A Novel Route to Enantioenriched α-Allyl α-Fluoroketones via Palladium Catalyzed Decarboxylation

by

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Thesis Committee:

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The Thesis Committee for Briana R. Barron certifies that this is the approved version of the following thesis:

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Abstract

This thesis details the development of a novel catalytic asymmetric route to α-fluorinated ketones. Enantioenriched α-fluoroketones were produced in good yields and high enantiomeric ratios via palladium-catalyzed decarboxylation of cyclic α-fluorinated β-keto allylic esters. A series of α-fluoroketones were produced to examine the scope and the conditions for this reaction.

In contrast to previous routes toward α-fluorinated ketones, this route is advantageous for several reasons. First, this route avoids the issues associated with the regiospecific generation of fluorinated ketone enolates by forming the enolate *in situ* by palladium-catalyzed decarboxylation. Secondly, this method requires only a catalytic amount of non-racemic material in contrast to chiral fluorinating reagents which are required in stoichiometric amounts. Lastly, the β-keto ester substrates for this reaction are easily synthesized and readily fluorinated by electrophilic fluorinating reagents.

Acknowledgements

This work is the culmination of the work that I did under the mentorship of Dr. Jon Tunge, and I thank him sincerely for advising me with this thesis project.

I would like to thank all of my professors; each has greatly shaped my knowledge and understanding and interest in organic chemistry. Specifically, I would like to thank Dr. Carlson who first sparked my interest in organic chemistry as an undergraduate. I would like to thank Dr. Heppert for encouraging me while writing this thesis and helping me to find new, exciting opportunities for future projects. I would also like to give special thanks to Erin Burger, who was instrumental in this project; her mentorship in and out of the lab was invaluable to me.

My family and friends have always been supportive of the things I do, and I don't take the opportunity to thank them for it often enough. My mom has been my greatest role model, her support has been instrumental in everything I have achieved or will achieve. I would also like to thank Nikki Perry and Holly Dunoon along with the entire Platonic Touch Brewery for their priceless companionship. Also, I am grateful to Chris Munson who has been a great friend in the department; I can only hope to master multitasking the way she has in her life.

I also need to thank the department which has provided several teaching and mentorship opportunities for me. Through teaching and mentoring I have had some of my most rewarding experiences in graduate school. Most notably, I can look forward to watching my former student, now friend, Ilana Schriger as she becomes a great scientist.

For my husband, Steve

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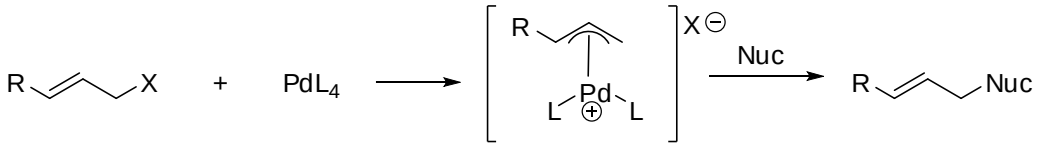
Part 1:
Introduction

Palladium-catalyzed Allylation Reactions:

Functionalization by allylation imparts an important handle for further transformations of organic molecules. The synthetic utility of palladium-catalyzed allylation reactions has been demonstrated in the literature many times since its development by Tsuji in 1965 (Figure 1).[1] The development of highly enantioselective allylation reactions represents an important focus for the design of complex naturally occurring organic molecules.[2] In addition to the application of these methods, their development increases the body of knowledge in the field of asymmetric catalysis and provides a greater understanding on which to build new and superior methods for a wider range of uses.[3]

Figure 1 *Formation of the π-Allyl Palladium Complex Followed by Nucleophilic Attack*



Palladium reacts with allylic substrates to produce a stabilized cationic π-allyl species. These π-allyl palladium species are generally attacked by nucleophiles at the least hindered position, displacing palladium to produce a carbon-carbon bond. Thus, reactants derived from chiral allylic alcohols are normally required for formation of chiral products. Furthermore, palladium catalysis can be an effective method for the synthesis of non-racemic molecules by inducing chirality via a ligand which is coordinated to palladium (Figure 2). The introduction of asymmetry into allylation reactions requires the use of a chiral reagent to transfer its chirality to the forming product. In order to cause enantiodiscrimination, the chiral ligand must span the plane of the allyl system. Generally, an appropriate bulky coordinated ligand blocks nucleophilic attack at one of the allylic termini, thus promoting a single transition state where the attack gives only

one enantiomer. Palladium catalysis also offers the advantage of using the often expensive chiral ligand in catalytic rather than stoichiometric amounts. Various chiral ligands have been screened or developed to effect enantiodiscrimination in palladium-catalyzed allylation reactions. (Figure 3).[4] The donor atoms of the ligands for palladium catalysis are often nitrogen or phosphorus-based; choice of donor atom allows electronic tuning of the reaction since the property of the donor atom can be transmitted through palladium to the allyl fragment.

Figure 2 *Stereochemical Outcomes of Nucleophilic Attack*

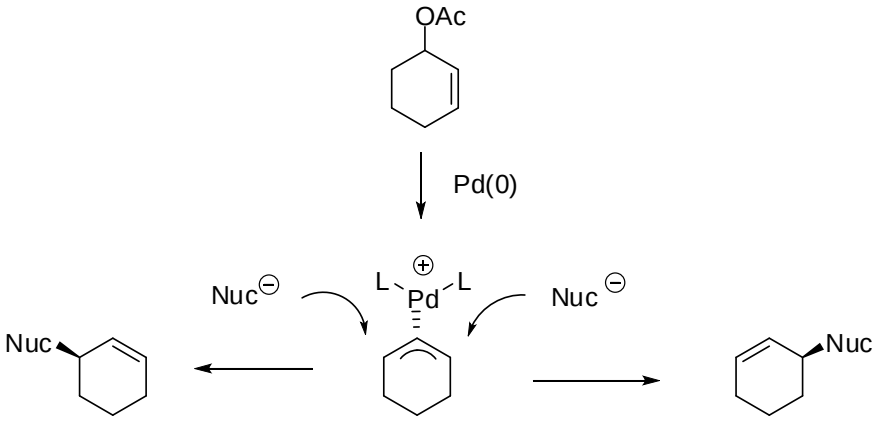
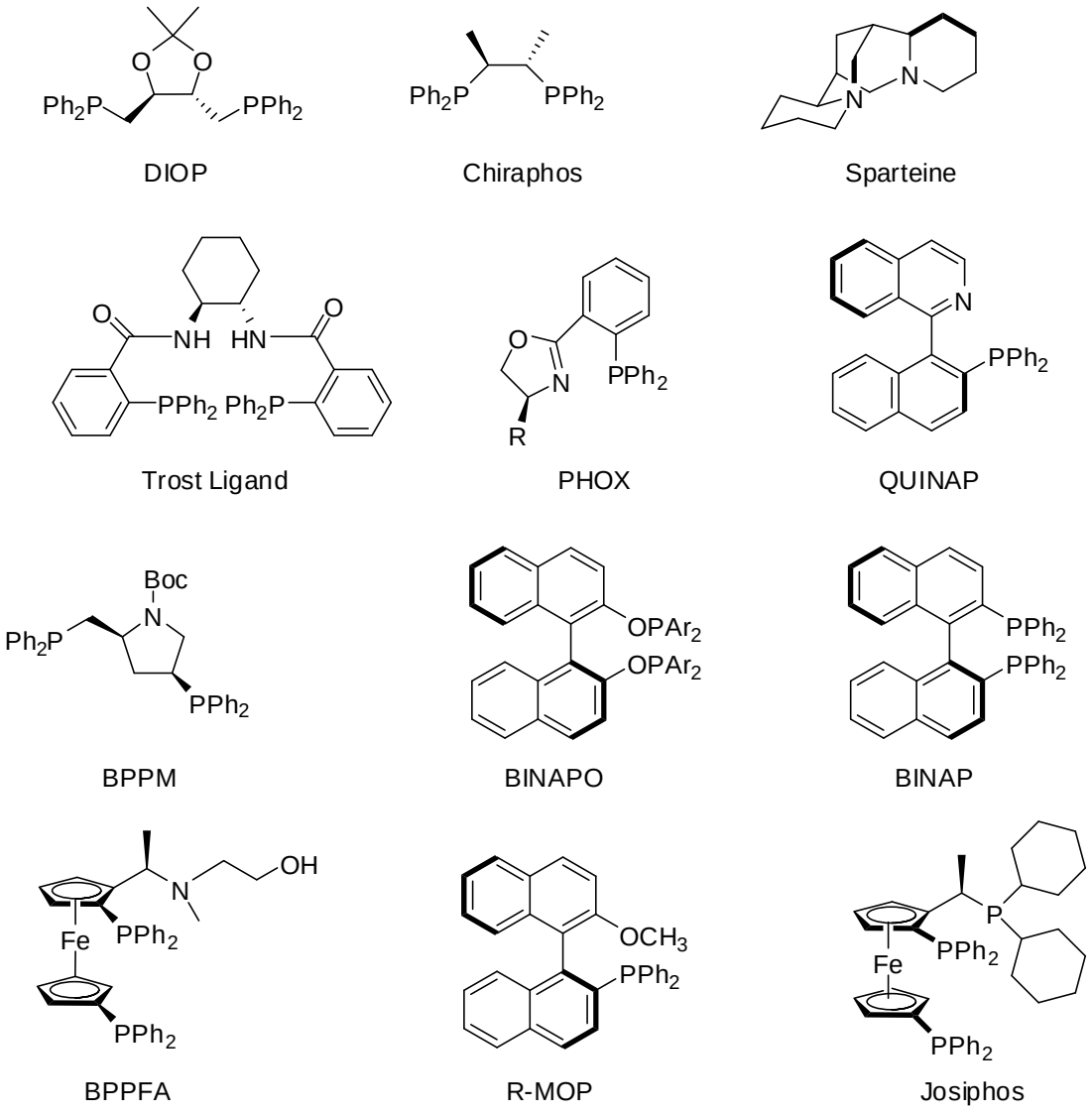


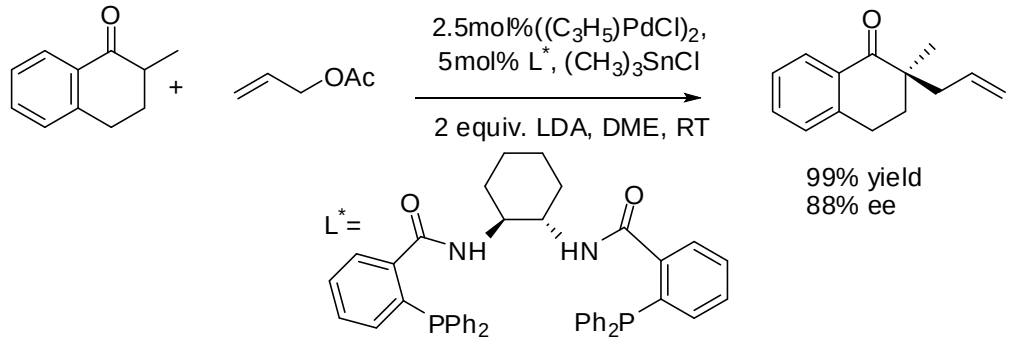
Figure 3 *Chiral Ligands used in Asymmetric Allylation Reactions*



The scope of nucleophiles for this reaction includes oxygen and other heteroatom nucleophiles;[4] however, this discussion will focus on the carbon-carbon bond forming potential of carbon nucleophiles. In particular, enolates have been a point of interest due to the synthetic utility of the resulting chiral ketones. The enolate counterion has been found to be crucial to the outcome of the reaction, with softer counterions giving better results than hard counterions in terms of reaction yield and, when applicable, enantiomeric excess.[5] With this in mind, Trost used a tin stabilized enolate as the

nucleophile for this reaction, producing γ,δ-unsaturated carbonyl compounds with high yields and with excellent enantiomeric excess, reaching 98% for select compounds.[6] Despite improvements since the development of the first palladium catalyzed asymmetric allylation reaction,[7] current methodologies (Figure 4) require strong bases and tin to generate high enantioselectivities. The strong bases required limit the substrate scope to α-substituted systems which exclude the possibilities of double allylation and racemization by deprotonation. Furthermore, tin is a toxin which requires special disposal and treatment. Thus, methods that do not require the use of tin are desirable.

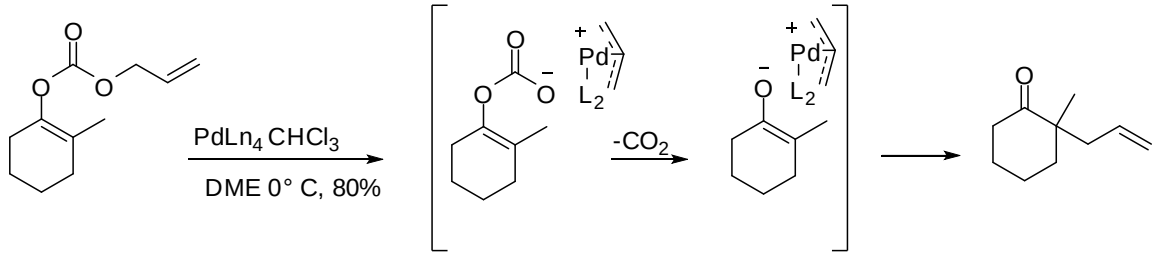
Figure 4 *Trost method for Allylic Alkylation*



Decarboxylative allylation reactions:

Palladium(0) is known to cause the rapid decarboxylation of several CO_2 containing substrates, where the release of carbon dioxide drives a coupling reaction. Tsuji and Saegusa demonstrated that allylic carbonates could be decarboxylated by palladium to form γ,δ-unsaturated ketones (Figure 5)[8]. Both Trost and Stoltz have expanded this chemistry using a chiral ligand to produce enantioenriched γ,δ unsaturated

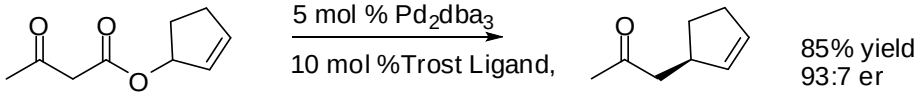
Figure 5 *Decarboxylative Allylation of an Allylic Carbonate*



ketones from the corresponding allylic carbonates.[9] These studies showed high yields and enantioselectivities reaching above 90% for some substrates. Decarboxylation generates the enolate *in situ*, leaving the π-allyl palladium species as the only counterion present. This successfully avoids the drawbacks associated with harder counterions.[10]

Saegusa demonstrated a similar decarboxylative metallation with palladium that could be used to produce γ,δ-unsaturated ketones from β-keto allylic esters.[8] In an extension of this chemistry, the Tunge lab has developed a program around the catalytic asymmetric decarboxylation of β-keto esters (Figure 6).

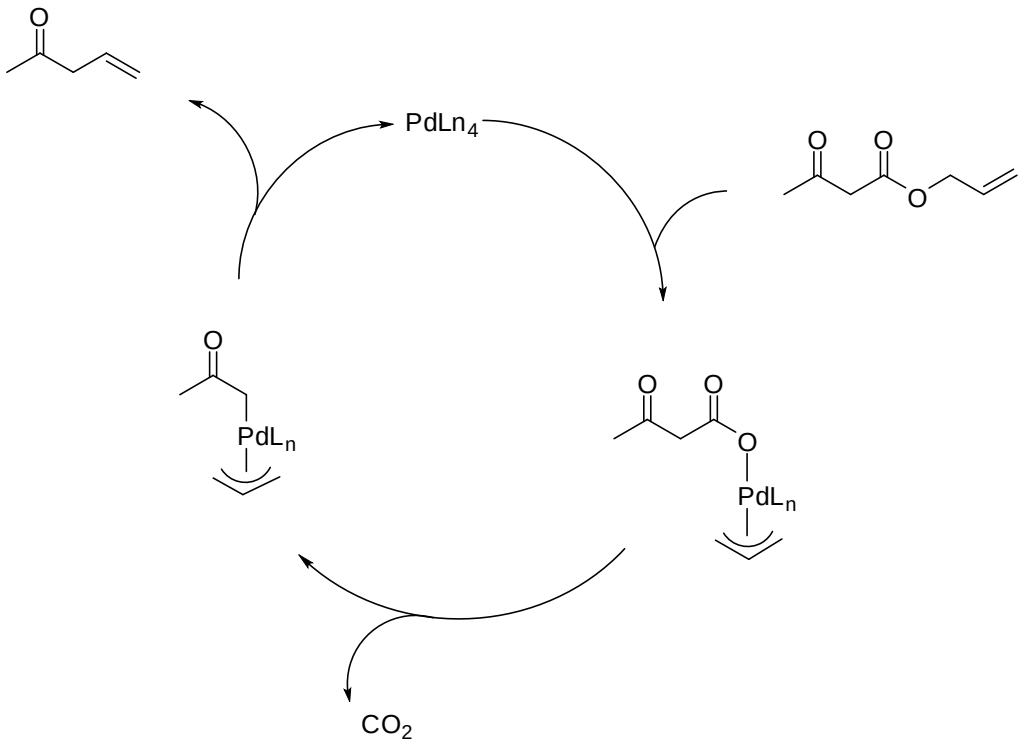
Figure 6 *Palladium-Catalyzed Decarboxylative Allylation*



Prior to the work detailed in this thesis, it was shown that ligands used in as asymmetric allylic alkylation reactions also facilitated decarboxylative coupling of β-keto esters.[11] Addition of palladium with a suitable chiral ligand to an allylic β-keto ester will produce a π-allyl palladium carboxylate, which then decarboxylates to form the enolate which attacks the π-allyl palladium species to form γ,δ-usaturated ketones (Figure 7). Mechanistic studies showed that C-C bond formation occurred after decarboxylation, suggesting the ketone enolate as a true intermediate in this process. This methodology for producing γ,δ-usaturated ketones has several advantages over previous methods. First, β-keto esters are synthetically easier to attain than allylic carbonates. In addition,

this reaction occurs without the presence of tin or strong base, increasing the mildness and thus its substrate scope. In addition, palladium-catalyzed decarboxylation of the β-keto ester is regiospecific for allylation at the carbon once bearing the allyl ester. Furthermore, the *in situ* generation of the non-stabilized enolate eliminates the use of a hard counterion, increasing the softness of the enolate which in turn leads to higher enantioselectivites.[5]

Figure 7 *Catalytic Cycle for Decarboxylative Allylation*



Decarboxylative allylation of α-fluoroketones:

It was our hypothesis that decarboxylative couplings similar to those previously described could be used to set fluorinated chiral centers alpha to a ketone with high levels of enantiopurity. Decarboxylative allylation provides a route to enantioenriched α-fluoroketones from the corresponding α-fluoro-β-keto allylic esters.

Compounds containing an α-fluoroketone moiety are of interest as building blocks for many desirable molecules. In particular, α-fluoroketones mimic the biological activity of α-hydroxyketones and are present in a number of compounds of pharmaceutical and agricultural interest.[12] Retrosynthetic analysis of α-fluoroketones suggests that they could be formed from chiral fluoroenolates, yet these reactions typically fail.[13] The synthesis of α-fluoroketones from enolates has remained problematic due to the instability of the fluorinated enolate particularly in the presence of base, as the equilibrium of the two possible enolates is shifted away from the fluorinated enolate (Figure 8).[14] While several methods for generating simple fluoroenolates have evolved (Figure 9), most synthetic routes to α-fluoroketones typically rely on electrophilic fluorination of standard enolates (Figure 9).[15]

Figure 8 *Equilibrium of Fluorinated Enolates*

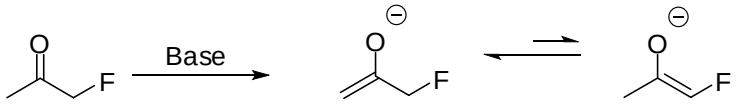


Figure 9 *Generation of a Fluorinated Enolate*

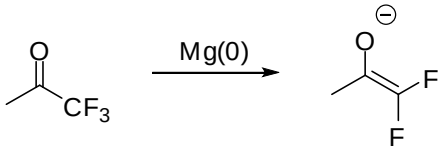
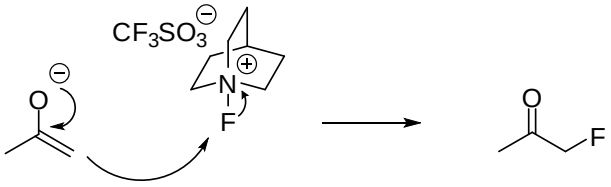


Figure 10 *Common Route to Fluorination of Enolate by Electrophilic Fluorinating Agent*



Synthetic routes to enantoenriched α-fluoroketones from racemic starting materials often employ chiral-non racemic fluorinating reagents with activated substrates. Several chiral fluorinating reagents have been developed that induce chirality in the product resulting from transfer of fluorine onto an achiral anion. *N*-fluorocamphorsultam derivatives have been synthesized (Figure 11) and explored by several groups in an attempt to produce α-fluoroketones (Figure 12). Unfortunately, fluorination by these methods required stoichiometric amounts of the *N*-fluorocamphorsultam in the presence of a strong base and gave only moderate yields and enantioselectivities.[16] In addition, the presence of hydrogen on the fluorinated α-carbon was not tolerated by the basic conditions and resulted in complete racemization, thus greatly limiting the substrate scope of this reaction.[16] Similar approaches have been used with limited success. For instance, naturally occurring cinchona alkaloids were fluorinated to produce a more powerful chiral fluorinating reagent capable of adding fluorine to silyl enol ethers with moderate enantioselectivities (Figure 12).[17]

Figure 11 *Formation of N-fluorocamphorsultam*

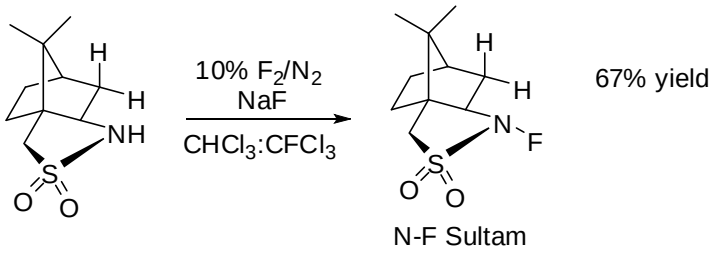


Figure 12 *Chiral Fluorination by N-fluorocamphorsultam*

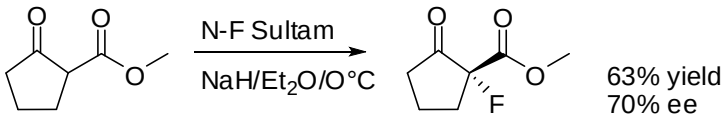


Figure 13 *Cinchona Alkaloids: N-Fluorocinchoinium tetrafluoroborate (F-Cn-BF_4) and N-Fluoroquininium tetrafluoroborate (F-QN-BF_4)*

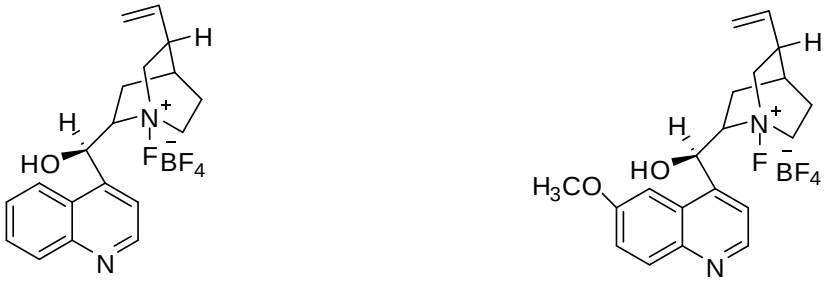
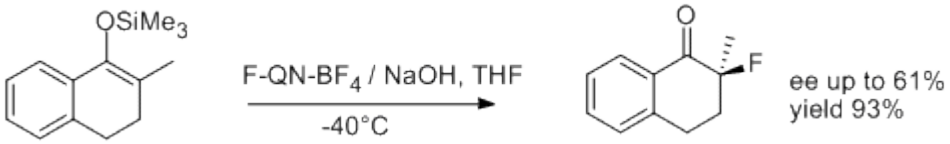
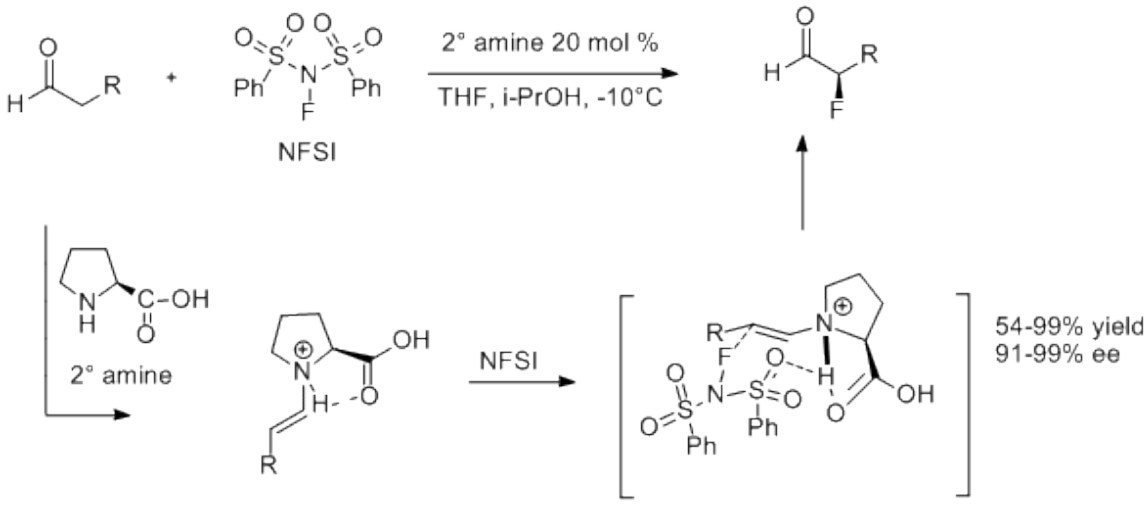


Figure 14 *Chiral Fluorination by Cinchona Alkaloid*



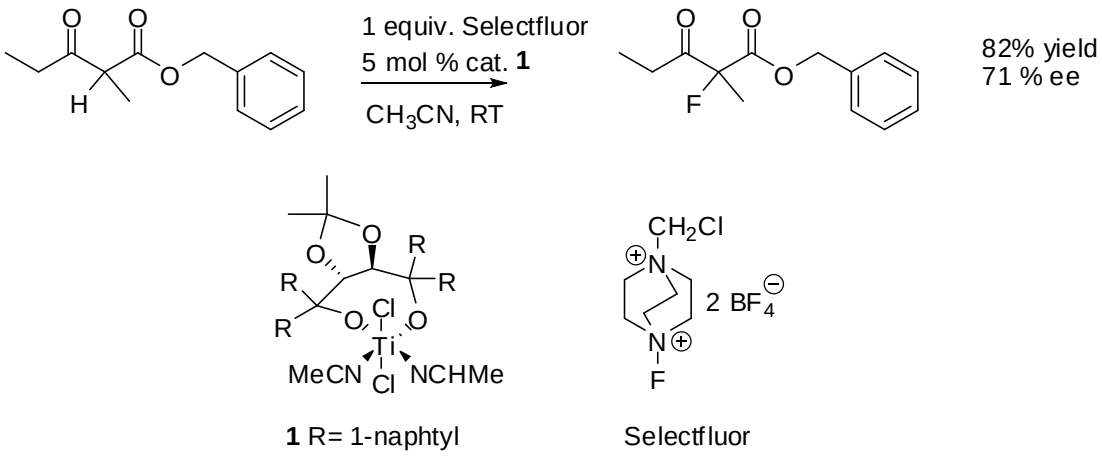
More recently catalytic fluorination for other functional groups has been developed. MacMillan described an asymmetric organocatalytic α-fluorination of a variety of aldehydes. The reaction proceeds by forming the corresponding enamine using a chiral secondary amine which reacts with *N*-fluorobenzenesulfonimide (NFSI), an achiral fluorinating reagent in a closed transition state (Figure 14). Excellent enantioselectivities and yields were reported, however, this system is limited to simple aldehydes.[18]

Figure 15 *Proposed Organocatalytic Route to α-Fluorinated Aldehydes*



A catalytic route to fluorinated β-keto esters using chiral titanium, palladium or copper complexes has been described (Figure 15).[19] These conditions worked well to set the α-stereocenter of the β-keto ester with high yields and enantioselectivities.

Figure 16 *Titanium Catalyzed Enantioselective Fluorination of β-Keto Esters*



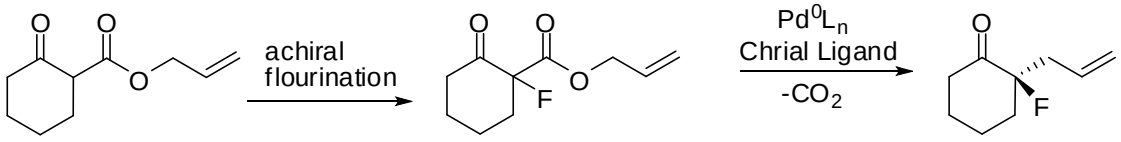
The focus of the research presented in this thesis is to circumvent the above limitations in the synthesis of chiral α-fluoroketones by using asymmetric palladium catalyzed decarboxylation of the α-fluorinated β-keto esters.

Part 2:
Methods

Rationale for Novel Route to Enantioenriched α-Fluoroketones:

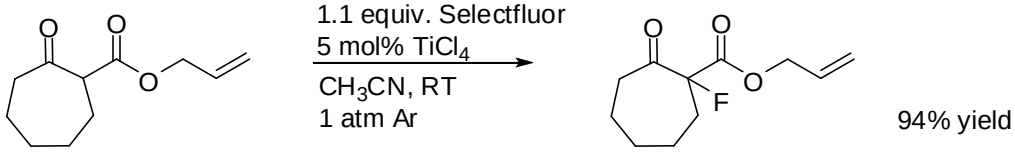
Using the previous success in the synthesis of γ,δ-unsaturated ketones as a guide, we embarked on the development of enantioenriched α-fluorinated ketones from β-keto esters. This route for constructing enantioenriched α-fluorinated ketones is fundamentally separate from previous methods of generation because it does not rely on enantioselective addition of fluorine. Instead, enantioselectivity is accomplished during the carbon-carbon bond formation.

Figure 17 *Proposed Route to Enantioenriched α-Fluoroketones*



In addition to being easy to synthesize, β-keto esters provide a highly acidic site for easy fluorination. A variety of electrophilic fluorinating agents have been developed in response to the difficulty in achieving selective fluorination via HF or F_2 as fluorine sources.[20] For our studies, we used Selectfluor as a reagent to selectively fluorinate the activated position alpha to the carbonyl groups.[21]

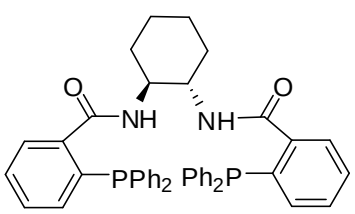
Figure 18 *Fluorination of β-Keto Ester Substrates*



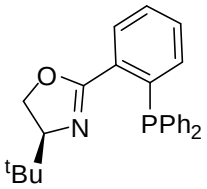
After constructing a series of fluorinated β-keto esters, a survey of potential chiral ligands for the decarboxylation reaction was conducted. It was found that ligands that coordinated through phosphorus and nitrogen provided high levels of reactivity and gave the best enantiomeric excess. The Trost ligand (Figure 19) has been used

successfully in the decarboxylative allylation of carbonates, however, the coupling of fluorinated enolates failed with the addition of the Trost ligand. ^{t}BuPHOX ligands showed good reactivity and enantioselectivities as described by Nakamura during the course of our study.[22] We noted that addition of QUINAP also produced high levels of enantioselectivity, which were in some cases higher than that given by the ^{t}BuPHOX ligand. Thus, QUINAP was selected and compared with the ^{t}BuPHOX ligand.

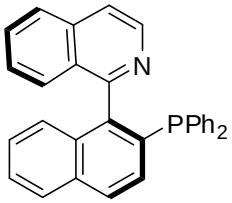
Figure 19 *Ligand Survey*



Trost Ligand



^{t}BuPHOX Ligand



QUINAP

Scope of Decarboxylative Allylation Reaction

The decarboxylation reaction was run on a series of fluorinated β-keto esters to produce the enantioenriched cyclic ketone products. Decarboxylation took place with the addition of 2.5 mol % $Pd_2(dba)_3$ in benzene. It was found that 5.5 mol % QUINAP produced optimal enantiomeric ratios in this system. The reactions were stirred under argon for the time specified in Table 1 at 40°C until NMR monitoring revealed there was no further increase in the ratio of product to starting material.

Figure 20 *General Scheme for Reaction Investigated in Table 1*

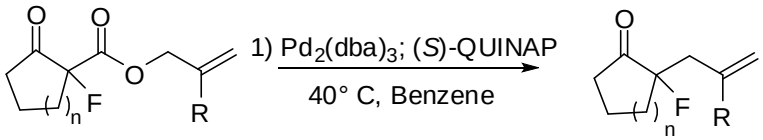
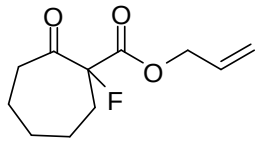
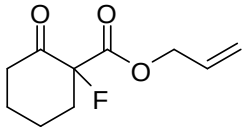
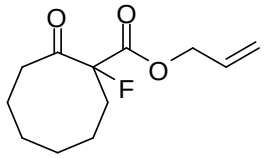
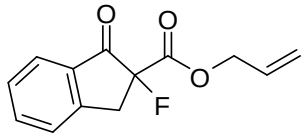
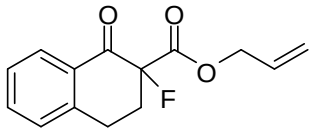
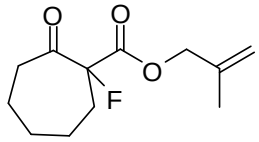
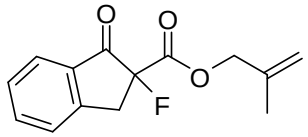
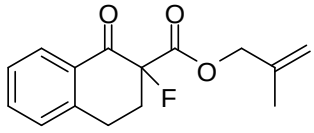


Table 1 *Decarboxylative Allylation reactions with (S)-QUINAP and (S)-^{t}BuPHOX. Small scale reactions with (S)-QUINAP are shown in parentheses for comparison.*

Substrate	Time (hr)	QUINAP Yield (%)	QUINAP er	^{t}BuPHOX Yield (%)	^{t}BuPHOX er
 **1a**	8	92	82:18	91	96:4
 **1b**	3.5	84	84:16 (92:8)	73	91:9
 **1c**	8	83	88:12 (91:9)	94	90:10
 **1d**	5	97	86:14	-	-
 **1e**	3	83	89:11	-	-
 **1f**	12	82	94:6	64	73:27
 **1g**	5	87	88:12	-	-
 **1h**	6	58	94:6	-	-

Conflicting results were obtained when changing the scale of the reaction. Specifically, NMR experiments with 10mg of the β-keto ester produced higher enantiomeric ratios than benchtop experiments using 70-100mg of the substrate, despite concentration and molar ratios remaining the same. The cause of this anomalous behavior is unknown.

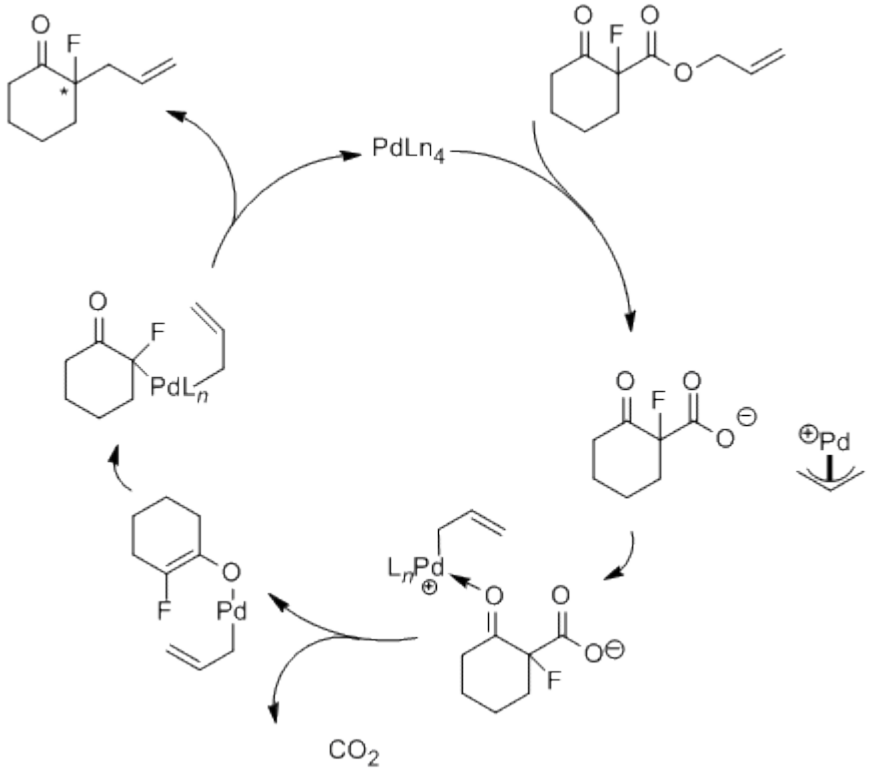
The corresponding α-fluoroketones were produced in good yields with the exception of **1h** which was produced in an unexpectedly low yield. For both ligands, substitution of an allyl group with a methallyl group increased the enantiomeric ratio. As shown above the (*S*)-^{t}BuPHOX ligand gives better yields for substrate **1c** and superior enantioselectivities for **1a-c**. The (*S*)-QUINAP ligand provides far superior yield and enantioselectivity of substrate **1f** and similar enantioselectivity for **1c** when comparing the small scale QUINAP results to the bench top ^{t}Bu-PHOX ligand. In addition, the (*S*)-^{t}BuPHOX ligand give the *R* enantiomer, while (*S*)-QUINAP gave the *S* enantiomer. Further research in the origin of enantioselectivity is needed to explain these results.

Reaction Mechanism:

The mechanism for palladium-catalyzed allylic allylation has been extensively studied.[23] The palladium-catalyzed decarboxylation of α-fluoro-β-keto esters is thought to proceed by a similar process. The catalytic cycle begins with oxidative addition of Pd(0) into the double bond of the allylic ester, ionization of the allyl group from the ester occurs as the π-allyl Pd(II) species forms. The release of CO_2 forms the α-fluoro-β-keto carboxylate thus generating the nucleophile *in situ*. The otherwise unstable fluoroenolate is stabilized by palladium. In order for palladium to maintain its 16-electron

configuration, a ligand must be dissociated. In this case, it is likely that the alkene dissociates to form an η^1-allyl complex. This allows it to maintain bidentate complexation with the chiral ligand. The chiral ligand can function by either favoring a single stereochemistry of a C-bound palladium enolate intermediate or by discriminating the enantiofaces of an achiral enolate in the transition state for allylation. The cationic enantiodifferentiated π-allyl Pd(II) species is attacked by the enolate, displacing Pd(0), concomitantly releasing the product and regenerating the catalyst (Figure 21).

Figure 21 *Catalytic Cycle for Palladium Catalyzed Allylation of α-Fluoro-β-Keto Esters*



Crossover experiments (Figures 22-23) were performed to give an insight to the mechanistic details of this reaction. It was noted that substrates **1b** and **1g** react at similar

rates. These substrates were subjected to decarboxylation conditions in the same vessel in a 1:1 molar ratio (Figure 22). Separation by gas chromatography and monitoring by NMR showed all four possible products arose from this experiment in near equal ratios suggesting complete scrambling. This process was repeated with substrates **1c** and **1d** which confirmed complete crossover (Figure 23). This suggests that the coupling reaction proceeds through loose ion pairing between the cationic π-allyl palladium complex and the enolate.

Figure 22 *Crossover Experiment 1*

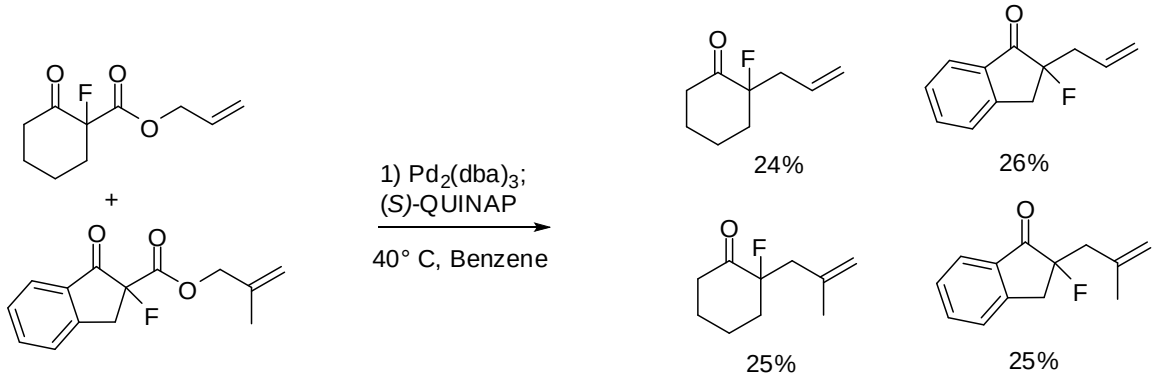
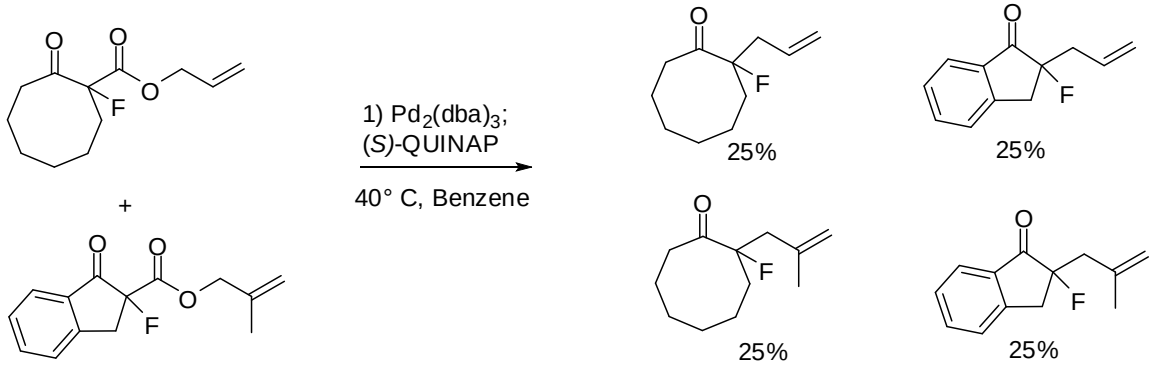


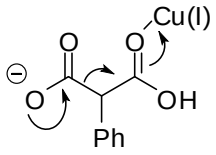
Figure 23 *Crossover Experiment 2*



The exact mechanism of decarboxylation for this reaction is unknown, but analogous copper(I)-catalyzed decarboxylation reactions have shown an intermediate

where the metal-allyl system coordinates to the ketone, allowing the release of CO_2 and subsequent formation of the enolate (Figure 24).[24] It should also be noted that the reaction gave products exclusively allylated at the fluorinated carbon; thus, there is no equilibration to the thermodynamic enolate under these conditions. Accordingly, enolate formation is regiospecific, allowing access to fluorinated enolates that are difficult to generate by standard methods.

Figure 24 *Proposed Mechanism of Decarboxylation*



Conclusions:

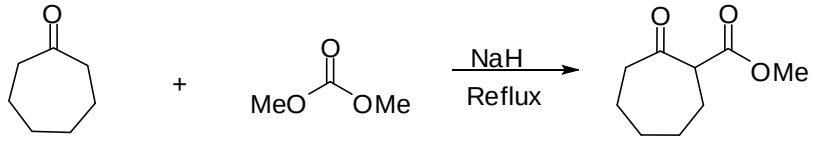
This thesis has outlined a novel route toward enantioenriched α-fluoroketones which produces the desired products in good yields and high enantiomeric ratios via palladium catalyzed decarboxylation. This method produces the fluorinated enolate nucleophiles *in situ*, effectively avoiding difficulties arising from its instability. The ease of synthesis of the α-fluoro-β-keto ester substrate gives this reaction a distinct advantage in comparison to methods which utilize decarboxylation of enol carbonates. In addition, the catalytic amount of chiral ligand required for this reaction is more cost effective than methods that rely on stoichiometric amounts of chiral fluorinating reagents.

Part 3:
Experimental

Synthesis of Starting Materials:

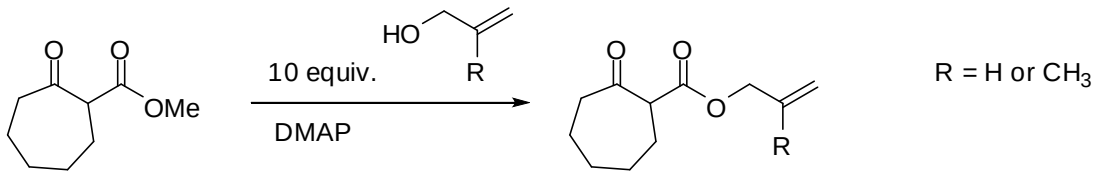
Substrates for the decarboxylation reaction were synthesized from the corresponding cyclic ketones according to a previous protocol (Figure 25).[25] The cyclic ketone (0.22 mol) was added dropwise to a solution of dimethyl carbonate (0.45 mol) and sodium hydride (1.45 mol) in 60mL of ether. The mixture was stirred for 6 hours, then cooled to 0°C and glacial acetic acid (0.45 mol) was added dropwise. After addition, 100mL cold water was added and the organic layer was extracted and dried with $MgSO_4$. Following solvent extraction the products were purified by column chromatography (SiO_2, 1:9 EtOAc-hexane) and obtained in 56-62% yield.

Figure 25 *Synthesis of β-keto Methyl Ester*



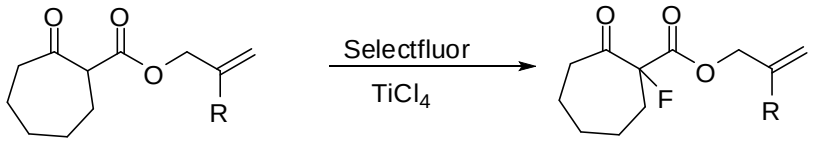
The ester (2.5mmol) was then allylated via transesterification (Figure 26). The β-keto ester was added to 1 equivalent DMAP (2.5mmol) (dimethylaminopyridine) and 10 equivalents of either allyl alcohol or methallyl alcohol (25mmol) to obtain the allyl β-keto esters and methallyl β-keto esters, respectively. The mixture was allowed to stir over a period of 2-3 days until ^1H NMR spectra showed completion of the reaction. The crude mixture was extracted twice with ether and NH_4Cl. The products were purified by flash chromatography (SiO_2, 1:9 Et_2O-hexane) and obtained in 53-76% yield.

Figure 26 *Transesterification*



The β-keto allyl esters were fluorinated according to the procedure by Togni. The β-keto allyl ester (3 mmol) was dissolved in 12mL of CH_3CN in a Schlenk tube under argon and cannula transferred to another Schlenk tube under argon with Selectfluor (3.3 mol) dissolved in 25mL CH_3CN. Using a syringe, 1 mol % of $TiCl_4$ was added. The solution was allowed to stir for 2 hours before quenching with NH_4Cl, and extracted with ether, and dried with $MgSO_4$. Following solvent evaporation, the crude product was purified by column chromatography (SiO_2, 1:9 Et_2O-hexane). The products were obtained in 86-94% yield.

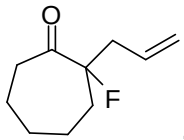
Figure 27 *Fluorination*



General Method for Benchtop Decarboxylative Allylation Reaction:

In a Schlenk tube under argon, $Pd_2(dba)_3$ (2.5 mol%) and QUINAP (5.5 mol%) were dissolved in benzene (2mL) which had previously been dried over sodium metal and degassed and the resulting mixture was stirred for 1-2 minutes at 40°C. The solution of catalyst was then cannula-transferred to a Schlenk tube containing the β-keto allylic ester (4mmol) in dry, degassed benzene (2mL). The reaction was stirred in a 40°C oil bath for the amount of time reported in Table 1. Following solvent evaporation, the crude extract was purified by flash column chromatography (SiO_2, 3:97 Et_2O-hexane).

Spectral Characterization of Products:



2a

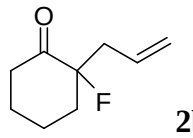
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (ddt, *J* = 7 Hz, 10 Hz, 18 Hz, 1H: $CH{=}CH_2$), 4.60 (d, *J* = 10 Hz, 1H: $CH(H)_{cis}$), 3.80(d, *J* = 18 Hz, 1H: $CH{=}CH(H)_{trans}$), 3.51 (m, 2H: overlapping diastereotopic allylic CH_2), 2.96 (m, 2H: overlapping diastereotopic cycloheptyl CH_2) 2.76 (m, 2H: overlapping cycloheptyl CH_2), 1.75 (m, 4H: cycloheptyl CH_2), 1.16 (m, 2H: overlapping cycloheptyl CH_2).

^{13}C NMR (125 MHz, $CDCl_3$ δ 210.82 (d, *J* = 24.0 Hz: C=O, 130.85 (=CH), 119.40 ($=CH_2$), 101.70 (d, *J* =185.22 Hz: CF), 41.11 (d, *J* = 22.6 Hz: allylic CH_2), 39.94 (cycloheptyl CH_2) 35.18 (d, *J* = 23.9 Hz: cycloheptyl CH_2), 27.80 cycloheptyl CH_2), 24.29 (d, *J* =2.5 Hz: cycloheptyl CH_2), 24.02 (d, *J* = 2.5 Hz: cycloheptyl CH_2).

^{19}F NMR (376MHz, $CDCl_3$) δ -161.66(m).

FTIR (CD_2Cl_2): ν_{max} 1712, 1606, and 1433

HRMS calcd for $C_{10}H_{15}OF$ [M + H] = 171.1184, found 171.1184



2b

^{1}H NMR (400MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 7 Hz, 10 Hz, 18 Hz, 1H: $CH{=}CH_2$), 5.19 (d, *J* = 10 Hz, 1H: $CH{=}CH(H)_{cis}$), 5.14 (d, *J* = 18 Hz, 1H: $CH{=}CH(H)_{trans}$), 2.73 (m, 2H: cyclohexyl CH_2), 2.67 (m, 1H: diastereotopic allylic CH_2), 2.44 (m, 1H: diastereotopic

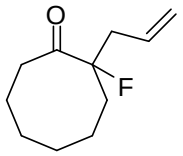
allylic CH_2), 2.08 (m, 1H diastereotopic cyclohexyl CH_2), 1.88 (m, 4H: overlapping cylohexyl CH_2), 1.70 (m, 1H diastereotopic cyclohexyl CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.28 (d, *J* = 20.2 Hz: C=O), 130.77 (=CH), 119.26 (=CH_2), 97.71 (d, *J* = 183.78 Hz: CF), 39.36 (allylic CH_2), 38.76 (d, *J* = 2.5 Hz: cyclohexyl CH_2), 37.19 (d, *J* = 2.5 Hz cyclohexyl CH_2), 27.18 (cyclohexyl CH_2), 21.42 (cyclohexyl CH_2).

^{19}F NMR (376MHz, $CDCl_3$) δ -156.44(m).

FTIR (CD_2Cl_2): ν_{max} 1728, 1604, 1413

HRMS calcd for $C_9H_{13}OF$ [M + H] = 157.1029, found 157.1034



2c

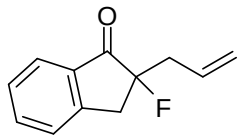
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddt, *J* = 7 Hz, 10 Hz, 17 Hz, 1H: $CH{=}CH_2$), 5.15 (d, *J* = 10 Hz, 1H: $CH{=}CH(H)_{cis}$), 5.11 (d, *J* = 17 Hz, 1H: $CH{=}CH(H)_{trans}$), 2.68 (m, 1H: cyclooctyl CH_2), 2.39 (m, 1H: diastereotopic allylic CH_2), 2.13 (m, *J* = 19 Hz, 1H: diastereotopic allylic CH_2), 2.23 (m, 1H: diastereotopic cyclooctyl CH_2) 2.10 (m, 1H: diastereotopic cyclooctyl CH_2), 1.98 (m, 2H: cyclooctyl CH_2), 1.87 (m, 6H: overlapping cyclooctyl CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.97 (d, *J* = 25.0 Hz C=O), 131.10 (=CH), 119.49 (=CH_2), 101.93 (d, *J* = 118.1 Hz: CF), 42.12 (d, *J* = 22.6 Hz: allylic CH_2), 39.70 (cyclooctyl CH_2), 37.68 (d, *J* = 22.6 Hz: cyclooctyl CH_2), 27.41 (cyclooctyl CH_2), 26.00 (cyclooctyl CH_2), 24.85 (cyclooctyl CH_2), 21.37 (cyclooctyl CH_2).

^{19}F NMR (376MHz, $CDCl_3$) δ -167.59(m).

FTIR (CD_2Cl_2): ν_{max} 1712, 1606, 1465

HRMS calcd for $C_{11}H_{17}OF$ [M + H] = 185.1342, found 185.1353



2d

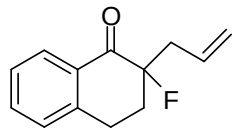
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 1H aromatic CH), 7.59 (t, *J* = 8 Hz, 1H aromatic CH, 7.36 (m, 2H: aromatic CH), 4.86 (s, 1H: diastereotopic $=CH_2$), 4.72 (s, 1H: diastereotopic $=CH_2$), 3.44 (dd, *J* = 12 Hz, 18 Hz, 1H: diastereotopic benzylic CH_2), 3.22 (dd, *J* = 18 Hz, 23 Hz, 1H: diastereotopic benzylic CH_2), 2.74 (t, 1H diastereotopic allylic CH_2), 2.35 (m, 1H: diastereotopic allylic CH_2), 1.72 (s, 3H: CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.59 (d, *J* = 17.75 Hz: C=O), 150.16 (aromatic C), 136/18 (aromatic CH), 133.89 (aromatic C), 130.32 (=CH), 128.11 (aromatic CH), 126.52 (aromatic CH), 124.87 (aromatic CH), 120.14 ($=CH_2$), 96.81 (d, *J* = 188.10 Hz: CF) 39.25 (d, *J* = 25.2 Hz: allylic CH_2), 37.46 (d, *J* = 23.9 Hz: benzylic CH_2).

^{19}F NMR (376MHz, $CDCl_3$) δ -155.97(m).

FTIR (CD_2Cl_2): ν_{max} 1728, 1610, 1429

HRMS calcd for $C_{12}H_{11}OF$ [M + H] =191.0872, found 191.0890



2e

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8 Hz, 1H: aromatic CH), 7.55 (m, *J* = 8 Hz 1H: aromatic CH), 7.38 (t, *J* = 8 Hz, 1H: aromatic CH) 7.29 (m, 1H: aromatic CH), 5.92 (ddt, *J* = 8 Hz, 10 Hz, 17 Hz, 1H: $CH=CH_2$), 5.25 (d, *J* = 10 Hz, 1H: $CH=CH(H)_{cis}$, 5.21 (d, *J* = 17 Hz, 1H: $CH=CH(H)_{trans}$, 3.14 (m, 1H: diastereotopic benzylic CH_2), 3.04 (m,

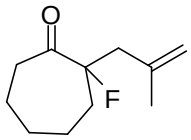
1H: diastereotopic benzylic CH_2), 2.74 (m, 1H: diastereotopic allylic CH_2), 2.61 (m, 1H: diastereotopic allylic CH_2), 2.42, (m, 2H: diastereotopic cyclohexyl CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 193.99 (d, *J* = 17.75 Hz: C=O), 142.71 (aromatic C), 134.08 (aromatic CH), 130.92 (aromatic C), 130.86 (=CH), 128.75 (aromatic CH), 128.31 (aromatic CH), 127.31 (aromatic CH), 119.89 (=CH2), 94.98 (d, *J* = 184.26 Hz: CF), 37.99 (d, *J* = 22.6 Hz, allylic CH_2), 31.91 (d, *J* = 22.6 Hz: cyclohexyl CH_2), 25.89 (d, *J* = 10.1 Hz, benzylic CH_2).

^{19}F NMR (376MHz, $CDCl_3$) δ -158.79(m).

FTIR (CD_2Cl_2): ν_{max} 1701, 1604, 1238

HRMS calcd for $C_{13}H_{13}OF$ [M + H] = 205.1029, found 205.1036



2f

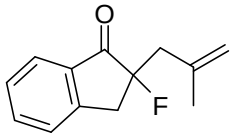
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 1H: diastereotopic =CH_2), 4.68 (s, 1H: diastereotopic =CH_2), 2.68 (m, 1H: diastereotopic cycloheptyl CH_2), 2.55 (dd, *J* = 14 Hz, 26 Hz, 1H: diastereotopic allylic CH_2), 2.37 (overlapping m, 2H cycloheptyl CH_2), 1.69 s, 3H: CH_3), 1.55 (m, 4H: cycloheptyl CH_2) 1.22 (m, 1H: diastereotopic cycloheptyl CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.93 (d, *J* = 23.8 Hz: C=O), 140.06 (=C), 115.60 (=CH_2), 102.65 (d, 186.9 Hz: CF), 44.46 (d, *J* = 22.6 Hz: allylic CH_2), 39.82 (cycloheptyl CH_2), 35.56 (d, *J* = 23.9 Hz: cycloheptyl CH_2), 27.92 (cycloheptyl CH_2), 24.59 (cycloheptyl CH_2), 24.16 (cycloheptyl CH_2), 23.95 (CH_3).

^{19}F NMR (376MHz, $CDCl_3$) δ -156.44(m).

FTIR (CD_2Cl_2): ν_{max} 1712, 1452, 1269

HRMS calcd for $C_{11}H_{17}OF$ [M + H] = 185.1342, found 185.1329



2g

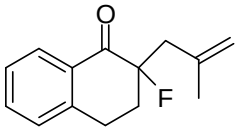
^{1}H NMR (400MHz, $CDCl_3$) δ 7.74 (d, *J* = 8 Hz, 1H: aromatic CH), 7.59 (m, *J* = 8 Hz, 1H: aromatic CH), 7.36 (m, 2H: aromatic CH), 4.86 (s, 1H: diastereotopic $=CH_2$), 4.72 (s, 1H: diastereotopic $=CH_2$), 3.44 (dd, *J* = 12 Hz, 18 Hz, 1H: diastereotopic benzylic CH_2), 3.22 (dd, *J* = 18 Hz, 23 Hz, 1H: diastereotopic benzylic CH_2), 2.74 (dd, 1H: diastereotopic allylic CH_2) 2.35 (dd, 1H: diastereotopic allylic CH_2), 1.72 (s, 3H: CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.64 (d, *J* = 18.2 Hz: C=O, 150.45 (aromatic C), 140.24 (=C), 136.25 (aromatic CH), 133.81 (aromatic C), 128.24 (aromatic CH), 126.71 (aromatic CH), 125.16 (aromatic CH), 115.87 ($=CH_2$), 97.67 (d, *J* = 188.6 Hz: CF), 42.36 (d, *J* = 24.5 Hz, allylic CH_2), 37.34 (d, *J* = 25.0 Hz: benzylic CH_2), 23.72 (CH_3).

^{19}F NMR (376MHz, $CDCl_3$) δ -155.97(m).

FTIR (CD_2Cl_2): ν_{max} 1728, 1608, 1222

HRMS calcd for $C_{13}H_{13}OF$ [M + H] = 205.1029, found 205.1045



2h

^{1}H NMR (400MHz, $CDCl_3$) δ 8.10 (d, *J* = 8 Hz, 1H: aromatic CH), 7.57 (m, *J* = 8 Hz, 1H: aromatic CH), 7.41 (m, *J* = 8 Hz, 1H, aromatic CH), 7.26 (d *J* = 8 Hz, 1H: aromatic CH), 4.93 (s, diastereotopic $=CH_2$) 4.69 (s, diastereotopic =CH2) 3.17 (m 2H: benzylic CH_2), 2.50 (dd, *J* = 15 Hz, *J* = 19 Hz, allylic, diastereotopic CH_2) 2.33 (m, 2H: cyclohexyl CH_2) 1.65, (s, 3H: CH_3).

^{13}C NMR (125MHz, CDCl3) δ 194.21 (d, *J* = 18.2 Hz: C=O), 142.61 (aromatic C), 140.27 (=C), 134.01 (aromatic CH), 130.93 (aromatic C), 128.68 (aromatic CH), 128.32 (aromatic CH), 127.11 (aromatic CH), 116.03 (=CH_2), 95.73 (d, *J* = 186.2 Hz: CF), 41.25 (d, *J* = 22.6 Hz: allylic CH_2), 31.71 (d, *J* = 23.0 Hz: cyclohexyl CH_2), 26.30 (d, *J* = 10.2 Hz: benzylic CH_2), 23.80 (CH_3).

^{19}F NMR (376MHz, $CDCl_3$) δ -158.79(m).

FTIR (CD_2Cl_2): ν_{max} 1704, 1602, 1290

HRMS calcd for $C_{14}H_{15}OF$ [M + H] = 219.1185, found 219.1189

Determination of Enantiomeric Ratios:

Enantiomers were separated by Gas Chromatography or High Performance Liquid Chromatography. Gas Chromatography was performed on a Shimadzu GC-17A. Samples were injected at 200°C. HPLC analysis was performed with a Shimadzu SCL-10A VP instrument. Enantiomeric ratios were calculated from the peak areas.

2a: Separated by GC on Chiraldex B-TA column. Hold 50°C for 5 min., ramp 1°C/min. to 95°C- t_r = 48.2 (minor), 49.5 (major) minutes.

2b: Separated by GC on Chiraldex B-TA column. Hold 50°C for 5 min., ramp 1°C/min. to 95°C- t_r = 40.3 (minor), 43.6 (major) minutes.

2c: Separated by GC on Chiraldex B-TA column. Hold 50°C for 5 min., ramp 1°C/min. to 100°C- t_r = 57.3 (minor), 58.1 (major) minutes.

2d: Separated by GC on Chrialdex B-TA column. Hold 50°C for 5 min., ramp 1°C/min. to 120°C, hold 20 min- t_r = 86.5 (minor), 87.6 (major) minutes.

2e: Separated by HPLC on Diacel Chiralpack AD column (99% Hexane/Isopropyl Alcohol), 0.5mL/min- t_r = 20.1 (minor), 22.2 (major) minutes.

2f: Separated by HPLC on Diacel Chiralpack AS-H column (99% Hexane/Isopropyl Alcohol), 0.5mL/min- t_r = 5.5 (minor), 6.1 (major) minutes.

2g: Separated by GC on Chrialdex B-TA column. Hold 50°C for 5 min., ramp 1°C/min. to 120°C, hold 35 min- t_r = 96.4 (minor), 101.9 (major) minutes.

2h: Separated by HPLC on Diacel Chiralpack AD column (99% Hexane/Isopropyl Alcohol), 0.5mL/min- t_r = 13.5 (minor), 14.7 (major) minutes.

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