, 3.1 Hz, 1H), 4.25 (ddd, *J* = 10.2, 9.5, 7.0 Hz, 1H), 2.80-2.63 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ211.7, 134.7, 132.1, 129.3 (d, *J* = 31 Hz), 129, 128.6, 126.3 (q, *J* = 5.5 Hz), 125.1, 122.9, 120.5, 78.6, 64.8, 36.8. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -58.79. **IR** (ATR, cm^{-1}) 2920, 2850, 1759, 1587, 1455, 1405, 1310, 1275, 1203, 1159, 1109, 1048, 1033. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{10}O_2F_3$ $[M+H]^+$ = 231.0627; found 231.0625.



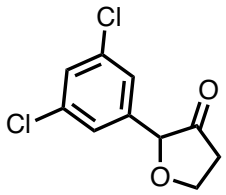
87. 17.0 mg; 74%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72-7.72 (m, 1H), 7.64-7.56 (m, 2H), 7.52-7.48 (m, 1H), 4.78 (s, 1H), 4.55-4.50 (m, 1H), 4.35-4.28 (m, 1H), 2.67-2.63 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ212.0, 136.5, 131 (d, *J* = 31.7 Hz), 129.3, 129, 125 (d, *J* = 4.1 Hz), 122.5 (d, *J* = 4.1 Hz), 80.1, 64.9, 36.4. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -63.79 **IR** (ATR, cm^{-1}) 2951, 2920, 2872, 2360, 1757, 1514, 1404, 1143, 1057, 1020, 985. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{10}O_2F_3$ $[M+H]^+$ = 231.0627; found 231.0626.



88. 13.1 mg; 57%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.58-7.56 (m, 2H), 4.80 (s, 1H), 4.55-4.49 (m, 1H), 4.32 (ddd, *J* = 9.4, 8.4, 7.6 Hz, 1H), 2.66-2.62 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 211.9, 139.4, 130.3 (d, *J* = 33.1 Hz), 126.0, 125.5 (q, *J* = 4.02 Hz), 123.0, 80.2, 64.9, 36.4. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -63.77. **IR** (ATR, cm^{-1}) 2917, 2882, 1760, 1619, 1415, 1323, 1162, 1120, 1110, 1066, 1017. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{10}O_2F_3$ $[M+H]^+$ = 231.0627; found 231.0629.

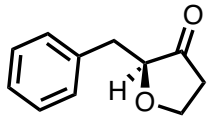


89. 14.5 mg; 73%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.04-7.00 (m, 2H), 6.76 (tt, *J* = 8.8, 2.4 Hz, 1H), 4.72 (s, 1H), 4.53-4.47 (m, 1H), 4.35-4.26 (m, 1H), 2.69-2.62 (m, 2H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 211.3, 164.1 (d, *J* = 12.1 Hz), 162.1 (d, *J* = 12.1 Hz), 139.3 (t, *J* = 8.8 Hz), 108.7 (dd, *J* = 20.5, 6.4 Hz), 103.5 (t, *J* = 25.6 Hz), 79.5, 64.9, 36.2. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -109.09 (t, *J* = 8.19 Hz). **IR** (ATR, cm^{-1}) 3092, 2887, 1759, 1728, 1624, 1596, 1443, 1326, 1228, 1137, 1118, 986. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_9O_2F_2$ $[M+H]^+$ = 199.0565; found 199.0565.



90. 13.4 mg; 58%; light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 3H), 4.67 (s, 1H), 4.52-4.46 (m, 1H), 4.33-4.26 (m, 1H), 2.65-2.61 (m, 2H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 211.4, 138.7, 135.2, 128.3, 124.2, 79.4, 65.0, 36.3. **IR** (ATR, cm^{-1}) 3080, 2992, 2919, 2879, 1759,

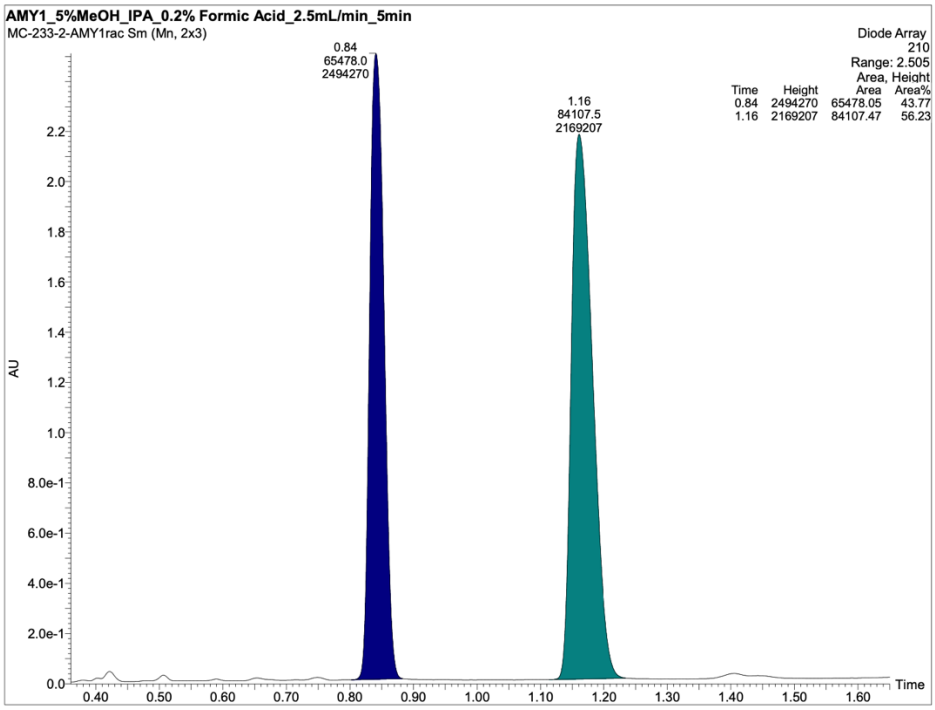
1587 1569, 1427, 1402, 1204, 1139, 1102, 1070, 989. **HRMS** (APCI+) *m/z* calcd for $C_{10}H_9O_2{}^{35}Cl_2$ $[M+H]^+$ = 230.9974; found 230.9978.



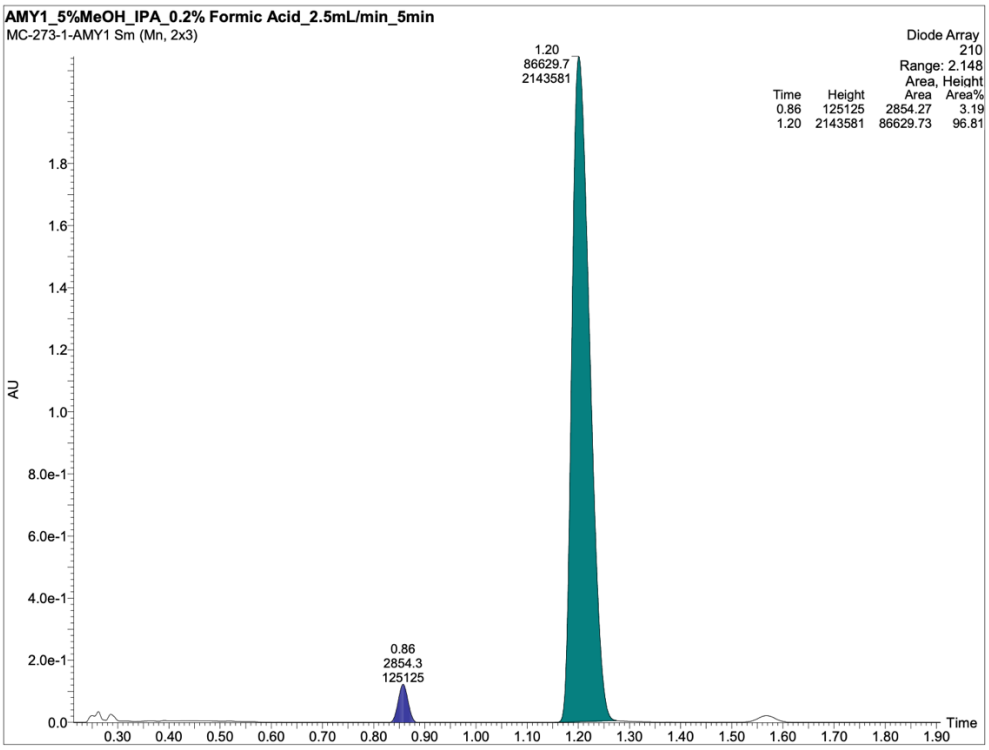
69'. 14.1 mg; 80%, 96% *ee*; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.26-7.21 (m, 3H), 4.20 (td, *J* = 9.2, 4.1 Hz, 1H), 4.03 (td, *J* = 9.3, 7.1 Hz, 1H), 3.98 (dd, *J* = 7.7, 3.7 Hz, 1H), 3.08 (dd, *J* = 14.5, 3.8 Hz, 1H), 2.86 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.46 (ddd, *J* = 18.1, 7.1, 4.0 Hz, 1H), 2.33 (dt, *J* = 18.2, 9.1 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 215.5, 137.2, 129.5, 128.4, 126.7, 80.6, 64.5, 37.0, 36.9. **IR** (ATR, cm^{-1}) 3062, 2920, 2871, 1754, 1496, 1455, 1403, 1147, 1076, 996. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}O_2$ $[M+H]^+$ = 177.0910; found 177.0909.

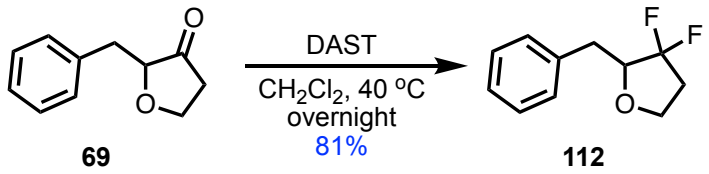
(AMY1_5%MeOH_IPA_0.2% Formic Acid_2.5mL/min_5min)

Racemic 69			
	RT (min)	Area (mAU*s)	% Area
1	0.84	65478.05	43.7700
2	16.766	84107.47	56.2300



Enantioenriched 69’			
	RT (min)	Area (mAU*s)	% Area
1	0.86	2854.27	3.1900
2	1.20	86629.73	96.8100

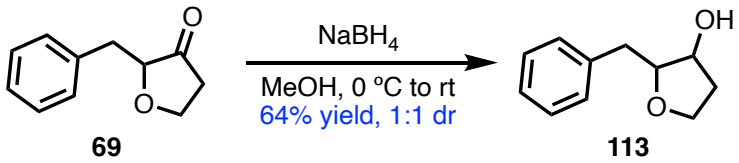




69 112

112. To a flame dried microwave tube equipped with a stir bar, 3-furanone **69** (1.0 equiv., 0.2 mmol, 35.2 mg) was dissolved in CH_2Cl_2 (0.1 M, 2 mL). To that solution, DAST (10.0 equiv., 2.0 mmol, 0.26 mL) was added all at once. The tube was sealed, and the solution was refluxed overnight for 20 hours. Upon completion the mixture was quenched with saturated sodium bicarbonate (20 mL), and the layers were separated. The aqueous phase was washed three times with CH_2Cl_2 (10 mL), the combined organic layers are then dried over Na_2SO_4. The mixture was filtered, and the volatiles removed under reduced pressure, and then purified via column chromatography (9:1 to 4:1 Hexanes:EtOAc) to afford **112** (32 mg, 81% yield) as a light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 4.10 (ddd, *J* = 9.2, 7.2, 5.7 Hz, 1H), 3.98

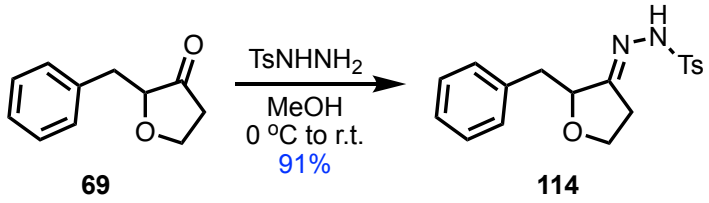
(dddd, *J* = 13.2, 11.7, 8.9, 4.1 Hz, 1H), 3.87 (ddd, *J* = 9.4, 8.6, 7.8 Hz, 1H), 3.01 (ddd, *J* = 14.6, 4.2, 1.1 Hz, 1H), 2.87 (ddd, *J* = 14.5, 8.9, 1.2 Hz, 1H), 2.46-2.35 (m, 2H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 137.3, 129.2, 128.5, 126.6, 82.4 (dd, *J* = 31.4, 25.2 Hz), 77.2, 64.97 (dd, *J* = 5.5, 4.7 Hz), 35.94 (dd, *J* = 25.6, 24.04 Hz), 34.7 (dd, *J* = 6.40, 1.7 Hz) . **^{19}F NMR** (376 MHz, $CDCl_3$) δ -103.73 (td, *J* = 13.4, 11.7 Hz), -104.34 (dt, *J* = 14.1, 12.2 Hz), -107.87 - -108.03 (m), -108.48 - -108.64 (m), -137.08 (q, *J* = 4.9 Hz). **IR** (ATR, cm^{-1}) 3031, 2873, 1497, 1455, 1435, 1330, 1302, 1173, 1118, 1098, 978. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{13}OF_2$ $[M+H]^+$ = 199.0929; found 199.0931.



69 **113**

69. In a flame dried vial, **69** (1.0 equiv., 0.2 mmol, 35.2 mg) was dissolved in 2 mL of MeOH (0.1 M, 2 mL), and cooled to 0 ºC. Next, $NaBH_4$ (1.0 equiv., 0.2 mmol, 7.56 mg) was added in one portion. The mixture was allowed to warm to room temperature and stirred for two hours. Upon completion the reaction, it was quenched with saturated. ammonium chloride solution (10 mL) and diluted with EtOAc (10 mL). The aqueous phase was extracted three times with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), and then dried over Na_2SO_4, filtered, and the volatiles removed under reduced pressure to give the crude product. The crude residue was purified by column chromatography (4:1 Hexanes:EtOAc) to afford **113** (22.60 mg, 64% yield) as a clear oil with a *dr* of 1.13:1.0. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49-7.10 (m, 5H), 4.24-4.06 (m, 1H), 4.03-3.91 (m, 1H), 3.89-3.75 (m, 1H), 3.05-2.98 (m, 1H), 2.96-2.73 (m, 1H), 2.28-2.04 (m, 1H), 2.02-1.82 (m, 1H), 1.80-1.65 (m, 1H). **^{13}C{1H} NMR** (100 MHz, $CDCl_3$) δ 138.7, 138.0, 129.2, 129.1, 128.6, 128.5, 126.5, 126.4, 86.8, 83.9, 75.4, 72.1, 66.5, 65.9, 39.9, 35.6,

35.2, 34.7. **IR** (ATR, cm^{-1}) 3395, 2925, 2881, 2244, 1603, 1495, 1454, 1289, 1065, 1047, 1030, 991, 907. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{15}O_2$ $[M+H]^+$ = 179.1066; found 179.1069.

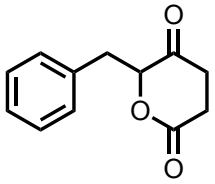


114. To a solution of **69** (35.2 mg, 0.2 mmol, 1.0 equiv.) in MeOH (0.2 M, 1.0 mL), TsNHNH2 (1.5 equiv., 0.3 mmol, 55.8 mg) was added at 0 °C. The reaction was warmed to room temperature and stirred overnight. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (hexane/EtOAc = 3/1) to give *N*-tosylhydrazone **114** (62.6 mg, 91%) as white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.85-7.82 (m, 2H), 7.43-7.40 (m, 2H), 7.11-7.07 (m, 3H), 6.93-6.91 (m, 2H), 4.38-4.45 (m, 1H), 3.91 (td, *J* = 8.56, 3.46 Hz, 1H), 3.76 (td, *J* = 8.56, 7.16 Hz, 1H), 2.97 (dd, *J* = 14.11, 3.84 Hz, 1H), 2.71 (dd, *J* = 14.1, 6.12 Hz, 1H), 2.51-2.46 (m, 1H), 2.44 (s, 1H), 2.15 (dtd, *J* = 17.31, 8.51, 1.66 Hz, 1 H). **^{13}C{1H} NMR** (100 MHz, CD_3OD) δ 166.3 144.0, 137.3, 136.1, 129.6, 129.2, 127.8, 127.6, 125.8, 79.5, 65.6, 38.6, 28.7, 20.1. **IR** (ATR, cm^{-1}) 3239, 3033, 3000, 2842, 1596, 1494, 1452, 1394, 1332, 1183, 1161, 1085, 1073, 1026. **HRMS** (APCI+) *m/z* calcd for $C_{18}H_{21}O_3N_2{}^{32}S$ $[M+H]^+$ = 345.1267; found 345.1268.

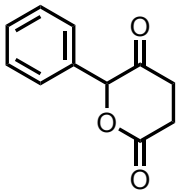
1.4.5 Representative procedure for palladium-catalyzed carbonylative lactonization reaction:

To a stirred solution of α-hydroxycyclopropanol **45** (1.0 equiv., 0.1 mmol) and DDQ (1.2 equiv., 0.12 mmol, 27.2 mg) in THF (0.01 M, 10 mL) under carbon monoxide atmosphere (the reactor was evacuated and backfilled three times using a carbon monoxide balloon) was added

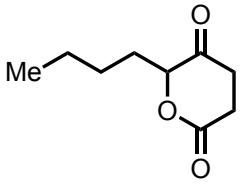
$Pd(OAc)_2$ (0.1 equiv., 0.01 mmol, 2.24 mg) in one portion. The resulting solution was stirred at room temperature for 8 h. The volatiles are then removed, and the reaction mixture is dissolved in EtOAc (30 mL) and transferred into a separatory funnel. Next, the organic layer is washed two times with a saturated $Na_2S_2O_3$ solution (10 mL), two times with a saturated $NaHCO_3$ solution (10 mL), and two times with brine (10 mL). The organic layer is then dried over $MgSO_4$, filtered through a short celite plug, and the volatiles are removed under reduced pressure. Column chromatography affords the pure desired 4-ketovalerolactones **50**.



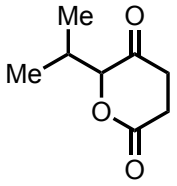
68. 12.1 mg; 59%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35-7.18 (m, 5H), 4.93-4.87 (m, 1H), 3.27 (dd, *J* = 14.5, 4.3 Hz, 1H), 3.19 (ddt, *J* = 14.5, 6.1, 1.5 Hz, 1H), 2.74-2.59 (m, 2H), 2.50-2.36 (m, 1H), 2.34-2.23 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 204.8, 169.4, 135.1, 130.0, 128.8, 127.4, 83.9, 37.3, 34.0, 27.5. **IR** (ATR, cm^{-1}) 2924, 1752, 1727, 1497, 1454, 1304, 1257, 1159, 1136, 1071, 1030, 1018. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$ = 205.0859; found 205.0861.



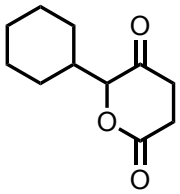
92. 10 mg; 52%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 746-7.33 (m, 5H), 5.71 (s, 1H), 2.97-2.87 (m, 1H), 2.87-2.75 (m, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.8, 169.6, 133.0, 129.1, 129.1, 125.9, 84.4, 33.4, 27.9. **IR** (ATR, cm^{-1}) 1732, 1271, 1176, 1043. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{11}O_3$ $[M+H]^+$ = 191.0702; found 191.0705.



93. 6.5 mg; 38%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.64 (dd, *J* = 8.0, 4.1 Hz, 1H), 2.97-2.83 (m, 2H), 2.79-2.60 (m, 2H), 2.01-1.91 (m, 1H), 1.86-1.75 (m, 1H), 1.52-1.26 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 205.5, 170.1, 83.3, 33.8, 30.5, 28.2, 26.8, 22.3, 13.8. **IR** (ATR, cm^{-1}) 2957, 2928, 2872, 2861, 1731, 1466, 1410, 1266, 1170, 1078. **HRMS** (APCI+) *m/z* calcd for $C_9H_{15}O_3$ $[M+H]^+$ = 171.1015; found 171.1017.

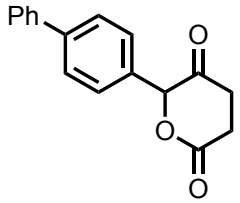


94. 5.4 mg; 34%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.50 (dd, *J* = 3.4, 0.7 Hz, 1H), 2.93 (ddd, *J* = 16.7, 6.0, 4.7 Hz, 1H), 2.85 (ddd, *J* = 16.7, 12.2, 5.6 Hz, 1H), 2.74 (ddd, *J* = 17.5, 5.6, 4.6 Hz, 1H), 2.63 (dddd, *J* = 17.5, 12.2, 6.0, 0.7 Hz, 1H), 2.45 (pd, *J* = 6.9, 3.4 Hz, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 205.4, 170.1, 87.5, 34.5, 30.1, 28.2, 18.8, 16.1. **HRMS** (APCI+) *m/z* calcd for $C_8H_{13}O_3$ $[M+H]^+$ = 157.0859; found 157.0860.

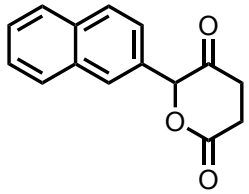


95. 7.0 mg; 36%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.47 (d, *J* = 3.4 Hz, 1H), 2.94-2.88 (m, 1H), 2.87-2.79 (m, 1H), 2.77-2.69 (m, 1H), 2.66-2.57 (m, 1H), 2.14-2.04 (m, 1H), 1.83-1.71 (m, 2H), 1.69-1.61 (m, 2H), 1.54-1.40 (m, 2H), 1.34-1.10 (m, 4H). **^{13}C{1H} NMR** (125 MHz,

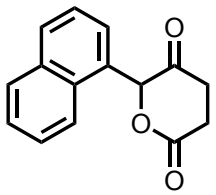
$CDCl_3$) δ 205.5, 170.1, 87.5, 39.9, 34.7, 29.0, 28.1, 26.3, 26.2, 25.9, 25.7. **IR** (ATR, cm^{-1}) 2927, 2854, 1752, 1729, 1450, 1263, 1176, 1162, 1101. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ = 197.1172; found 197.1175.



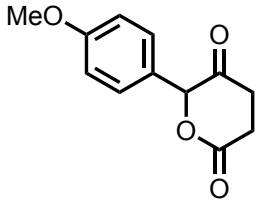
96. 14.0 mg; 53%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67-7.61 (m, 2H), 7.60-7.56 (m, 2H), 7.48-7.42 (m, 4H), 7.41-7.33 (m, 1H), 5.75 (s, 1H), 2.99-2.90 (m, 1H), 2.90-2.79 (m, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.8, 169.6, 142.1, 140.1, 131.9, 128.9, 127.8, 127.8, 127.2, 126.4, 84.3, 33.5, 27.9. **IR** (ATR, cm^{-1}) 2922, 1733, 1489, 1410, 1334, 1269, 1162, 1140, 1036, 1021. **HRMS** (APCI+) *m/z* calcd for $C_{17}H_{15}O_3$ $[M+H]^+$ = 267.1015; found 267.1020.



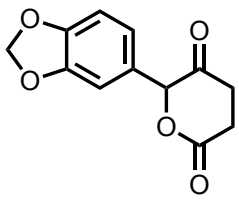
97. 15.3; 64%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93-7.78 (m, 4H), 7.56-7.43 (m, 3H), 5.87 (s, 1H), 3.00-2.79 (m, 4H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.8, 169.7, 133.3, 133.0, 130.3, 129.2, 128.2, 127.8, 127.0, 126.9, 125.2, 123.1, 84.6, 33.5, 27.9. **IR** (ATR, cm^{-1}) 2922, 1756, 1735, 1261, 1170, 1156, 1123, 1039. **HRMS** (APCI+) *m/z* calcd for $C_{15}H_{13}O_3$ $[M+H]^+$ = 241.0859; found 241.0864.



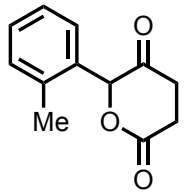
98. 9.2 mg; 38%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94-7.84 (m, 3H), 7.59-7.51 (m, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.1 Hz, 1H), 6.31 (s, 1H), 3.12-3.06 (m, 2H), 3.06-2.90 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 203.5, 169.6, 134.1, 130.9, 130.6, 129.4, 129.0, 127.1, 126.3, 124.9, 123.8, 83.4, 33.9, 28.4. **IR** (ATR, cm^{-1}) 3052, 2923, 1735, 1260, 1164, 1137, 1030. **HRMS** (APCI+) *m/z* calcd for $C_{15}H_{13}O_3$ $[M+H]^+$ = 241.0859; found 241.0860.



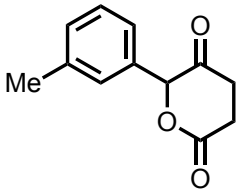
99. 9.7 mg; 44%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30-7.22 (m, 2H), 6.97-6.89 (m, 2H), 5.65 (s, 1H), 3.81 (s, 1H), 2.95-2.88 (m, 1H), 2.88-2.76 (m, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 203.2, 169.8, 160.2, 127.5, 125.0, 114.5, 84.3, 55.4, 33.4, 28.0. **IR** (ATR, cm^{-1}) 2961, 2922, 2852, 1733, 1614, 1520, 1461, 1270, 1257, 1175, 1027. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{13}O_4$ $[M+H]^+$ = 221.0808; found 221.0810.



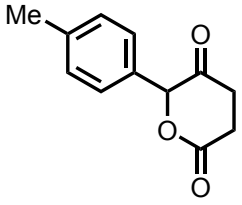
100. 10.3 mg; 44%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.86-6.76 (m, 3H), 5.99 (s, 2H), 5.59 (s, 1H), 2.96-2.84 (m, 2H), 2.84-2.76 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.9, 169.6, 148.4, 126.6, 120.0, 108.6, 106.7, 101.6, 84.2, 33.4, 28.0. **IR** (ATR, cm^{-1}) 2923, 1755, 1734, 1503, 1490, 1445, 1248, 1171, 1135, 1102, 1035. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{11}O_5$ $[M+H]^+$ = 235.0601; found 235.0605.



101. 13.2 mg; 65%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36-7.15 (m, 1H), 5.83 (s, 1H), 3.07-3.01 (m, 2H), 2.92-2.83 (m, 2H), 2.34 (s, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 203.8, 169.7, 137.1, 131.9, 131.2, 129.6, 127.8, 126.3, 83.3, 33.9, 28.4, 19.7. **IR** (ATR, cm^{-1}) 3023, 2923, 1733, 1331, 1259, 1172, 1136, 1037, 1016. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$ = 205.0859; found 205.0862.

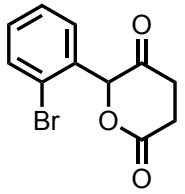


102. 11.4 mg; 56%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33-7.26 (m, 1H), 7.21-7.12 (m 3H), 5.66 (s, 1H), 2.95-2.87 (m, 1H), 2.86-2.77 (m, 3H), 2.36 (s, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.9, 169.8, 139.0, 132.9, 129.9, 129.0, 126.4, 122.9, 84.5, 33.4, 27.9, 21.5. **IR** (ATR, cm^{-1}) 2952, 2923, 2854, 1758, 1737, 1261, 1164, 1153, 1136, 1047. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$ = 205.0859; found 205.0862.

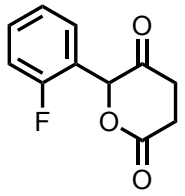


103. 10.6 mg; 52%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H), 5.67 (s, 1H), 2.95-2.86 (m, 1H), 2.86-2.73 (m, 3H), 2.36 (s, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 203.0, 169.8, 139.1, 130.1, 129.8, 125.9, 84.5, 33.4, 27.9, 21.2. **IR** (ATR, cm^{-1}) 2955, 2921, 2853,

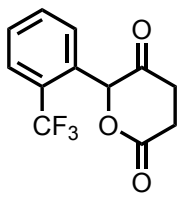
1732, 1266, 1177, 1131, 1039, 1020. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$ = 205.0859; found 205.0862.



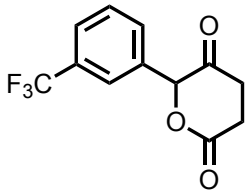
104. 16.0 mg; 60%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64-7.59 (m, 1H), 7.39-7.32 (m, 2H), 7.30-7.26 (m, 1H), 6.02 (s, 1H), 3.18-3.02 (m, 2H), 2.97-2.83 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 201.9, 169.4, 133.2, 132.9, 131.0, 130.0, 127.8, 123.8, 84.1, 33.5, 28.5. **IR** (ATR, cm^{-1}) 2923, 1759, 1738, 1262, 1172, 1137, 1056, 1039, 1028. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{10}O_3{}^{79}Br$ $[M+H]^+$ = 268.9807; found 268.9812.



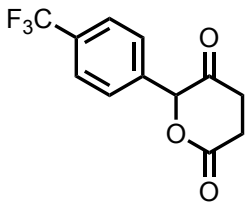
105. 10.0 mg; 48%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45-7.36 (m, 1H), 7.32 (td, *J* = 7.4, 1.8 Hz, 1H), 7.19 (tdd, *J* = 7.6, 3.4, 1.2 Hz, 1H), 7.16-7.08 (m, 1H), 5.83 (s, 1H), 3.09-3.02 (m, 2H), 2.94-2.85 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.4, 160.5 (d, *J* = 247 Hz), 131.6 (d, *J* = 9.5 Hz), 130.1 (d, *J* = 3 Hz), 124.9, 124.5 (d, *J* = 3.3 Hz), 121.2 (d, *J* = 13 Hz), 115.9 (d, *J* = 21 Hz), 80.5, 33.5, 28.3. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -116.6 (dt, *J* = 11.5, 6.4 Hz). **IR** (ATR, cm^{-1}) 2922, 1759, 1738, 1494, 1458, 1263, 1235, 1171, 1136, 1041, 1030. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_{10}O_3F$ $[M+H]^+$ = 209.0608; found 209.0611.



106. 16.5 mg; 64%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74-7.71 (m, 1H), 7.64-7.59 (m, 1H), 7.55-7.50 (m, 1H), 7.47-7.43 (m, 1H), 6.03 (s, 1H), 3.17 (ddd, *J* = 16.5, 13.8, 6.4 Hz, 1H), 3.06 (ddd, *J* = 16.5, 5.7, 2.4 Hz, 1H), 2.92 (ddd, *J* = 18.9, 6.5, 2.4 Hz, 1H), 2.81 (ddd, *J* =19.1, 13.9, 5.7 Hz, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 201.9, 169.3, 132.4, 131.2, 129.7 (d, *J* = 41 Hz), 128.8 (d, *J* = 31.5 Hz), 127.2, 126.3 (q, *J* = 5.7 Hz), 123.9 (d, *J* = 274 Hz), 120.6, 80.9, 33.1, 28.5. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -59.1. **IR** (ATR, cm^{-1}) 2959, 2923, 2853, 1764, 1741, 1313, 1261, 1158, 1118, 1048, 1033. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{10}O_3F_3$ $[M+H]^+$ = 259.0576; found 259.0578.

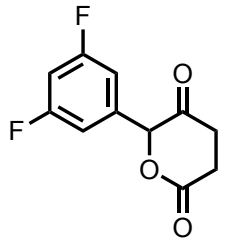


107. 10.9 mg; 42%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69-7.62 (m, 2H), 7.61-7.53 (m, 2H), 5.75 (s, 1H), 3.04-2.95 (m, 1H), 2.95-2.79 (m, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.1, 168.9, 133.8, 131.5 (d, *J* = 33.3 Hz), 129.6 (d, *J* = 22 Hz), 126 (d, *J* = 5.4 Hz), 124. 8, 123.2 (d, *J* = 3.7 Hz), 122.6, 83.5, 33.4, 27.9. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -63.9. **IR** (ATR, cm^{-1}) 2924, 1761, 1738, 1328, 1259, 1163, 1121, 1074. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{10}O_3F_3$ $[M+H]^+$ = 259.0576; found 259.0579.

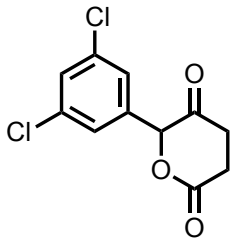


108. 18.0 mg; 70%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 5.76 (s, 1H), 3.03-2.94 (m, 1H), 2.92-2.76 (m, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 202.0, 169.0, 136.6, 131.4 (d, *J* = 39 Hz), 131.2, 131.0, 126 (q, *J* = 3.7 Hz), 124.8, 122.7,

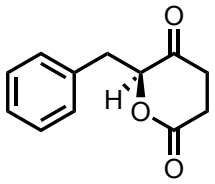
83.6, 33.4, 27.9. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -64.0. **IR** (ATR, cm^{-1}) 2920, 1736, 1330, 1272, 1180, 1159, 1110, 1068, 1047. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{10}O_3F_3$ $[M+H]^+$ = 259.0576; found 259.0580.



109. 14.2 mg; 63%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.00-6.91 (m, 2H), 6.84 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.66 (s, 1H), 3.03-2.91 (m, 1H), 2.90-2.76 (m, 3H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 201.5, 168.6, 164.3 (d, *J* = 13.3 Hz), 162.3 (d, *J* = 13.3 Hz), 136.4 (t, *J* = 8.9 Hz), 109.3 (dd, *J* = 21, 7.2 Hz), 104.6 (t, *J* = 26 Hz) 82.9, 33.4, 27.8. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -108.6. **IR** (ATR, cm^{-1}) 2956, 2922, 2851, 1744, 1731, 1601, 1456, 1306, 1121. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_9O_3F_2$ $[M+H]^+$ = 227.0514; found 227.0519.



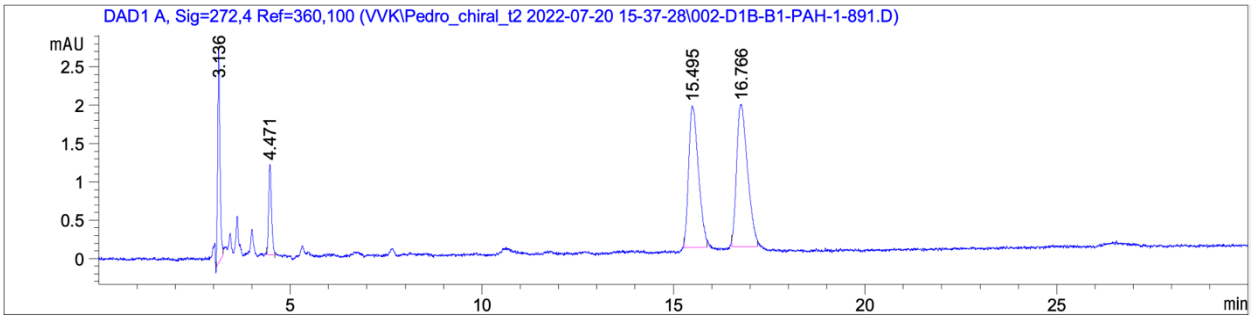
110. 12.9 mg; 48%; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.37 (m, 1H), 7.30-7.27 (m, 2H), 5.63 (s, 1H), 2.98 (ddd, *J* = 17.4, 9.4, 6.4 Hz, 1H), 2.93-2.88 (m, 1H), 2.87-2.77 (m, 2H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 201.6, 168.7, 135.9, 135.7, 129.4, 124.7, 82.7, 33.4, 27.8. **IR** (ATR, cm^{-1}) 2922, 2852, 1741, 1731, 1572, 1434, 1269, 1180, 1158, 1050. **HRMS** (APCI+) *m/z* calcd for $C_{11}H_9O_3{}^{35}Cl_2$ $[M+H]^+$ = 258.9923; found 258.9927.



68'. 12.1 mg; 59%, 94% *ee*; light yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H), 4.93-4.90 (m, 1H), 3.28 (dd, *J* = 14.7, 4.3 Hz, 1H), 3.20 (dd, *J* = 14.5, 6.1, 1H), 2.72-2.63 (m, 2H), 2.45-2.38 (m, 1H), 2.32-2.26 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 204.9, 169.4, 135.1, 130.0, 128.8, 127.4, 83.9, 37.3, 34.0, 27.5. **IR** (ATR, cm^{-1}) 2924, 1752, 1727, 1497, 1454, 1304, 1257, 1159, 1136, 1071, 1030, 1018. **HRMS** (APCI+) *m/z* calcd for $C_{12}H_{13}O_3$ $[M+H]^+$ = 205.0859; found 205.0862.

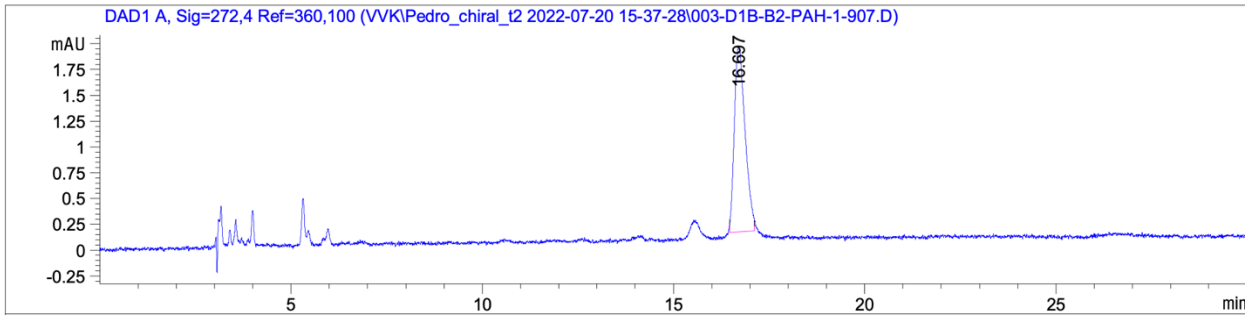
SFC (Chiralpak IA column) 3% MeOH/CO_2 (2.0 mL/min, λ = 210 nm)

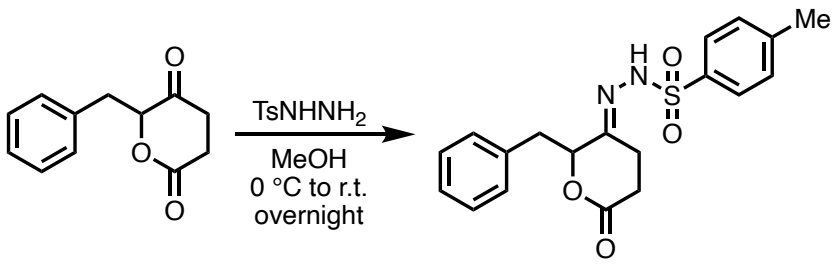
Racemic 68			
	RT (min)	Area (mAU*s)	% Area
1	15.495	6816.87354	47.1827
2	16.766	7630.96143	52.8173



Enantioenriched 68'			
	RT (min)	Area (mAU*s)	% Area
1	15.553	582.559	7.3821

2	16.702	7308.97	92.6179





68 **119**

119. To a solution of **68** (40.8 mg, 0.2 mmol, 1.0 equiv.) in MeOH (0.2 M, 1.0 mL), $TsNHNH_2$ (1.5 equiv., 0.3 mmol, 55.8 mg) was added at 0 °C. The reaction was warmed to room temperature and stirred overnight. The volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (hexane/EtOAc = 3/1) to give *N*-tosylhydrazone **119** (69.5 mg, 97%) as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 (bs, 1H), 7.84 (d, *J* = 7.9 Hz, 2H), 7.37-7.33 (m, 2H), 7.25-7.20 (m, 3H), 7.17 (dd, *J* = 7.6, 2.0 Hz, 2H), 4.99 (dd, *J* = 7.9, 3.8 Hz, 1H), 3.39 (dd, *J* = 14.7, 3.8 Hz, 1H), 2.89 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.69-2.50 (m, 3H), 2.46 (s, 3H), 2.43-2.31 (m, 1H). **^{13}C{1H} NMR** (125 MHz, $CDCl_3$) δ 170.7, 151.5, 144.9, 136.3, 134.7, 129.9, 129.8, 128.5, 128.1, 126.9, 79.9, 36.7, 27.4, 22.2, 21.7. **IR** (ATR, cm^{-1}) 3204, 2924, 1741, 1341, 1164, 1018. **HRMS** (APCI+) *m/z* calcd for $C_{19}H_{21}O_4N_2{}^{32}S$ $[M+H]^+$ = 373.1216; found 373.1218.

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