Synthetic Strategies to Access Biologically Important Fluorinated Motifs:

Fluoroalkenes and Difluoroketones

By

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Abstract

Ming-Hsiu Yang

Department of Medicinal Chemistry, April 2017
The University of Kansas

Fluorine plays an important role in drug design, because of some unique features imparted by fluorine. The incorporation of fluorine into small molecules can modulate molecular physicochemical properties, metabolic stability, lipophilicity, and binding affinity to the target proteins. However, few fluorinated molecules are biosynthesized by enzymes. This means incorporating fluorine into the molecules relies on synthetic methods. Thus, efficient synthetic strategies to access the molecules bearing a variety of privileged fluorinated moieties are important for drug discovery.

Fluoroalkenes are an isopolar and isosteric mimic of an amide bond with distinct biophysical properties, including decreased H-bond donating and accepting abilities, increased lipophilicity, and metabolic stability. Moreover, fluoroalkenes can also serve as probes for conducting conformational analyses of amides. These potential applications require the development of efficient methods to access fluoroalkenes. In chapter 2, a Shapiro fluorination strategy to access peptidomimetic fluoroalkenes is demonstrated. The Shapiro fluorination reactions convert a ketone into a fluoroalkene in one or two steps. Moreover, this method uses inexpensive and readily available reagents, and no transition metals are involved in the reactions. Thus, it provides an operation-simple alternative to access fluoroalkenes in medicinal chemistry.

α,α-difluoroketones represent a privileged substructure in medicinal chemistry, and serves as inhibitors to many hydrolytic enzymes, such as serine and aspartyl proteases. From chapters 3 to 5, palladium-catalyzed decarboxylative methods are developed for accessing α-alkyl- and α-aryl-α,α-difluoroketones. This decarboxylative strategy overcomes two major challenges associated with alkylation reactions of α,α-difluoroketone enolates. Chapter 3 demonstrates that decarboxylation regioselectively generates α,α-difluoroketone enolates, which are difficult to access by base
deprotonation. Moreover, palladium catalysis enables the coupling of the $\alpha,\alpha$-difluoroketone enolate with benzylic electrophiles to form a key $C(\alpha)–C(sp^3)$ bond. In chapter 4, an orthogonal catalytic system is developed for accessing linear and branched $\alpha$-allyl-$\alpha,\alpha$-difluoroketones. Two distinct mechanisms are involved in the formation of the regioisomers. Chapter 5 describes a base-mediated selective para-$C–H$ difluoroalkylation of arenes, which represents a different strategy for para-$C–H$ functionalization of arenes compared to the known methods. These decarboxylative coupling reactions provide structurally diverse $\alpha,\alpha$-difluoroketone derivatives, and should be useful for accessing potential biological probes and therapeutics.
Acknowledgements

Six years of graduate study is not an easy thing. I feel blessed to stay in KU for my graduate career, and have enjoyable and knowledgeable life. I would like to express my deepest gratitude to many people whom I have worked with, and have received help from. Without their assistance, I would never have been able to finish my graduate study and obtain the degree.

First and foremost, I would like to thank my advisor, Professor Ryan Altman, for accepting me into his lab, and providing me with a good atmosphere for doing research. His guidance in poster and oral presentation, academic writing, thinking and solving scientific problems, and engaging me in research ideals help me to become a well-educated and professional chemist. His demand on high-quality of work in all my endeavors makes me a scientist. I am grateful for his patience as I know it is very hard to instruct me, an international student whose native language is not English.

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### Abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>Acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl (substituted aromatic ring)</td>
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<tr>
<td>Asp</td>
<td>aspartic acid</td>
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<tr>
<td>BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
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<td>BEt3</td>
<td>triethylborane</td>
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<td>BINAP</td>
<td>2,2′-bis(diphenylphosphino)-1,1′-binaphthyl</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<td>Boc</td>
<td>t-butoxycarbonyl</td>
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<td>BSA</td>
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<td>Bz</td>
<td>benzoyl</td>
</tr>
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<td>ca</td>
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<td>calcld</td>
<td>calculated</td>
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<tr>
<td>cat.</td>
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<td>diastereomeric excess</td>
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<td>DMAP</td>
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<td>DMEDA</td>
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DMF $N,N$-dimethylformamide
DMP Dess-Martin periodinane
DMSO dimethylsulfoxide
dppBz 1,2-Bis(diphenylphosphino)benzene
dppe 1,2-$bis$(diphenylphosphino)ethane
dppf 1,1$'$-$bis$(diphenylphosphino)ferrocene
dppp 1,3-$bis$(diphenylphosphino)propane
dr diastereomeric ratio
EDG electron-donating group
ee enantiomeric excess
Et ethyl
EWG electron-withdrawing group
GABA gamma-aminobutyric acid
Het heteroaromatic
His histidine
HMPA hexamethylphosphoric acid triamide
$i$ iso
IBX o-iodoxybenzoic acid
KHMDs potassium $bis$(trimethylsilyl)amide
$L_n$ ligand
LAH lithium aluminum hydride
LDA lithium diisopropylamide
LHMDS lithium $bis$(trimethylsilyl)amide
lit. literature value (abbreviation used with period)
MAD methyl aluminum $bis$(2,6-di-$t$-butyl-4-methylphenoxide)
Me methyl
MeOH methanol
Mes mesityl
2-Me-THF 2-methyltetrahydrofuran
mp melting point
NaH sodium hydride
NaHMDS sodium $bis$(trimethylsilyl)amide
\( n \) normal (e.g. unbranched alkyl chain)
NBS $N$-bromosuccinimide
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<td>n-BuLi</td>
<td>n-butyllithium</td>
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<td>Nu</td>
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</table>
Chapter 1. Importance and Application of Fluorine in Drug Design

Before the discovery of fluorinated drugs in 1950s, fluorine was regarded as a dangerous and negligible element. In 1953, Fried and Sabo reported the first synthetic fluorinated agent, fludrocortisone, possessing glucocorticoid activity.¹ Later, in 1957, Heidelberger and coworkers invented the anti-cancer drug, 5-fluorouracil, a mechanism-based inhibitor that irreversibly bound to thymidylate synthase and inhibited DNA biosynthesis of cancer cells.² These two breakthroughs changed the stereotype of fluorine as a trivial element and demonstrated its importance and potential applications in drug discovery. The continuing research of fluorine in drug design caused a flourish in the development of fluorinated drugs.³ Nowadays, many drug (~20%) candidates in clinical trials and marketed drugs contain at least one fluorine or fluorinated group.⁴

Fluorine plays an important role in the campaign of drug discovery, because of some unique features imparted by fluorine. For example, the use of fluorine and fluorinated groups as isosteres in drug design,⁵ (i.e., F vs H, CF₃ vs i-Bu, and CF₂Me vs OMe), can modulate molecular properties, including the lipophilicity and conformations, and improve metabolic stability. Moreover, the incorporation of fluorine into small molecule drugs modifies ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, in which it is possible to convert a bad drug candidate to a potential therapeutic. Because of these potential applications of fluorine on drug design, the following sections elaborate the influence of fluorine substitution on physicochemical properties, molecular conformations, metabolic stability, binding affinity, and potency of therapeutic agents.

1.1 The Effect of F on Physicochemical Properties

Fluorine is the most electronegative element (χ = 4.0), and its incorporation into molecules strongly affects the acidity or basicity of the neighboring groups, thus lowering pKₐ values (Table 1.1).⁵,⁶
The $\sigma$-inductive effect of fluorine atoms decreases the basicity of the amine group. For acyclic amines, the extent of $pK_a$ change depends on the distance of fluorine to the amine group, and the number of fluorine atoms. For example, in the case of alkyl amines, the $pK_a$ is lowered by 1.7 for $\beta$-F, and by 0.3 for $\delta$-F, thus demonstrating the impact of the fluorinated position on the $pK_a$ shift (Table 1.2A). Moreover, the trifluoroethyl amine has an attenuated $pK_a$ of 5.7 due to the additive effect of three F atoms compared to the monofluoroethyl amine with a $pK_a$ of 9.0 (Table 1.2B). However, the influence of fluorine on basicity of cyclic amines also requires the consideration of conformational factors (axial F vs. equatorial F) in addition to the calculation of distances of fluorine to amine functionality (Table 1.2C). For example, in the case of 3-fluoropiperidine, an equatorial F substituent causes a $pK_a$ shift of 2.3 ($\Delta pK_a = –2.3$), while an axial F substituent only reduces $pK_a$ of 1.4 ($\Delta pK_a = –1.4$). This $pK_a$ difference between these two conformations of 3-fluoropiperidine derives from a preferential conformation of the protonated base, in which the dipole of the H–N$^+$ bond presents antiparallel to the dipole of the C–F bond. This conformational alignment stabilizes protonated 3-fluoropiperidine, thus causing a higher $pK_a$ value and smaller $\Delta pK_a$. Similarly, fluorine on an axial or equatorial position of 4-fluoropiperidine also causes different $pK_a$ change with $\Delta pK_a$ of $–1.7$ for an axial F atom and $\Delta pK_a$ of $–0.9$ for an equatorial F atom. Moreover, for aromatic amines, $pK_a$ alteration by fluorine depends on the position of fluorine atoms and the degree of fluorination (Table 1.2D). Generally, fluorine on an ortho-position causes a larger impact on $pK_a$ than a meta-F atom does ($pK_a$ of 1 < $pK_a$ of 2; $pK_a$ of 3 < $pK_a$ of 4), and highly fluorinated amines have lower $pK_a$ than mono- or difluorinated counterparts ($pK_a$ of 1 > $pK_a$ of 3; $pK_a$ of 2 > $pK_a$ of 4).
The perturbation of pKₐ alters pharmacokinetic properties of drug candidates. For example, alkyl amines, anilines and N-containing heterocycles are common structural components in bioactive molecules or drug candidates. However, excessive number of basic amine groups in the amine-containing therapeutics cause low oral bioavailability, which decreases the potency and limits their development as potential drugs. To modulate these properties, the introduction of fluorine in N-bearing molecules decreases the basicity of the amine groups by the inductive effect and improves the bioavailability,⁷ as exemplified in the case of 3-piperidinylindole antipsychotics (Table 1.3).⁶a,⁸ These fluorinated analogues express much better bioavailability than the non-fluorinated counterpart. Thus, fluorine substitution can be utilized in tuning the basicity of amine-type molecules in drug design to achieve the expected physicochemical properties and distribution.⁶a,⁸
On the other hand, fluorine substitution increases the acidity of carboxylic acids and phenol derivatives, and changes physicochemical features that can also bring beneficial applications to drug design. For example, methotrexate is used to treat rheumatoid arthritis and cancer, but it possesses high toxicity associated with the formation of poly-γ-glutamate metabolites. Fluorination of the γ-glutamate moiety of methotrexate increases the acidity of γ-carboxyl group and causes labile amide linkages, which disfavor the accumulation of poly-γ-glutamate metabolites inside the cells, and significantly reduce the toxicity (Figure 1.1A). Another example is the utilization of 2,6-difluorophenol as a lipophilic isostere of a carboxylic acid. The inductive effect of two fluorine atoms remarkably reduces pKₐ of 2,6-difluorophenol to 7.1 from pKₐ of 9.8 of phenol, and causes its ionization to form phenoxides at pH = 8.5, where a carboxylic acid also exists as the ionized form (Figure 1.1B). Thus, 2,6-difluorophenols can efficiently mimic a carboxylic acid functionality, and this idea has been applied in designing inhibitors of GABA aminotransferases.

### Table 1.3. Fluorination Decreases Basicity of Amine-Type Drugs and Improves Bioavailability

<table>
<thead>
<tr>
<th>R¹, R²</th>
<th>5-HT₂A (nM)</th>
<th>pKₐ</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H, H</td>
<td>0.99</td>
<td>10.4</td>
<td>poor</td>
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<tr>
<td>H, F</td>
<td>0.43</td>
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<td>18</td>
</tr>
<tr>
<td>F, F</td>
<td>0.06</td>
<td>-</td>
<td>80</td>
</tr>
</tbody>
</table>
1.2 The Effect of F on Lipophilicity

Lipophilicity is an important parameter in evaluating drug-like molecules. This property affects the absorption of orally administrated drugs into the intestinal system, protein-ligand non-specific binding interactions, and the solubility. High lipophilicity increases oral absorption of drugs and lipophilic binding interactions, but excessive lipophilicity can also cause poor solubility and undesired side effects. Thus, moderate lipophilicity is required for ideal drugs. Fluorine substitution can modulate molecular lipophilicity, as shown in Figure 1.2. Generally, the incorporation of fluorine into the molecules increases the lipophilicity (positive log $D$ difference in Figure 1.2A). Herein, log $D$ means the logarithmic coefficient of the distribution of a charge-bearing molecule between water and octanol at a specific pH. Increased lipophilicity usually occurs in molecules bearing fluorine adjacent to a $\pi$ system, such as aryl or vinyl fluorides. In these molecules bearing C(sp$^3$)–F bonds, good overlap of lone pair orbitals of fluorine with $\pi^*$ orbital of the C=C bond depolarizes the C–F bond and decreases molecular polarity. However, in some cases, fluorine substitution actually decreases the lipophilicity (negative log $D$ difference in Figure 1.2A). Specifically, the presence of fluorine close to an oxygen atom polarizes the
adjacent oxygen atom and enhances the solvation of the molecule in water, thus leading to a decrease of the lipophilicity (Figure 1.2B).\textsuperscript{11a,b} Moreover, the strong electron-withdrawing effect of fluorine atoms polarizes C–F bonds of saturated fluoroalkanes, which decreases lipophilicity compared to their non-fluorinated counterparts.\textsuperscript{11b,c}

1.3 The Effect of F on Molecular Conformations

Fluorine substitution alters the dipole moment of molecules, and provides electrostatic interactions with the adjacent groups, both of which affect molecular conformations. A change in the conformation affects protein-ligand binding interactions, which in turn modifies the potency and selectivity.

For vicinally fluorinated aliphatic systems, such as 1,2-difluoroalkanes, the two vicinal fluorine atoms adapt a gauche conformation (Figure 1.3A).\textsuperscript{12} The preference of the gauche conformer derives from the stabilization by hyperconjugative interactions between $\sigma$ orbitals of C–H bonds and low-lying $\sigma^*$ orbitals of C–F bonds ($\sigma_{C-H} \rightarrow \sigma^*_{C-F}$). The gauche alignment of these two C–F bonds enables the C–F and the C–H bonds to an anti-arrangement that causes a good orbital overlap and overcomes the electronic repulsion of the two fluorine atoms. Additionally, the molecules, in which one fluorine atom is replaced with an electron-withdrawing group, also prefer the gauche conformation (Figure 1.3B).\textsuperscript{12} This gauche effect has
been applied in designing fluorinated analogues of HIV-1 protease inhibitor indinavir with comparable inhibitory activity (Figure 1.3C).  

![Figure 1.3. The Gauche Effect and Its Application in Fluorinated Indinavir Inhibitors](image)

A) Gauche-Comformer Is More Stable than Anti-Comformer Because of Good Orbital Overlap

B) Examples Representing the Gauche-Comformation and Their Relative Energies

C) Utilization of Gauche Effect in Designing Fluorinated Indinavir Analogues

However, the gauche arrangement is not always the preferential conformation for some fluorinated molecules. For example, N-β-fluoroethylamides (F–C–C–NH=O) prefer the gauche conformation, while α-fluoroamides (F–C–C=O–NH) prefer to exist in the trans conformation. In these cases, the trans conformer is more stable than the gauche conformer by 6 kcal/mol, due to the synergistic dipole-dipole interaction between the C–F and C=O bonds, and the electrostatic interaction between electronegative F atom and electropositive H atom of the amide bond (Figure 1.4A). Such a conformational perturbation due to fluorine substitution near an amide has been applied to probe the bioactive conformation of an amide ligand bound to the target protein. As in the case of fluorinated ligands for the calcitonin gene-related peptide receptor (CGRP), the two regioisomers, both of which bear a fluorine atom adjacent to the amide bond, represent distinct CGRP binding affinity (Figure 1.4B).
extended structure expresses lower $K_i$ (red color in Figure 1.4B), and it is the bioactive conformation that the ligand adapts when binding to the CGRP receptor. The conformational information in protein-ligand binding modes enables development of more potent CGRP inhibitors.

Moreover, the introduction of trifluoromethyl or difluoromethene groups on a heteroatom also changes molecular structures. For example, the three-dimensional structures of fluorinated alkyl aryl ethers (Ar-OCF$_3$ or Ar-OCF$_2$H) are different from their non-fluorinated counterparts (Ar-OCH$_3$). Specifically, anisole (PhOCH$_3$) adapts a planar conformation, in which the methoxy group is coplanar with the phenyl ring (left, Figure 1.5A).$^{16\text{a}}$ The planar conformation comes from the resonance stabilization of lone pair electrons of the oxygen atom into the phenyl ring. In contrast, the trifluoroanisole counterpart (PhOCF$_3$) adapts a non-planar conformation, in which the trifluoroethoxy group is orthogonal to the plane of the phenyl ring (right, Figure 1.5A).$^{16\text{b-d}}$ This conformational change is attributed to the decreased resonance stabilization of oxygen lone pair electrons into the phenyl ring as a result of the hyperconjugation between lone-pair orbitals of the O atom and low-lying $\sigma^*$ orbitals of C–F bonds and the inductive effect of the CF$_3$ group. The same conformational alteration due to fluorination also occurs in difluoroanisoles (PhOCF$_2$H), but they represent more flexible conformational exchange between the coplanar and perpendicular structures.$^{16\text{d,e}}$ Such a conformational modification of fluoroalkyl...
aryl ethers plays an important role in protein-ligand binding interactions, and has been exploited in drug design. As in the case of developing potent inhibitors of the cholesteryl ester transfer protein (CETP) to reduce the incidence of coronary heart disease, the tetrafluoroethyl substituted analog reveals an 8-fold increase in the CETP inhibitory activity compared to ethyl substituted counterparts (Figure 1.5B).\textsuperscript{17}

### 1.4 The Effect of F on Metabolic or in vivo Stability

The metabolic or \textit{in vivo} stability, expressed as the half-life, is a key factor in determining a successful drug molecule. An ideal and safe drug should possess a moderate half-life that enables it to reach the action site, maintain efficient drug concentration for a desired period of time, and be excreted out of the body.\textsuperscript{18} However, many drug candidates possess short half-lives as a result of bearing chemical structures or functional groups that undergo enzymatic metabolism or hydrolysis. The short half-life can cause low efficacy, and produce metabolites that may interact with other proteins, which in turn can lead to toxicity. To address these stability issues, the introduction of fluorine on the metabolically labile sites can improve chemical stability, enhance the potency, and decrease the toxicity.

An example demonstrating the impact of fluorination on chemical stability of potential therapeutics involves prostacyclins. Prostacyclin inhibits platelet aggregation, but has limited clinical application due to the \textit{in vivo} degradation. The chemical instability derives from the presence of the enol ether functionality in the molecule, which undergoes hydrolysis to form inactive metabolites under neutral or acidic conditions (Figure 1.6A),\textsuperscript{19a} thus revealing a $t_{1/2} = 10$ mins at pH = 7.4. However, fluorine introduction on the position adjacent to the enol ether destabilizes the cationic intermediate formed during
hydrolysis, and enhances chemical stability in vivo, as represented $t_{1/2} > 1$ month at pH = 7.4 for monofluorinated analog\textsuperscript{19b} and $t_{1/2} = 90$ days at pH = 7.4 for difluorinated analog (Figure 1.6B).\textsuperscript{19c}

The improved efficacy as a result of fluorine substitution to block metabolic pathways is exemplified in the development of Ezetimibe as a cholesterol-lowering agent (Figure 1.7).\textsuperscript{20} Initially, the lead underwent extensive CYP450-catalyzed metabolism, including benzylic oxidation, para-hydroxylation of the aromatic ring, dealkylation of two OMe groups, and ring-opening of the cyclic lactam to produce many metabolites. Thus, high doses were required to maintain sustained in vivo action (left in Figure 1.7, shown in red color). SAR studies found that some of the metabolites are more potent than the parent drug (oxidative activation), while some of them are not (oxidative deactivation). The redesign of the drug aims on installing beneficial groups that are generated by oxidative bioactivation and blocking the sites that potentially undergo oxidative deactivation. Thus, the modification, including the incorporation of hydroxyl groups on the benzylic and the para-position, and the placement of two fluorine atoms on para-positions of the two lower aromatic rings, inhibited metabolic labile sites, and produced the drug Ezetimibe that expresses high potency in lower doses (right in Figure 1.7, shown in blue color).
Fluorine substitution can also reduce toxicity derived from the intrinsically chemical properties of therapeutic agents. For example, the drug thalidomide possesses an acidic hydrogen atom on α-carbon vicinal to a carbonyl group, which undergoes the in vivo epimerization (Figure 1.8A). Thus, the single enantiomer does not exist in the body, and thalidomide instead exists as a racemic mixture. However, only the (R)-enantiomer provides the desired sedative hypnotic activity, while the (S)-enantiomer produces the teratogenic side effects. For this drug, the replacement of the α-hydrogen atom by an F atom inhibits the in vivo epimerization (Figure 1.8B), and enables to access individual enantiomers for the biological evaluation of other potential pharmacological activities.
Other examples illustrating fluorination on chemically or metabolically labile sites to improve the stability of drug candidates are presented in Figure 1.9. The difluorooxetane acetal moiety (a) is more stable than the parent acetal under neutral and acidic conditions, thus providing a potential application in designing drug molecules bearing labile acetal functionality. Moreover, the benzodioxole is an undesired motif on drug molecules, because it undergoes CYP450 oxidative metabolism to form a metabolite ortho-quinone, which can react with nucleophilic residues of other proteins, and cause the toxicity. However, incorporating two fluorine atoms into the methylene position of the benzodioxole inhibits the metabolic pathway and reduces the toxicity (b). Another example of fluorination to block metabolism is the replacement of the ethyl group on a nitrogen atom by a trifluoroethyl moiety (e), which retards oxidative dealkylation. Additionally, unique fluorinated motifs are utilized as metabolically stable isosteres of certain functional groups, such as the trifluoroethylamine moiety as a mimic of an amide bond (d), the trifluoromethylcyclopropyl and 1,1,1-trifluoro-2-methylpropyl as bioisosteres of a tert-butyl group (e and f), and the replacement of the C=O group by a C–F bond in acid-labile lactones (g).
1.5 The Effect of F on Protein-Ligand Binding Interactions

Fluorine can play a direct role in modulating protein-ligand binding affinity. The strongly electronegative fluorine atom enables participation in polar interactions with the electropositive residues on the target protein and increase the binding affinity. An example representing such a direct effect of fluorine on binding affinity involved fluorinated thrombin inhibitors (Figure 1.10). The analog bearing a fluorine atom on aromatic C4 position of the N-benzyl moiety provided better potency ($K_i = 0.057 \mu M$) than the non-fluorinated counterpart ($K_i = 0.27 \mu M$). The X-ray crystal structure of the fluorinated ligand bound to thrombin revealed a close contact between the fluorine on aromatic C4 of the ligand and the amide moiety of the Asn 98 residue in the hydrophobic pocket of thrombin. In this region, the C–F bond represents an orthogonal arrangement to the C=O group of the amide moiety. Specifically, the fluorine atom formed non-covalently multipolar interactions with the partially positive charged C of the C=O group (C–F…C=O) and α-H adjacent to the C=O group (C–F…H–Cα), which enhanced the protein-ligand binding interactions, and the potency.

![Figure 1.10. Fluorination Provides Multipolar Interactions and Enhances Potency](image)

Additionally, fluorine substitution can directly enhance the binding affinity via lipophilic interactions. For example, in the series of human fXa inhibitors (Figure 1.11), the fluorinated analog ($K_i = 11 \text{ nM, } R=F$) was more potent than non-fluorinated counterpart ($K_i = 19 \text{ nM, } R=H$). Moreover, the potency (lower $K_i$ values) increased with increasing sizes of the lipophilic R group on the analogues, then remarkably decreased with the analog bearing a CF3 group. In this case, the improved potency
presumably derived from the increased non-specific (lipophilic) binding interactions between the fluorine atom and the fXa hydrophobic pocket. In the CF₃-substituted analog, the decreased potency was due to a steric clash between a large CF₃ group and the hydrophobic pocket.

<table>
<thead>
<tr>
<th>R</th>
<th>A value</th>
<th>fXa Kᵢ,app (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>F</td>
<td>0.15</td>
<td>11</td>
</tr>
<tr>
<td>Cl</td>
<td>0.43</td>
<td>0.32</td>
</tr>
<tr>
<td>Br</td>
<td>0.38</td>
<td>0.46</td>
</tr>
<tr>
<td>CF₃</td>
<td>2.1</td>
<td>&gt; 5000</td>
</tr>
</tbody>
</table>

Fluorine can also interact indirectly with the protein by inductively modulating the polarity of neighboring functional groups, and affecting their binding to the target protein. An example representing the indirect effect of fluorine on the binding affinity involves carbonic anhydrase II (CAII) inhibitors (Figure 1.12A).²⁴ᵃ The inhibitors usually possess a sulfonamide group that can ionize and bind to the zinc center of carbonic anhydrase II. The non-fluorinated inhibitor CH₃SO₂NH₂ is a weak acid (pKₐ = 10.5) and cannot ionize and bind to the enzyme efficiently. However, the fluorinated inhibitor CF₃SO₂NH₂ is a stronger acid (pKₐ = 5.8), and easily dissociated to form the anion that bound to the enzyme strongly. Thus, CF₃SO₂NH₂ revealed much higher potency (Kᵢ = 2 nM) than CH₃SO₂NH₂ (Kᵢ = 100 μM). The distinction between these two Kᵢ values demonstrated the strong fluorine effect on modulating molecular polarity and binding affinity. Additionally, the indirect effect of fluorine can also in perturb binding affinity through the modification of the protein-ligand binding mode (Figure 1.12B). As in the case of carbonic anhydrase II (CAII) inhibitor SBB, the non-fluorinated analog binds to the enzyme differently from the fluorinated counterpart.²⁴ᵇ,c The X-ray structure of the non-fluorinated analog bound to CAII represented an atom-to-face interaction, in which the electropositive hydrogen atom on the aromatic ring of the Phe-131 residue interacted with the ring current of the benzyl moiety of the inhibitor.²⁴ᵇ In contrast, a face-to-face interaction dominated the fluorinated ligand to CAII binding. Specifically, the fluoroaromatic ring of the inhibitor interacted with the phenyl ring of the Phe-131 residue, and
demonstrated a \( \pi - \pi \) stacking interaction.\textsuperscript{24b,c} These two binding modes provided slightly different binding affinities (CAII \( K_d = 2.1 \) nM for non-fluorinated inhibitor vs. CAII \( K_d = 1.5 \) nM for fluorinated inhibitor).

![Figure 1.12. Indirect Effect of Fluorine on Protein-Ligand Binding Affinity](image)

**A)** Modulating the Polarity of Neighboring Groups of the Molecule

- \( pK_a = 10.5 \)
- \( K_i = 100 \mu M \)
- \( pK_a = 5.8 \)
- \( K_i = 2.0 \) nM

*\( K_i \) inhibition of catalytic hydration of CO\(_2\) using barbital buffer

**B)** Adapting Different Binding Modes

- SBB
- Carbonic anhydrase II inhibitors

- Electrostatic interaction
- \( K_d = 2.1 \) nM

- \( \pi - \pi \) stacking interaction
- \( K_d = 1.5 \) nM

**1.6 Fluorine as a Key Component of Drugs**

Because of the beneficial influences of fluorine on physicochemical properties, lipophilicity, conformational modulation, metabolic stability, and binding affinity, fluorine atoms or fluorinated groups represent key structural components of therapeutic agents. Many drugs on the market contain fluorinated motifs, including but not limited to single fluorine atom, difluoromethylene CF\(_2\) unit, trifluoromethyl CF\(_3\) group. Moreover, these fluorine-containing drugs range from the derivatives of natural products to small molecules, and comprise a variety of pharmacological activities as shown in Figure 1.13.\textsuperscript{4} For example, flurithromycin is a fluorinated analog of the antibiotic erythromycin. Erythromycin undergoes an acid-induced degradation to generate the ketal side product on the C9 position.\textsuperscript{25a} However, Fluorination on the C8 position of erythromycin disfavors the degradative pathway and inhibits the formation of the ketal side product.\textsuperscript{25b} Thus, flurithromycin displays higher stability under acidic conditions than erythromycin.\textsuperscript{25b} Moreover, Efavirenz is an antiretroviral drug that acts at an allosteric site of NNRT (non-nucleoside
reverse transcriptase), and inhibits the synthesis of viral DNA. The presence of a strong electron-withdrawing CF₃ group lowers pKₐ, and increases the ionization of the N–H bond of the cyclic carbamate, which improves the solubility of the drug.²⁵c In other drugs, fluorinated groups serve different purposes, such as conformational modification (Fluoxetine),²⁵d enhanced potency and selectivity (Celecoxib),²⁵e and the modulation of pharmacological activity (Faslodex),²⁵f while some of them bear fluorine for unclear reasons.

**Figure 1.13. Representative Examples of Fluorine-Containing Drugs Approved**

**Flurithromycin**
anti-bacterial drug

**Efavirenz**
anti-HIV drug

**Faslodex**
anti-cancer drug

**Fluoxetine**
anti-depressant drug

**Lipitor**
cholesterol-lowering drug

**Lansoprazole**
gastric acid-inhibiting drug

**Fluticasone propionate**
anti-inflammatory drug

**Travoprost**
glaucoma drug

**Sitagliptin**
anti-diabetic drug

**Celecoxib**
nonsteroidal anti-inflammatory drug
1.7 Conclusion

Fluorine atoms or fluorinated groups are popular structural motifs in drug design because of unique features transmitted by fluorine. However, fluorine atoms need to be installed on the appropriate positions to achieve maximum beneficial effects. Incorporating fluorine into the improper position can result in reverse effects, as observed in 3-fluoropyrrolidine. In this case, the 3-fluoropyrrolidine analog undergoes metabolic activation followed by elimination of HF to generate the Michael acceptor, which reacts with the protein to form covalent adducts, and causes the toxicity (Figure 1.14).

In order to place fluorine atoms on the correct position, a fluorine scan is a common method for SAR (structure-activity relationship) studies unless key metabolic hot spots are already known. Fluorine scans require a series of analogues with fluorine or fluorinated groups on different positions of the molecules for the bioassays. Thus, the strategies to synthesize the designed fluorinated molecules are important. However, few fluorinated molecules are biosynthesized by enzymes, because 1) high oxidation potential of fluorine prevents the formation of the hypohalous species, which are key intermediates involved in the enzymatic halogenation; and 2) high hydration energy makes fluoride a poor nucleophile, which cannot attack epoxides generated in biological systems. This means the introduction of fluorine into molecules exclusively relies on chemically synthetic pathways. Thus, chemical methodologies to access fluorinated building blocks are necessary, and they benefit the development of fluorinated drugs, and biological probes.
18 References for Chapter 1


Chapter 2. Preparation of Peptidomimetic Fluoroalkenes \textit{via} a Shapiro Reaction

2.1 Introduction to Fluoroalkenes

Fluoroalkenes represent an underappreciated functional group with applications in medicinal, synthetic, and materials chemistry. In medicinal chemistry, the fluoroalkene motif is broadly found in a variety of bioactive compounds with distinct pharmacological profiles, including antimicrobial, anti-cancer, anti-diabetic, and anti-HIV activities (Figure 2.1).\(^1\)

Moreover, the fluoroalkene group serves as an isopolar and isosteric mimic of an amide (Figure 2.2), and provides an alternative in the design of peptidomimetic drugs.\(^2\) First, amide molecules and fluoroalkenes have similar electrostatic potential maps, which mean a similar charge distribution between the two molecules. Second, the dipole moment of fluoroalkenes is closer to that of amides, indicating fluoroalkenes and amides have similar molecular polarity and geometry. Third, fluorine on fluoroalkenes has an atomic size that is similar to the size of oxygen of an amide bond. Additionally, because of the electronegative similarity between the oxygen and fluorine atoms, fluorinated alkenes preserve the dipolar nature of an amide bond, and may participate in weak H-bond or polar interactions with the receptors compared to nonpolar and H-bond lacking olefins.\(^2\)
However, amide bonds and fluoroalkenes have some distinct biophysical properties. Compared to amides, fluoroalkenes possess decreased H-bond donating and accepting abilities, and they can pass through the lipid bilayers with less expenditure of the desolvation energy. Thus, the strategic incorporation of a fluoroalkene into a biological probe can increase lipophilicity and membrane permeability. Additionally, fluorinated peptidomimetics are not subject to hydrolysis by proteases, and the electron-withdrawing effect of fluorine can prevent or slow chemical decomposition of a chemically labile molecule imposed by adjacent reactive groups in the structure. Therefore, the incorporation of this fluorinated group can improve the metabolic and chemical stability of a peptide.
Additionally, amide bonds can exist in the equilibrium of cis- and trans-isomers; however, fluoroalkenes do not undergo the isomerization and are conformationally locked (Figure 2.3A). Thus, fluoroalkenes can serve as probes for conducting conformational analyses of amides by selective preparation of E- and Z-fluoroalkene isomers (Figure 2.3B).6

In addition to these biological applications, fluoroalkenes also function as useful intermediates in synthetic sequences. For example, they have been used as precursors for elaborating fluoroalkene derivatives,7 employed as dienophiles in Diels-Alder reactions,8 converted to cyclopropane derivatives,9 and polymerized to access fluorinated materials.10

2.2 Literature Review to Access Fluoroalkenes

Fluoroalkenes broadly comprise monofluoroalkenes and gem-difluoroalkenes. Generally, monofluoroalkenes are considered amide isosteres, and gem-difluoroalkenes are precursors to access monofluoroalkene derivatives. According to the substitution pattern, monofluoroalkenes are divided into several subtypes, including di-, tri-, and tetra-substituted fluoroalkenes, each of which can be accessed by preferable synthetic methods (Table 2.1).7b The following sections present several conventional strategies for preparing various fluoroalkenes.
Table 2.1. Classification of Fluoroalkenes and Synthetic Methods

<table>
<thead>
<tr>
<th>substitution pattern</th>
<th>structure</th>
<th>common synthetic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>disubstitution</td>
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<td>addition-elimination, electrophilic fluorination, transition metal-catalyzed coupling reactions</td>
</tr>
<tr>
<td>trisubstitution</td>
<td><img src="image" alt="Diagram" /></td>
<td>addition-elimination, olefination reactions, transition metal-catalyzed coupling reactions, reactions of allylic germ-difluorides</td>
</tr>
<tr>
<td>tetrasubstitution</td>
<td><img src="image" alt="Diagram" /></td>
<td>olefination reactions, transition metal-catalyzed coupling reactions</td>
</tr>
</tbody>
</table>

Structures bearing wavy bonds possess E/Z isomers, and which isomer depends on R and R'.

2.2.1 Elimination of Fluoroalkanes

The elimination strategy of fluoroalkanes bearing a leaving group provides an alternative to synthesize fluoroalkene derivatives. In the literature, many elimination methods were disclosed by different research groups, and major reactions, including oxidative deselenenylation,\(^{11 \text{a,b}}\) HX elimination,\(^{11 \text{c-f}}\) sulfoxide/sulfone elimination\(^{11 \text{g-k}}\) and deoxyfluorination,\(^{11 \text{l}}\) are summarized in the Scheme 2.1. However, the reactions possess some drawbacks: 1) prefunctionalization of fluoroalkanes as reactants; 2) harsh reaction conditions; 3) narrow substrate scope; and 4) substrate-dependent E/Z selectivity, all of which restrict the development and utilization of the method.
2.2.2 Allylic Gem-Difluorides Oriented Methods

The allylic gem-difluoride oriented strategy utilizes pre-functionalized allylic gem-difluorides as starting materials to access fluoroalkene derivatives via 1) transition metal-catalyzed reactions; 2) transition metal-free reductive defluorination; or 3) nucleophilic defluorination. First, the Nemoto lab reported substitution reactions of allylic gem-difluorides with phenylzinc chloride or tributylphenyl tin via a gem-difluoro Pd-π-allyl intermediate (Scheme 2.2A). Subsequently, the Fujii and Paquin groups applied allylic C–F bond activation to generate a similar fluorinated Pd-π-allyl complex, which reacts with hydrides and N-based nucleophiles to access fluoroalkenes (Scheme 2.2B). In addition to palladium catalysts, other transition metals have been explored for coupling reactions. For example, the Gu lab used rhodium (I) to couple α-(difluoromethyl)styrenes with arylboronic esters via 1,2-addition of phenylrhodium(I) species followed by β-fluoride elimination to generate fluoroalkenes (Scheme 2.2C).
and a similar rhodium(I) catalyst has been employed in synthesizing ketone-substituted fluoroalkenes by a different mechanism in the Murakami group (Scheme 2.2D). In 2012, the Qing lab demonstrated a regio- and diastereoselective nickel-catalyzed reductive coupling strategy of dienes and aldehydes to access fluoroolefinic alcohols (Scheme 2.2E).

The Fujii and Taguchi labs utilized reductive defluorination of \(\delta\)-amino-\(\gamma,\gamma\)-difluoro-\(\alpha,\beta\)-enoates for accessing \(\alpha\)-alkyl-\(\gamma\)-fluoro-\(\beta,\gamma\)-enoates. These methods involved Me\(\text{2CuLi}\) and SmI\(_2\)-mediated single electron transfer followed by electrophilic alkylation on the \(\alpha\) position and Cu(I)-mediated alkyl transfer with trialkylaluminum to generate fluoroalkene products, respectively (Scheme 2.3A). Later, the
Otaka group extended this strategy to the reactions of \( \gamma,\gamma\)-difluoro-\( \alpha,\beta\)-enoysilanes with \( N \)-heterocyclic carbenes and cyanide ions as nucleophiles to generate ester-type and amide-type fluoroalkenes via a Brook rearrangement (Scheme 2.3B).\textsuperscript{13d,e} The Paquin lab reported a series of \( S_n2' \) reactions of allylic \( gem \)-difluorides with \( C^- \), \( N^- \), and \( S^- \)-based nucleophiles for the construction of \( C-C \), \( C-N \), and \( C-S \) bonds, which enabled to access heteroatom-containing fluoroalkene products (Scheme 2.3C).\textsuperscript{13f}

---

**Scheme 2.3. Non-Transition Metal-Catalyzed Reactions of Allylic \( gem \)-Difluorides to Access Fluoroalkenes**

**A) Fujii and Taguchi Methods via Reductive Defluorination**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_2\text{Cu(CN)}\text{Li}_2, 2\text{LiCl} (2.0 \text{ equiv}) )</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{O}_2\text{(g)}, \text{THF} ), ( -78 ) °C, 25–40 min, 45–64%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{Sml}_2 ) (3–6 equiv), electrophiles (3–6 equiv)</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{t- BuOH, BzlBr, CH}_3\text{COCH}_3, (\text{EtOCO})_2\text{O} ), HCHO</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{THF} ), 0 °C, 1 h, 65–94%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>(( \text{CH}_2\text{)}_2\text{CuL} ) (5.0 equiv), R-X (10 equiv, R: Me, Bn)</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{THF} ), ether, ( -78 ) to 0 °C, 75–95%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{Cul.2LiCl} ) (2.5 equiv), ( \text{RaL} ) (5.0 equiv, R: Me, t-Bu)</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>and X = OH, ( \text{THF} ), 0 °C, 3 h, 25–90%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
</tbody>
</table>

**B) Otaka Method to Access Ester- and Amide-Type Fluoroalkenes**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{DBU} ) (30 mol%), ( \text{EtOH} ), rt–70 °C, 2–24 h, 37–91%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{BnNH}_2 ), amino acids, chiral amines (1.1–5.0 equiv)</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{KCN/18-crown-6} ) (1.05 equiv), 0 °C or ( \text{n-Bu}_4\text{NCN} ) (1.05 equiv), ( -78 ) °C</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>(chiral auxiliary amines: 40 °C)</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>2–20 h, 26–95%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
</tbody>
</table>

**C) Paquin Method via Nucleophilic Defluorination**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{carbon-based nucleophiles: C(sp^3)-Li, C(sp^3)-Li, C(sp)-Li (&gt; 1 equiv)} )</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{THF} ), ( -78 ) to 66 °C, 30–88%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{nitrorgen-based nucleophiles: amines, anilines, Ph}_2\text{C}=\text{NH, n-BuLi (2–3 equiv)} )</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{THF/toluene = 1:1, rt, 28–98%} )</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{sulfur-based nucleophiles: C(sp^3)-SH, C(sp^3)-SH, n-BuLi (2.0 equiv)} )</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
<tr>
<td>( \text{THF} ), 66 °C, 63–94%</td>
<td>( \text{EtO}_2\text{CF}_2\text{Q} )</td>
</tr>
</tbody>
</table>
2.2.3 Addition-Elimination of Gem-Difluoroalkenes

Nucleophilic addition of gem-difluoroalkenes (CF₂ unit on the vinylic position) followed by elimination of a fluoride anion provides a common approach to generate fluoroalkenes. For these transformations, intermolecular reactions required the use of hydrides, and carbon-based nucleophiles (Scheme 2.4A), while intramolecular additions were limited to heteroatom-based nucleophiles and formed five-membered heterocycles (Scheme 2.4B).

2.2.4 Olefination Reactions

The reactions of fluorinated phosphorus ylides with carbonyl compounds represent conventional methods for accessing tri- and tetra-substituted functionalized fluoroalkenes, which enable further modifications to generate complex fluoroolefin-containing molecules. However, the selectivity for E- and Z-isomers of olefination reactions is difficult to predict, and depends on many factors, including reaction conditions, ylides, and substituents of carbonyl groups. To ameliorate the E/Z selectivity, several subtypes of olefination reactions were developed, including Wittig, Horner-Wadsworth-Emmons (HWE), Julia-Kocienski, and Peterson olefinations, each of which bears different auxiliary groups on the ylides. In 1985, the Burton lab reported Wittig reactions of a stabilized ylide CF(PBu₃)₂Cl with aldehydes, and the stereoselectivity was controlled by structure of the aldehydes with aliphatic substrates providing the E-isomer and aromatic substrates forming the Z-isomer. The formation of less common Z-isomers in the
Wittig reaction was attributed to two possible reasons: 1) through-space cation-π attraction between the phosphonium center of ylides and the aromatic ring of aldehydes or 2) electron-electron repulsion between the electronegative fluorine atom and π-electrons in an aromatic aldehyde (Scheme 2.5).15

In modified HWE reactions, the Penne group applied the fluorinated phosphonate (EtO)_2P(O)CHFCO_2Me to HWE reactions, and the selectivity was influenced by the reaction temperature, with E-fluoroalkenes dominating at –78 °C.16a Additionally, many research groups developed similar HWE reactions using sulfone-,16b nitrile-,16c phenyl-,16d and alkyne16e-substituted fluorinated phosphonates for accessing a variety of functionalized fluoroalkenes in good yield with low to modest stereoselectivity (Scheme 2.6).
Julia-Kocienski olefinations represent common approaches for the formation of fluoroalkene derivatives. The use of electron-withdrawing aryl sulfones increases the reactivity of reagents toward carbonyl compounds and allows the reaction to proceed under mild conditions. Various fluorinated aryl sulfone reagents have been explored for realizing the transformation. The Zajc group prepared a series of α-EWG-embedded α-fluorobenzothiazolyl (BT)-derived sulfones and condensed these reagents with aldehydes to generate fluoroalkenes as a mixture of E/Z isomers (Scheme 2.7A). In 2015, the same group reported a stereoselective synthesis of 4-(1-fluorovinyl)triazoles using a second-generation Julia-Kocienski reagent, α-triazole-BT sulfone, which provided the E-isomer with DBU as a base and the Z-isomer with LHMDS as a base. Additionally, the Nájera and Hu labs independently developed 3,5-bis(trifluoromethyl)phenyl (BTFP)- and 1-tert-butyl-1H-tetrazol-5-yl (TBT)-sulfones for accessing functionalized fluoroalkenes with low to modest stereoselectivity. To improve E/Z selectivity, the Lequeux and Hu groups applied a pyrimidinylsulfone-directed condensation with aldehydes and a synergistic cooperation of fluorosulfoximines and nitrones for realizing stereoselective synthesis of Z-fluoroalkenes (>98%), respectively (Scheme 2.7B).
Peterson olefination reactions generally provide comparable yields and stereoselectivity compared to HWE and Julia reactions, and therefore they are less discussed in literature. The Welch lab employed a bulky α-fluoro-α-(trimethylsilyl)acetate in coupling reactions of carbonyl groups to access Z-selective fluoroalkenes through a open transition state irregardless of the enolate geometry (Scheme 2.8). The Iio group reported the reactions of α-fluoro-α-silyl sulfones with aldehydes to generate E-selective fluoroalkenes via a chelated four-centered transition state. In 2008, Mukaiyama disclosed a Lewis base-
catalyzed fluoroolefination of fluoro(trimethylsilyl)ketene trimethylsilyl acetal for constructing Z-fluoroalkenes (>98%).

### 2.2.5 Electrophilic Fluorination of Alkenylmetal Species

This type of reactions utilizes alkenylmetal species, including alkenyllithiums, alkenylstannanes, alkenylsilanes, and alkenylboronic acid derivatives, to couple with electrophilic fluorinating reagents XeF$_2$, Selectfluor$^a$, and N-fluoro-sulfonamides for accessing fluorinated alkenes (Scheme 2.9). However, these methods typically encounter two problems: 1) the formation of protonated alkenes and 2) low $E/Z$ selectivity, which increases the difficulty of compound purification.
2.2.6 Monofluorofunctionalization of Alkynes

Monofluorofunctionalization of alkynes concurrently incorporates a fluorine atom and a functional group into the molecules, and represents an important and efficient strategy for accessing highly functionalized fluorinated alkenes, which enable further elaboration to produce complex fluorine-containing molecules. Many research groups have explored this area and developed a variety of methods including, fluorosulfenylation, fluoroselenation, halofluorination, hydrofluorination, and transition metal-catalyzed processes for introducing a fluorine atom followed by forming a C–C bond, whose methods were reviewed in 2015 (Scheme 2.10). However, these transformations have some deficiencies. While aromatic unsymmetric alkynes followed Markovnikov’s rule to generate one regioisomer rather than the other one, aliphatic unsymmetric alkynes provided a mixture of regioisomers in most cases. Moreover, the reactions with unactivated alkynes require the use of a strong fluoride source such as pyridinium poly(hydrogen fluoride), and the use of excess HF reagents cause the formation of gem-difluorides (–CF₂CH₂–) instead of fluoroalkenes (–CF=CH–).
Scheme 2.10. Monofluorofunctionalization of Alkynes to Access a Variety of Fluoroalkenes

**R1, R2** = alkyl, aryl, H

**fluorosulfonylation**
- **Q = S**
- Electrophilic sulfur reagents
- Fluoride anions

**fluoroselenation**
- **Q = Se**
- Electrophilic selenium reagents
- Fluoride anions

**halofluorination**
- **Q = I, Br, Cl**
- Electrophilic halogen reagents
- Fluoride anions

**hydrofluorination**
- **Q = H**
- *R2* = EWG, NRR', SR, in most cases
- Electrophilic hydrofluorinating reagents
- Additives/catalysts

To solve these problems associated with regioselectivity, the Sadighi lab developed an electrophilic catalyst, (NHC)Au(I), to activate internal alkynes, which in turn allowed the use of less acidic Et$_3$N.3HF reagent as a fluoride source.\(^{21a}\) In 2009, the Miller group further introduced the carbamate as a directing group on the substrate to control the regioselective addition of HF to internal alkynes with high regioselectivity under the Sadighi reaction conditions (Scheme 2.11A).\(^{21b}\) In 2016, the Zhu lab demonstrated an auxiliary group-mediated orthogonal catalyst system for regioselective formation of a C–F bond on α and β-position of ynamides, in which the combination of the copper(I) catalyst and an oxazolidinone group generated β-fluoroenamides, while the use of the silver(I) catalyst with a sulfonamide group afforded α-fluorinated products (Scheme 2.11B).\(^{21c}\)
2.2.7 Transition Metal-Catalyzed Cross-Coupling Reactions

Transition metal-catalyzed carbon-carbon forming strategies represent an important direction for accessing fluorinated alkenes, because these methods possess high functional-group compatibility and good stereoselectivity. Many coupling reactions, including Stille, Kumada, Suzuki, and Negishi reactions, have been applied in the synthesis of a variety of fluoroalkenes with fluoro vinyl components serving as either nucleophiles \(^{22a-c}\) or electrophiles \(^{22d-i}\) (Scheme 2.12A and 2.12B). Moreover, transition metals enabled coupling reactions of fluoro vinyl moieties with alkynes \(^{22j,k}\) and alkenes \(^{22l,m}\) via the functionalization of C–H bonds (Scheme 2.12C and 2.12D). However, these methods require prefunctionalization of a single isomer of fluoro vinyl substrates, which in turn increases the number of synthetic steps, and greatly reduces the use of the methods. In 2016, the Buchwald lab developed a Pd-catalyzed coupling reaction of cyclic vinyl triflates with KF as a fluoride source using bulky and electron-donating phosphine ligands. \(^{22n}\) This method used easily prepared vinyl triflates as coupling components, and didn’t require the manipulation of fluoro vinyl species, which significantly increased the synthetic efficiency and ease of application.
2.2.8 Miscellaneous Methods

In addition to the conventional methods, fluoroalkenes were accessed by alternative routes. For example, ring-closing metathesis (RCM) of fluorinated dienes provided a good method for the formation of cyclic fluoroalkenes that are difficult to access by other methods.\(^{23a,b}\) Moreover, \([3,3']\)-sigmatropic rearrangement of vinyl fluorides,\(^{23c,d}\) ring-opening of cyclopropanes,\(^{23e,f}\) and fluorination of substituted allenes\(^{23g,h}\) enabled the access of fluoroalkenes from structurally diverse starting materials. Recently, transition metal catalysis has been utilized in accessing fluoroalkenes \textit{via} C–H activation,\(^{23i,j}\) transition metal-mediated coupling,\(^{23k}\) and defluorination reactions,\(^{23l}\) which afforded better stereoselective control and high tolerance of functional groups under mild conditions.
2.3 Shapiro Fluorination to Access Fluoroalkenes

Despite the many methods that have been developed to access fluoroalkenes, convergent and straightforward strategies are desirable, especially for introducing the fluoroalkene motif at a late stage of a synthesis through modification of a compound already in hand and using commercially available fluorinating reagents (Scheme 2.13).

It was envisaged that fluoroolefins could be accessed through a Shapiro fluorination reaction (Scheme 2.14). The Shapiro reaction has been widely applied in the synthesis of natural products, and for the preparation of polysubstituted alkenes, many of which are not easily accessed by other means. A prototypical Shapiro reaction involves: 1) condensation of an N-sulfonyl hydrazide with a ketone to provide a sulfonyl hydrazone; 2) treatment of the sulfonyl hydrazone with a base to provide a vinyl lithium intermediate; and 3) trapping of the vinyl anion with H⁺ to afford an alkene-based product. Alternatively, the in situ formed alkenyllithium intermediate can also be trapped with a variety of electrophiles to generate allylic alcohols, acrylic acids, acrylic aldehydes, vinylsilanes, and vinyl iodides and bromides. However, the Shapiro reaction has not been employed to access fluoroalkenes. Herein, we describe a Shapiro fluorination reaction to provide fluoroalkenes in high diastereoselectivity (Scheme 2.14).
The Shapiro fluorination reaction was scouted using a variety of commercially available electrophilic fluorinating reagents, and biphenyl 2,4,6-triisopropylbenzenesulfonyl (trisyl) hydrazone (2.1a or also called (E)-N’-(1-(1,1’-biphenyl]-4-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonylhydrazide) as a test substrate. Trisyl hydrazones were employed instead of tosylsulfonyl or mesitylsulfonyl moieties, because the former group: 1) does not undergo ortho-lithiation or α-lithiation, which allows for the reaction to proceed using fewer equivalents of base and electrophilic trapping agent (Scheme 2.15A); and 2) decomposes more easily than unhindered aryl hydrazones, a phenomenon that likely arises from the release of steric compression at the transition state (Scheme 2.15B).
The preparation of trisyl hydrazones involved condensation reactions of ketones with 2,4,6-triisopropylbenzenesulfonyl hydrazide in the presence of catalytic amount of hydrochloric acid, and the conventional procedure provided hydrazone products in reasonable yields (Scheme 2.16).24

Scheme 2.16. General Procedure for Preparing Acetophenone-Derived and Aliphatic Trisyl Hydrazones

A) Acetophenone-Derived Trisyl Hydrazones

B) Aliphatic Trisyl Hydrazones

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>92%</td>
</tr>
<tr>
<td>O</td>
<td>Me</td>
<td>60%</td>
</tr>
<tr>
<td>MeS</td>
<td>Me</td>
<td>89%</td>
</tr>
<tr>
<td>MeO</td>
<td>Me</td>
<td>90%</td>
</tr>
<tr>
<td>MeO</td>
<td>Ph</td>
<td>85%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>Me</td>
<td>32%</td>
</tr>
<tr>
<td>C8H10</td>
<td></td>
<td>48%</td>
</tr>
<tr>
<td>C6H5</td>
<td>Ph</td>
<td>48%</td>
</tr>
<tr>
<td>C6H5</td>
<td>Me</td>
<td>60%</td>
</tr>
<tr>
<td>C6H5</td>
<td>Ph</td>
<td>69%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>80%</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>30%</td>
</tr>
<tr>
<td>C8H10</td>
<td></td>
<td>64%</td>
</tr>
<tr>
<td>C6H5</td>
<td>N</td>
<td>65%</td>
</tr>
<tr>
<td>C8H10</td>
<td>N</td>
<td>88%</td>
</tr>
<tr>
<td>TBDPSO</td>
<td></td>
<td>25%</td>
</tr>
</tbody>
</table>
Decomposition of the trisyl hydrazone (2.1a) was accomplished by lithiation with 2.5 equivalents of \( n \)-butyllithium (\( n \)-BuLi) in THF from \(-78 \) to \( 0 \) °C, followed by cooling to \(-78 \) °C for the addition of the electrophilic fluorinating reagents. No fluorinated product was observed by \( ^{19} \)F NMR when the \textit{in situ} formed vinyl anion was allowed to react with \( N \)-fluoropyridinium salts or selectfluor. Potentially, the poor reactivity of these reagents arose from the low solubility of the ionic reagents in THF at low temperature. In contrast, employment of \( N \)-fluorobenzenesulfonimide (NFSI), a neutral fluorinating agent that maintains good solubility in ethers and hydrocarbon solvents at lower temperature,\(^3\) provided the desired fluoroalkene product in 70% yield based on \( ^{19} \)F NMR spectroscopy (Scheme 2.17).

\[
\begin{align*}
\text{Scheme 2.17: Screening of Different Electrophilic Fluorinating Reagents} \\
\begin{array}{c}
\text{2.1a} \quad \text{N-H-tris} \\
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Me}
\end{array}
\end{array}
\quad \text{i.} \quad n\text{-BuLi (2.5 equiv), THF} \\
\quad \text{\(-78 \) °C, 30 min \( \rightarrow 0 \) °C, 20 min} \\
\quad \text{ii.} \quad \text{fluorinating reagent} \\
\quad \text{\(-78 \) °C, 30 min \( \rightarrow \) rt, 1 h} \\
\begin{array}{c}
\text{2.2a} \\
\begin{array}{c}
\text{Ph} \\
\text{F}
\end{array}
\end{array}
\end{align*}
\]

\[
\begin{array}{c}
\text{NFSI} \\
\begin{array}{c}
\text{Ph} \\
\text{SO_2-N=S-SO}_2-\text{Ph}
\end{array}
\end{array}
\quad 70\% \text{a} \\
\begin{array}{c}
\text{BF}_4^- \\
\begin{array}{c}
\text{Me} \\
\text{BF}_4^-
\end{array}
\end{array}
\quad 0\% \\
\begin{array}{c}
\text{Cl} \\
\text{N=Cl}
\end{array}
\quad 0\%
\]

Features of NFSI:
\( > \) better solubility in nonpolar solvents
\( > \) low temperatures
\( > \) soft and neutral fluorinating reagents

\(^a\) Yields were determined by \( ^{19} \)F NMR analysis with \( \alpha,\alpha,\alpha \)-trifluorotoluene as an internal standard.
Optimization of the Shapiro fluorination reaction by the evaluation of alternate bases, solvents and additives provided an increased yield of product (Table 2.2). The use of THF as a solvent (entry 1) proved superior to the use of TMEDA, DME, and hexane/TMEDA (entries 5–7), although the use of a mixture of THF/TMEDA provided a comparable yield (entry 4). The addition of NFSI as a solid provided a lower yield of product (entry 3) compared to addition of NFSI as a solution in THF (entry 1). The use of n-BuLi and s-BuLi afforded higher yields than that of MeLi (entries 1, and 8–9). The use of cation-chelating agents, such as HMPA, did not improve the yield of 2.2a (entry 10). Further optimization of the reaction concentration and stoichiometry of base did not improve the yield (entries 11–12). Finally, the highest yield was obtained by decreasing the quantity of base employed to 2.2 equivalents (entry 13).

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>NFSI dissolved in</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>THF</td>
<td>THF</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi</td>
<td>THF</td>
<td>toluene</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi</td>
<td>THF</td>
<td>solid added</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi</td>
<td>THF/TMEDA(4:1)</td>
<td>THF</td>
<td>68</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n-BuLi</td>
<td>TMEDA</td>
<td>toluene</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi</td>
<td>Hexane/TMEDA(9:1)</td>
<td>toluene</td>
<td>53</td>
</tr>
<tr>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n-BuLi</td>
<td>DME</td>
<td>toluene</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>s-BuLi</td>
<td>THF</td>
<td>THF</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>CH3Li</td>
<td>THF</td>
<td>THF</td>
<td>28</td>
</tr>
<tr>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n-BuLi</td>
<td>THF</td>
<td>THF</td>
<td>18</td>
</tr>
<tr>
<td>11&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n-BuLi</td>
<td>THF</td>
<td>THF</td>
<td>68</td>
</tr>
<tr>
<td>12&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n-BuLi</td>
<td>THF</td>
<td>THF</td>
<td>65</td>
</tr>
<tr>
<td>13&lt;sup&gt;e&lt;/sup&gt;</td>
<td>n-BuLi</td>
<td>THF</td>
<td>THF</td>
<td>78 (75)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Standard reaction conditions: 2.1a (1.0 equiv, 0.20 M solution), base (2.5 equiv), NFSI (1.5 equiv, 0.50 M THF solution or 0.20 M toluene solution).<sup>b</sup>Yields were determined by <sup>19</sup>F NMR using α,α,α-trifluorotoluene as an internal standard.<sup>c</sup>Reaction temperatures of -60 °C for 30 min followed by 0 °C for 20 min.<sup>d</sup>HMPA (1.0 equiv) was added during lithiation.<sup>e</sup>NFSI (2.0 equiv).<sup>f</sup>0.10 M solution was used in the step i. <sup>g</sup>n-BuLi (2.2 equiv).<sup>h</sup>Isolated yield of material deemed to be >95% pure by <sup>1</sup>H NMR.
Using the optimized reaction sequence, several acetophenone-derived substrates afforded fluoroalkene products (Scheme 2.18). Electron-rich aryl-substituted trisyl hydrazones including para-morpholine, –SMe and –OMe were converted to fluoroalkenes 2.4a–d. The para-chloro-substituted fluorostyrene (2.4e) was provided in 52% yield. Reactions of substrates bearing substituents at the β-position provided Z-fluoroalkene products in good to excellent diastereoselectivities (2.4g–i). Presumably, the stereochemistry of these reactions was dictated by the unfavorable steric repulsion of the syn arrangement of the organic substituents. In contrast, the E-fluoroalkene was accessed for a cyclic ketone (2.4f). However, no fluoroalkene products were obtained in reactions of substrates bearing para- and meta-CF₃ and meta-chloro electron-withdrawing groups. As control experiments, subjecting these three substrates to the Shapiro conditions and quenching of the presumed vinyllithium intermediate with D₂O did not provide the anticipated deuterated or protonated alkenes (GC-MS), indicating that these three substrates were not compatible with the lithiation step.³²
**Scheme 2.18. Shapiro Fluorination of Acetophenone-Derived Trisyl Hydrazones to Provide Fluorostyrenes**

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
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<tr>
<td>O</td>
<td>N</td>
<td>NHTris</td>
<td>N</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>Ph</td>
<td>F</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>MeO</td>
<td>F</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>Cl</td>
<td>F</td>
</tr>
<tr>
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<td>F</td>
<td>F</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>Me</td>
<td>F</td>
</tr>
</tbody>
</table>

i. Base (2.2 equiv)
-78 °C, 30 min → 0 °C, 20 min

ii. NFSI (1.5 equiv)
-78 °C, 30 min → rt, 2 h

<table>
<thead>
<tr>
<th>2.4a</th>
<th>2.4b</th>
<th>2.4c</th>
</tr>
</thead>
<tbody>
<tr>
<td>75% (67%)</td>
<td>68% (65%)</td>
<td>67% (54%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.4d</th>
<th>2.4e</th>
<th>2.4f</th>
</tr>
</thead>
<tbody>
<tr>
<td>67% (43%)</td>
<td>52% (42%)</td>
<td>57% (50%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.4g</th>
<th>2.4h</th>
<th>2.4i</th>
</tr>
</thead>
<tbody>
<tr>
<td>87% (79%) (Z only)</td>
<td>81% (77%) (E:Z = 1.8:5)</td>
<td>45% (43%) (E:Z = 1.6:5)</td>
</tr>
</tbody>
</table>

---

**Notes:**
- Standard reaction conditions: 2.3a–i (1.0 equiv, 0.20 M solution in THF), n-BuLi (2.2 equiv), NFSI (1.5 equiv, 0.5 M solution in THF). Yields were determined by $^{19}$F NMR analysis using α,α,α-trifluorotoluene as an internal standard (average of two runs) and the figure in the parenthesis indicates the isolated yield (average of two runs).
- NFSI (1.1 equiv).
- n-BuLi (2.5 equiv) and NFSI (1.75 equiv).
- s-BuLi (2.2 equiv).
- The E/Z ratios were determined by integration of the $^{19}$F NMR spectrum of the crude reaction mixture.

---

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Aliphatic N-trisyl hydrazones also provided the corresponding fluoroalkene analogues (Scheme 2.19). Using t-BuLi, the reaction of 2-phenyl cyclohexanone trisyl hydrazone provided two regioisomers, 2.6aA and 2.6aB in a 15:1 ratio (crude reaction mixture), and 60% of the pure tetra-substituted fluoroalkene 2.6aA, an amide mimic of a δ-lactam.

The substrate 2.5c afforded E-fluoroalkene in 5.7:1 diastereoselectivity. In contrast to the Z-selectivity observed for products 2.4g–i, the reaction to selectively generate E-2.6c seems to be controlled by a syn-dianion chelation effect, which is frequently observed in Shapiro reactions (Scheme 2.20). The chelation of lithium bases to nitrogen of the hydrazone enables syn-deprotonation, which puts the alkyl group away from the hydrazone to reduce allylic strain. Subsequently, the release of nitrogen gas from the dianion forms the configurationally stable Z-vinyl anion that generates the E-fluoroalkene upon trapping with electrophilic F sources (Scheme 2.20).
Additionally, amines protected with benzyl groups were compatible with the reaction conditions, and afforded 28%–70% yields, depending on the substrates (2.6d–e in Scheme 2.19). Pyrrolidine-based derivative 2.6e could prove useful for strategic replacement of proline-based residues to form fluorinated peptide-based probes with distinct biophysical properties. Finally, the method was used to rapidly access new fluorinated analogues of natural products, including camphor and a protected steroid (2.6b and 2.6f). However, the silyl protecting group was not necessary, and the steroid substrate bearing an unprotected hydroxyl group provided 33% yield by $^{19}$F NMR analysis (not shown in Scheme 2.19, 3.2 equiv $n$-BuLi employed). Thus, the present reaction provides a new entrypoint for the preparation of fluorinated steroids, which are clinically employed for the treatment of various disease states.
In order to accomplish the direct conversion of ketones to fluoroalkenes, a one-pot reaction sequence was developed (Scheme 2.21). The use of an acid catalyst, in combination with molecular sieves, facilitated the initial condensation reaction, and was compatible with the subsequent lithiation and fluorination steps. Using this one-pot procedure, yields of the fluoroalkene products were comparable with those from the isolated hydrazones (2.8a vs. 2.2a; 2.8b vs. 2.4e; 2.8c vs. 2.4c). This sequence enables easy access to a variety of fluoroalkenes from ketones without purification of intermediates, and it is anticipated that this one-pot procedure could be optimized to access nonstyrenyl fluoroalkenes by improving the efficiency of condensation reactions of ketones with trisyl hydrazides.

2.4 Conclusion

A procedure was developed for converting a ketone into a fluoroalkene analog through a Shapiro fluorination reaction. The reaction employs inexpensive and readily available reagents, and no expensive transition metal catalysts/reagents and ligands are required. Compared with many currently available methods, the Shapiro fluorination reaction provides improved diastereoselectivities (dr > 5.5:1), and represents an orthogonal strategy that should be useful for preparing fluoroalkene analogues that might be difficult to access otherwise. Moreover, the extensive number of ketone functional groups that exist in natural products and pharmaceutically important building blocks provides a wide variety of potential substrates for this transformation.
References for Chapter 2


Reactivity of R₃Al-Cu(I) and Me₂CuLi


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Fluoromethyl Sulfone (TBTSO 2CH2F): A Versatile Fluoromethylidene Synthon and Its Use in the Catalysis

H.-J. Synthesis of Phenyl-Substituted Fluoro-Olefins


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33 For the 4-piperidone trisylhydrazone, N-Bn and N-PMP protected substrates provided similar yields of fluoroalkene products.

Chapter 2 Appendix

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General Information

Unless otherwise noted, reactions were performed under nitrogen atmosphere using oven-dried glassware. The Shapiro fluorination reactions were performed in the round-bottom flasks, which were sealed with three-way valves for transferring nitrogen and reagents, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Unless otherwise noted, reagents purchased from commercial sources were used without further purification. THF was dried by passage through activated alumina columns. All alkyllithium bases were titrated prior to each reaction using diphenylacetic acid as an indicator.\(^1\) Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing with fluorescence quenching, KMnO\(_4\) solution, nihydrins, or ceric ammonium molybdate solution (CAM). \(^{19}\text{F\ NMR\ yields\ reported\ in\ the\ manuscript\ represent\ an\ average\ of\ at\ least\ two\ independent\ runs.\ Isolated\ yields\ reported\ in\ the\ manuscript\ represent\ either\ the\ result\ of\ one\ purification,\ or\ of\ an\ average\ of\ two\ independent\ purifications.\ Yields\ reported\ in\ the\ supporting\ information\ refer\ to\ a\ single\ experiment.\ Proton\ nuclear\ magnetic\ resonance\ (\(^1\text{H\ NMR}\)\ spectra,\ carbon\ nuclear\ magnetic\ resonance\ (\(^{13}\text{C\ NMR}\)\ spectra\ were\ recorded\ on\ Bruker\ 400\ AVANCE\ spectrometer\ (400\ and\ 100\ MHz,\ respectively)\ or\ Bruker\ 500\ AVANCE\ spectrometer\ (500\ and\ 125\ MHz,\ respectively).\ Chemical\ shifts\ (\(\delta\))\ for\ protons\ are\ reported\ in\ parts\ per\ million\ downfield\ from\ tetramethylsilane\ and\ are\ referenced\ to\ proton\ resonance\ of\ residual\ CHCl\(_3\)\ in\ the\ NMR\ solvent\ (CHCl\(_3\) = 7.27\ ppm).\ Chemical\ shifts\ (\(\delta\))\ for\ carbon\ are\ reported\ in\ parts\ per\ million\ downfield\ from\ tetramethylsilane,\ and\ are\ referenced\ to\ the\ carbon\ resonances\ of\ the\ solvent\ residual\ peak\ (CDCl\(_3\) = 77.23\ ppm).\ Fluorine\ nuclear\ magnetic\ resonance\ (\(^{19}\text{F\ NMR}\)\ spectra\ were\ recorded\ on\ a\ Bruker\ 400\ AVANCE\ spectrometer\ (376\ MHz);\ chemical\ shifts\ (\(\delta\))\ are\ reported\ in\ parts\ per\ millions,\ and\ are\ referenced\ to\ \(\alpha,\alpha,\alpha\)-trifluorotoluene\ (\(\delta = -63.72\ ppm\)).\ NMR\ data\ are\ represented\ as\ follows:\ chemical\ shift\ (ppm),\ multiplicity\ (s = singlet,\ d = doublet,\ t = triplet,\ q = quartet,\ quin = quintet,\ sept = septet,\ m = multiplet),\ coupling\ constant\ in\ Hertz\ (Hz),\ integration.\ High-resolution\ mass\ data\ were\ recorded\ on\ a\ high-resolution\ mass\ spectrometer\ in\ the\ ESI\ mode.\ Infrared\
spectra were measured at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Melting points were uncorrected and measured on Thomas Hoover Capillary Melting Point apparatus.

**Preparation of 2,4,6-Triisopropylbenzenesulfonyl Hydrazide (TPSH)**

Using a syringe pump, hydrazine (2.3 mL, 2.2 mmol) was added dropwise over a period of 15 min to a pre-cooled solution of 2,4,6-triisopropylbenzenesulfonyl chloride (10 g, 33 mmol) in THF (30 mL) at –10 °C (ice-salt freezing mixture). The reaction solution was warmed to 0 ºC, and stirred for additional 3 h at this temperature. Water (15 mL) was added to dissolve the precipitated solids. The products were then transferred to a separation funnel. The organic layer was separated, and the aqueous layer was extracted with ether (2 x 30 mL). The organic layers were washed with ice-cold brine (2 x 30 mL), dried over anhydrous Na₂SO₄, filtered, and then concentrated under reduced pressure below room temperature (25 ºC). Pentane was added to the solid obtained, and the mixture was sonicated at rt for 3 min until fine solids formed. The solid was collected by filtration, washed with cold pentane, and dried in vacuo to give TPSH as a colorless solid (9.6 g, 97%).

**1H NMR (CDCl₃, 400 MHz)** δ 7.21 (s, 2 H), 5.52 (s, 1 H), 4.16 (sept, J = 6.7 Hz, 2 H), 3.65 (br, 2 H), 2.92 (sept, J = 6.9 Hz, 1 H), 1.28 (d, J = 6.7 Hz, 12 H), 1.27 (d, J = 6.9 Hz, 6 H) ppm.

**13C NMR (CDCl₃, 125 MHz)** δ 154.0, 152.0, 128.9, 124.2, 34.4, 30.0, 25.1, 23.7 ppm.

**HRMS (ESI, m/z):** calcld for C₁₅H₂₇N₂O₂S [M+H]+ 299.1793, found 299.1794.

**General Procedure for Preparation of Trisyl Hydrazones via Ketone Condensation**

A ketone (1.0 equiv) was added to a suspension of 2,4,6-triisopropylbenzenesulfonyl hydrazide TPSH (>1.0 equiv) in THF or MeOH (generally c = 1.0 M) at room temperature, and stirred for several hours (generally 1–5 h) under N₂. In some cases (hindered substrates), the addition of several drops of concentrated HCl or the heating facilitated the reaction.

Workup A: The reaction was quenched with a solution of aqueous NaHCO₃, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated to provide the crude product. The residue was triturated with MeOH (or a minimal amount
of CH₂Cl₂ and a large amount of pentane) and sonicated until white solid precipitated. The solid was filtered, washed with pentane, and dried in vacuo.

Workup B: The extraction procedure was the same as workup A, but the crude products were purified by column chromatography using gradient elution.

Workup C: The solvent was removed under reduced pressure, and the residue dissolved in MeOH or pentane/CH₂Cl₂, and sonicated until solids precipitated. The solid was filtered, washed with pentane and dried in vacuo. (In some cases, compounds were purified by column chromatography using gradient elution).

(E)-N’-(1-(1,1’-biphenyl)-4-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.1a)

The general procedure was followed using TPSH (3.35 g, 11.2 mmol), 4-phenylacetophenone (2.00 g, 10.2 mmol), and 4 drops of HCl with THF (0.010 L) as solvent for 1.5 h at rt. Workup A (precipitation in MeOH) afforded the title compound 2.1a as a colorless solid (4.46 g, 92%). ¹H NMR (CDCl₃, 400 MHz) δ 7.74–7.72 (m, 3 H), 7.60–7.54 (m, 4 H), 7.46–7.43 (m, 2 H), 7.38–7.34 (m, 1 H), 7.19 (s, 2 H), 4.35 (sept, J = 6.7 Hz, 2 H), 2.91 (sept, J = 6.9 Hz, 1 H), 2.22 (s, 3 H), 1.32 (d, J = 6.7 Hz, 12 H), 1.26 (d, J = 6.9 Hz, 6 H) ppm. ¹³C NMR (CDCl₃, 125 MHz) δ 153.6, 151.6, 150.6, 142.4, 140.5, 136.4, 131.6, 129.0, 127.8, 127.2, 127.0, 126.9, 124.0, 34.4, 30.2, 25.1, 23.7, 13.3 ppm. IR (film) 3225, 2959, 1599, 1383, 1362, 1331, 1165, 1153, 1059, 1038, 910, 841, 766, 704, 660 cm⁻¹. HRMS (ESI, m/z): calcd for C₂₉H₃₆N₂O₂SNa [M+Na]⁺ 499.2395, found 499.2387. mp 164–165 °C.

(E)-2,4,6-triisopropyl-N’-(1-(4-morpholinophenyl)ethylidene)benzenesulfonohydrazide (2.3a)

(E)-2,4,6-triisopropyl-N’-(1-(4-morpholinophenyl)ethylidene)benzenesulfonohydrazide (2.3a)
The general procedure was followed using TPSH (1.74 g, 5.84 mmol), 4-morpholinoacetophenone (1.00 g, 4.87 mmol) and 4 drops of HCl with MeOH (4.50 mL) as solvent for 6.0 h at rt. Workup B followed by chromatographic purification (CH$_2$Cl$_2$/MeOH) provided the title compound 2.3a as a colorless solid (1.41 g, 60%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.58 (d, $J = 9.0$ Hz, 2 H), 7.42 (s, 1 H), 7.16 (s, 2 H), 6.81 (d, $J = 9.0$ Hz, 2 H), 4.32 (sept, $J = 6.8$ Hz, 2 H), 3.85 (t, $J = 4.8$ Hz, 4 H), 3.19 (t, $J = 4.8$ Hz, 4 H), 2.89 (sept, $J = 6.9$ Hz, 1 H), 2.13 (s, 3 H), 1.30 (d, $J = 6.8$ Hz, 12 H), 1.25 (d, $J = 6.9$ Hz, 6 H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 153.4, 152.2, 151.5, 150.9, 131.8, 128.7, 127.6, 123.9, 114.6, 66.9, 48.7, 34.4, 30.2, 25.0, 23.7, 13.0 ppm. IR (film) 3180, 2959, 2864, 1603, 1518, 1425, 1377, 1331, 1306, 1232, 1167, 928, 739, 704 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{27}$H$_{39}$N$_3$O$_3$SNa [M+Na]$^+$ 508.2610, found 508.2596. mp 186 °C (dec).

(E)-2,4,6-triisopropyl-N'-[1-(4-(methylthio)phenyl)ethylidene]benzenesulfonohydrazide (2.3b)

The general procedure was followed using TPSH (1.97 g, 6.62 mmol), 4-(methylthio)acetophenone (1.00 g, 6.02 mmol) with MeOH (7.00 mL) as solvent for 6.0 h at rt. Workup C (precipitation in MeOH) provided the title compound 2.3b as a light yellow solid (2.39 g, 89%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.56 (d, $J = 8.0$ Hz, 2 H), 7.49 (s, 1 H), 7.17 (s, 2 H), 7.16 (d, $J = 8.0$ Hz, 2 H), 4.30 (sept, $J = 6.8$ Hz, 2 H), 2.90 (sept, $J = 6.9$ Hz, 1 H), 2.48 (s, 3 H), 2.14 (s, 3 H), 1.30 (d, $J = 6.8$ Hz, 12 H), 1.25 (d, $J = 6.9$ Hz, 6 H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 153.5, 152.2, 151.5, 150.9, 131.8, 128.7, 127.6, 123.9, 114.6, 66.9, 48.7, 34.4, 30.2, 25.0, 23.7, 15.6, 13.1 ppm. IR (film) 3227, 2959, 1599, 1383, 1310, 1165, 1153, 1059, 910, 820, 770, 675 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{24}$H$_{34}$N$_2$O$_2$S$_2$Na [M+Na]$^+$ 469.1959, found 469.1955. mp 143–144 °C.
(E)-2,4,6-triisopropyl-\(N'\)-(1-(4-methoxyphenyl)ethylidene)benzenesulfonohydrazide (2.3c)³

The general procedure was followed using TPSH (2.20 g, 7.33 mmol), \(p\)-methoxyacetophenone (1.00 g, 6.66 mmol), 2 drops of HCl with THF (0.010 L) as solvent for 5.0 h at rt. Workup A (precipitation in pentane/\(\text{CH}_2\text{Cl}_2\)) provided the title compound 2.3c as a colorless solid (2.59 g, 90%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.61–7.59 (m, 3 H), 7.17 (s, 2 H), 6.83 (d, \(J = 9.0\) Hz, 2 H), 4.32 (sept, \(J = 6.8\) Hz, 2 H), 3.81 (s, 3 H), 2.90 (sept, \(J = 6.9\) Hz, 1 H), 2.15 (s, 3 H), 1.30 (d, \(J = 6.8\) Hz, 12 H), 1.25 (d, \(J = 6.9\) Hz, 6 H) ppm. \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 160.9, 153.5, 151.5, 150.5, 139.1, 131.5, 129.3, 124.0, 119.1, 115.4, 111.8, 55.4, 34.4, 30.2, 25.0, 23.7, 13.2 ppm. HRMS (ESI, \(m/z\)): calcd for C\(_{25}\)H\(_{34}\)N\(_2\)O\(_3\)SNa [M+Na]\(^+\) 453.2188, found 453.2187.

(\(E\))-2,4,6-triisopropyl-\(N'\)-(1-(3-methoxyphenyl)ethylidene)benzenesulfonohydrazide (2.3d)

The general procedure was followed using TPSH (2.09 g, 6.99 mmol), \(m\)-methoxyacetophenone (1.00 g, 6.66 mmol) with MeOH (7.00 mL) as solvent for 3.0 h at rt. Workup C (precipitation in MeOH) provided the title compound 2.3d as a colorless solid (2.44 g, 85%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.61 (s, 1 H), 7.23–7.17 (m, 5 H), 6.88 (dt, \(J = 7.3, 2.0\) Hz, 1 H), 4.31 (sept, \(J = 6.8\) Hz, 2 H), 3.77 (s, 3 H), 2.89 (sept, \(J = 6.9\) Hz, 1 H), 2.16 (s, 3 H), 1.30 (d, \(J = 6.8\) Hz, 12 H), 1.25 (d, \(J = 6.9\) Hz, 6 H) ppm. \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 159.7, 153.5, 151.5, 150.5, 139.1, 131.5, 129.3, 124.0, 119.1, 115.4, 111.8, 55.4, 34.4, 30.1, 23.7, 13.5 ppm. IR (film) 3246, 2961, 2928, 1597, 1585, 1462, 1467, 1364, 1329, 1232, 1165, 1155, 1059, 856, 785, 721, 663 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{25}\)H\(_{34}\)N\(_2\)O\(_3\)SNa [M+Na]\(^+\) 453.2188, found 453.2194. mp 147–148 °C.
(E)-N’-(1-(4-chlorophenyl)ethylidene)-2,4,6-triisopropylbenzenesulfonylhydrazide (2.3e)

The general procedure was followed using TPSH (2.12 g, 7.12 mmol), 4’-chloroacetophenone (1.00 g, 6.47 mmol) with THF (6.00 mL) as solvent for 3.0 h at rt. Workup A (precipitation in pentane/CH2Cl2) provided the title compound 2.3e as a colorless solid (0.900 g, 32%). 1H NMR (CDCl3, 400 MHz) δ 7.66 (br, 1 H), 7.57 (dd, J = 1.9, 6.8 Hz, 2 H), 7.28 (dd, J = 6.8, 1.9 Hz, 2 H), 7.18 (s, 2 H), 4.30 (sept, J = 6.8 Hz, 2 H), 2.90 (sept, J = 6.9 Hz, 1 H), 2.15 (s, 3 H), 1.30 (d, J = 6.8 Hz, 12 H), 1.25 (d, J = 6.9 Hz, 6 H) ppm. 13C NMR (CDCl3, 125 MHz) δ 153.7, 151.6, 149.5, 136.1, 135.6, 131.5, 128.6, 127.7, 124.0, 34.4, 30.2, 25.0, 23.7, 13.3 ppm. IR (film) 3244, 2961, 2926, 1599, 1462, 1383, 1362, 1331, 1306, 1265, 1165, 1099, 908, 831, 739, 679 cm⁻¹. HRMS (ESI, m/z): calcd for C23H31ClN2O2SNa [M+Na]⁺ 457.1692, found 457.1689. mp 150–151 °C.

(E)-N’-(3,4-dihydronaphthalen-1(2H)-ylidene)-2,4,6-triisopropylbenzenesulfonylhydrazide (2.3f)

The general procedure was followed using TPSH (2.24 g, 7.52 mmol), alpha-tetralone (1.00 g, 6.84 mmol) with MeOH (7.00 mL) as solvent for 5.0 h at rt. Workup C (precipitation in MeOH) provided the title compound 2.3f as a colorless solid (1.40 g, 48%). 1H NMR (CDCl3, 400 MHz) δ 7.94 (dd, J = 7.9, 1.0 Hz, 1 H), 7.50 (s, 1 H), 7.23 (dd, J = 7.4, 7.4, 1.4 Hz, 1 H), 7.17 (s, 2 H), 4.32 (sept, J = 6.8 Hz, 2 H), 2.90 (sept, J = 6.9 Hz, 1 H), 2.74 (t, J = 6.0 Hz, 2 H), 2.46 (t, J = 6.6 Hz, 2 H), 1.97–1.90 (m, 2 H), 1.32 (d, J = 6.8 Hz, 12 H), 1.25 (d, J = 6.9 Hz, 6 H) ppm. 13C NMR (CDCl3, 125 MHz) δ 153.4, 151.6, 150.8, 139.7, 132.0, 131.8, 129.4, 128.5, 126.3, 125.3, 123.9, 34.3, 30.2, 29.5, 25.5, 25.0, 23.7, 21.6 ppm. HRMS (ESI, m/z): calcd for C25H34N2O2SNa [M+Na]⁺ 449.2239, found 449.2237.
(E)-N’-(1,2-diphenylethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.3g)

The general procedure was followed using TPSH (1.67 g, 5.60 mmol), deoxybenzoin (1.00 g, 5.09 mmol), 4 drops of HCl with THF (0.010 L) as solvent for 1.5 h at rt. Workup A (precipitation in pentane/CH₂Cl₂) provided the title compound 2.3g as a colorless solid (1.14 g, 48%). ¹H NMR (CDCl₃, 400 MHz) δ 7.72 (d, J = 8.0 Hz, 2 H), 7.59 (s, 1 H), 7.35–7.27 (m, 6 H), 7.18–7.15 (m, 4 H), 4.13 (sept, J = 6.8 Hz, 2 H), 4.06 (s, 2 H), 2.90 (sept, J = 7.0 Hz, 1 H), 1.25 (d, J = 6.8 Hz, 2 H), 1.23 (d, J = 6.8 Hz, 12 H) ppm. ¹³C NMR (CDCl₃, 125 MHz) δ 153.6, 152.9, 151.8, 137.3, 134.1, 131.6, 129.8, 129.7, 128.5, 128.1, 127.6, 126.8, 124.0, 33.6, 30.4, 25.1, 23.7 ppm. HRMS (ESI, m/z): calcd for C₂₀H₂₆N₂O₂SNa [M+Na]⁺ 499.2395, found 499.2392.

(E)-2,4,6-triisopropyl-N’-(2-phenylcyclohexylidene)benzenesulfonohydrazide (2.5a)

The general procedure was followed using TPSH (1.72 g, 5.76 mmol), 2-phenylcyclohexanone (1.00 g, 5.74 mmol), 4 drops of HCl with MeOH (6.00 mL) as solvent for 3.0 h at rt. Workup C (precipitation in MeOH) provided the title compound 2.5a as a colorless solid (2.09 g, 80%). ¹H NMR (CDCl₃, 400 MHz) δ 7.45 (s, 1 H), 7.18 (s, 2 H), 7.12–7.05 (m, 3 H), 6.87 (d, J = 6.5 Hz, 2 H), 4.18 (sept, J = 6.7 Hz, 2 H), 3.60 (t, J = 5.0 Hz, 1 H), 2.95 (sept, J = 6.9 Hz, 1 H), 2.35–2.24 (m, 2 H), 2.00–1.88 (m, 2 H), 1.78–1.60 (m, 4 H), 1.30 (dd, J = 6.9, 2.1 Hz, 6 H), 1.21 (d, J = 6.7 Hz, 6 H), 1.18 (d, J = 6.8 Hz, 6 H) ppm. ¹³C NMR (CDCl₃, 125 MHz) δ 160.2, 153.2, 151.4, 140.2, 131.7, 128.3, 127.6, 126.2, 123.8, 47.9, 34.4, 30.8, 29.9, 25.9, 24.9, 23.8, 22.5 ppm. IR (film) 3232, 2955, 2359, 1643, 1599, 1427, 1393, 1327, 1263, 1167,
1009, 926, 883, 729, 702, 669 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{27}H_{39}N_{2}O_{2}S\) [M+H]\(^+\) 455.2732, found 455.2747. mp 130–131 °C.

\((E)-2,4,6\text{-triisopropyl-}\text{N'}-(1S,4S)-1,7,7\text{-trimethylbicyclo[2.2.1]heptan-2-ylidene)benzenesulfonohydrazide (2.5b)}\)

The general procedure was followed using TPSH (2.16 g, 7.23 mmol), camphor (1.00 g, 6.57 mmol), 2 drops of HCl with acetonitrile (0.010 L) as solvent for 6.0 h at rt. Workup C (precipitation in pentane/CH\(_2\)Cl\(_2\)) provided the title compound 2.5b as a colorless solid (0.860 g, 30%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.15 (s, 2 H), 6.97 (br, 1 H), 4.21 (sept, \(J = 6.8\) Hz, 2 H), 2.91 (sept, \(J = 6.9\) Hz, 1 H), 2.23 (dt, \(J = 16.6, 3.6\) Hz, 1 H), 1.96 (t, \(J = 4.4\) Hz, 1 H), 1.85–1.78 (m, 1 H), 1.73 (d, \(J = 16.7\) Hz, 1 H), 1.63 (td, \(J = 12.2, 4.2, 1\) H), 1.28–1.25 (m, 19 H), 1.17–1.10 (m, 1 H), 0.87 (d, \(J = 1.5\) Hz, 6 H), 0.62 (s, 3 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 169.1, 153.1, 151.5, 131.7, 123.7, 53.0, 48.1, 44.2, 34.3, 33.8, 32.5, 30.0, 27.4, 25.0, 23.7, 19.5, 18.8, 11.1 ppm. HRMS (ESI, \(m/z\)): calcd for C\(_{25}H_{40}N_{2}O_{2}SNa\) [M+Na]\(^+\) 455.2708, found 455.2692.

\(N'-(1\text{-benzylpiperidin-4-ylidene)-2,4,6\text{-triisopropylbenzenesulfonohydra}}zide (2.5d)\)

The general procedure was followed using TPSH (0.870 g, 2.90 mmol), \(N\)-benzyl-4-piperidone (0.500 g, 2.64 mmol) and 2 drops of HCl with THF (3.00 mL) as solvent for 3.5 h at rt. Workup B followed by chromatographic purification (CH\(_2\)Cl\(_2\)/MeOH) provided the title compound 2.5d as a colorless solid (0.800 g, 65%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.73 (br, 1 H), 7.30–7.22 (m, 5 H), 7.15 (s, 2 H), 4.24 (sept, \(J = 6.7\) Hz, 2 H), 3.48 (s, 2 H), 2.89 (sept, \(J = 6.9\) Hz, 1 H), 2.50 (t, \(J = 5.7\) Hz, 2 H), 2.46 (t, \(J = 5.7\) Hz, 2
H), 2.36–2.31 (m, 4 H), 1.24 (d, $J = 6.6$ Hz, 18 H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 156.9, 153.1, 151.4, 138.2, 131.6, 129.0, 128.4, 127.3, 123.8, 62.4, 53.5, 52.0, 34.6, 34.2, 29.9, 26.7, 24.9, 23.7 ppm. IR (film) 3236, 2959, 2868, 1599, 1458, 1425, 1364, 1319, 1165, 1151, 1032, 739, 698, 660 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{27}$H$_{39}$N$_3$O$_2$SNa [M+Na]$^+$ 492.2661, found 492.2638. mp 136–138 °C.

Preparation of Trisyl Hydrazone 2.3h

(E)-2,4,6-triisopropyl-$N'$-(1-phenylethylidene)benzenesulfonohydrazide (2.3h')

The general procedure was followed using TPSH (5.96 g, 20.0 mmol), acetophenone (2.00 g, 16.7 mmol) with MeOH (0.020 L) as solvent for 3.0 h at rt. Workup C (precipitation in MeOH) provided the title compound 2.3h' as a colorless solid (4.75 g, 71%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.75 (br, 1 H), 7.66–7.63 (m, 2 H), 7.34–7.29 (m, 3 H), 7.18 (s, 2 H), 4.33 (sept, $J = 6.8$ Hz, 2 H), 2.90 (sept, $J = 6.9$ Hz, 1 H), 2.18 (s, 3 H), 1.31 (d, $J = 6.8$ Hz, 12 H), 1.25 (d, $J = 6.9$ Hz, 6 H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 153.6, 151.6, 150.9, 137.6, 131.6, 129.6, 128.4, 126.5, 124.0, 34.4, 30.2, 25.0, 23.7, 13.3 ppm. HRMS (ESI, $m/z$): calcd for C$_{23}$H$_{32}$N$_2$O$_2$SNa [M+Na]$^+$ 423.2082, found 423.2086.

(E)-2,4,6-triisopropyl-$N'$-(1-phenylnonylidene)benzenesulfonohydrazide (2.3h)

n-BuLi (2.26 ml, 5.50 mmol) was added dropwise via syringe pump over a period of 15 min to a cooled solution of 2.3h' (1.00 g, 2.50 mmol) in THF (12.5 mL) at −78 °C. The reaction solution was stirred at −78 °C for 30 min, and then 1-bromoheptane (0.590 ml, 3.75 mmol) was added dropwise to the solution over a period of 5 min at −78 °C. The resulting solution was stirred at −78 °C for 1 h. Water was added at −78 °C, and then the solution was allowed to warm to rt. The aqueous layer was extracted with EtOAc (2 x 0.015 L), and combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using gradient hexane / ethyl acetate for elution to afford the compound 2.3h as a colorless solid (1.50 g, 60%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.65–7.62 (m,
3 H), 7.34–7.28 (m, 3 H), 7.17 (s, 2 H), 4.29 (sept, \( J = 6.8 \) Hz, 2 H), 2.90 (sept, \( J = 6.9 \) Hz, 1 H), 2.57 (t, \( J = 7.9 \) Hz, 2 H), 1.56–1.49 (m, 2 H), 1.44–1.36 (m, 2 H), 1.30 (d, \( J = 6.8 \) Hz, 12 H), 1.25 (d, \( J = 6.9 \) Hz, 6 H), 1.36–1.24 (m, 8 H), 0.89 (t, \( J = 6.9 \) Hz, 3 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 154.6, 153.5, 151.7, 136.9, 131.6, 129.7, 129.5, 128.4, 127.1, 126.6, 124.0, 123.9, 38.4, 34.4, 32.0, 30.2, 29.5, 29.3, 27.0, 26.0, 25.1, 23.7, 22.8, 21.4 ppm. IR (film) 3196, 2957, 2928, 1599, 1464, 1383, 1317, 1165, 1153, 941, 922, 764, 692, 662 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{30}\)H\(_{46}\)N\(_2\)O\(_2\)SNa [M+Na]\(^+\) 521.3178, found 521.3162. mp 97–98 °C.

**Preparation of Trisyl Hydrazine 2.3i**

\( (E) - N'-(1,3\text{-diphenylpropyldiene})-2,4,6\text{-triisopropylbenzenesulfonohydrazide} \) (2.3i)

\( n\)-BuLi (3.40 ml, 8.18 mmol) was added dropwise to a solution of 2.3h' (1.49 g, 3.72 mmol) in THF (20.0 mL) over a period of 15 min at –78 °C via syringe pump. The reaction solution was stirred at –78 °C for 1 h, and then benzyl bromide (0.670 ml, 5.58 mmol) was added dropwise to the solution over a period of 5 min at –78 °C. The resulting solution was stirred at –78 °C for 1.5 h, water was added at –78 °C, and then the solution was recovered to rt. The aqueous layer was extracted with EtOAc (2 x 0.015 L), and combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated. The crude product was purified by column chromatography using gradient hexane / ethyl acetate for elution to afford the compound 2.3i as a colorless solid (1.25 g, 69%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.68–7.65 (m, 2 H), 7.47 (s, 1 H), 7.37–7.28 (m, 6 H), 7.24–7.22 (m, 2 H), 7.17 (s, 2 H), 4.30 (sept, \( J = 6.8 \) Hz, 2 H), 2.93–2.82 (m, 5 H), 1.30 (d, \( J = 6.8 \) Hz, 12 H), 1.25 (d, \( J = 6.9 \) Hz, 6 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 153.5, 151.8, 140.3, 136.6, 131.4, 129.6, 128.9, 128.5, 128.4, 126.9, 126.6, 124.0, 34.4, 31.8, 30.2, 29.0, 25.1, 23.7 ppm. IR (film) 3233, 2961, 2928, 1599, 1458, 1425, 1383, 1315, 1165, 1153, 1036, 916, 740, 694,
660 cm⁻¹. HRMS (ESI, m/z): calcd for C₃₀H₃₈N₂O₂SNa [M+Na]⁺ 513.2552, found 513.2540. mp 155–157 °C.

**Preparation of Trisyl Hydrazone 2.5c**

![Reaction Scheme](image)

(E)-N’-(1-cyclohexylethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.5c)⁷

The general procedure was followed using TPSH (1.28 g, 4.29 mmol), 1-cyclohexylethanone (0.540 g, 4.29 mmol with MeOH (4.00 mL) as solvent for 5.0 h at rt. Workup C (precipitation in MeOH) provided the title compound 2.5c as a colorless solid (1.33 g, 76%). ¹H NMR (CDCl₃, 400 MHz) δ 7.16 (s, 3 H), 4.21 (sept, J = 6.7 Hz, 2 H), 2.91 (sept, J = 6.9 Hz, 1 H), 2.10–2.05 (m, 1 H), 1.73 (s, 3 H), 1.67–1.59 (m, 5 H), 1.28–1.25 (m, 18 H), 1.22–1.08 (m, 5 H) ppm. ¹³C NMR (CDCl₃, 125 MHz) δ 159.7, 153.2, 151.4, 131.8, 123.7, 46.8, 34.3, 30.0, 26.2, 26.0, 25.0, 23.7, 14.0 ppm. HRMS (ESI, m/z): calcd for C₂₅H₄₂N₃O₂S [M+NH₄]⁺ 424.2998, found 424.2990.

(E)-N’-(1-cyclohexyl-3-phenylpropylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.5c)

n-BuLi (0.480 ml, 1.08 mmol) was added dropwise to a solution of 2.5c (0.200 g, 0.490 mmol) in THF (2.50 mL) over a period of 5 min at −78 °C via syringe pump. The reaction solution was stirred at −78 °C for 1 h, and then benzyl bromide (0.090 ml, 0.735 mmol) was added dropwise to the solution over a period of 2 min at −78 °C. The resulting solution was stirred at −78 °C for 1 h. Water was added at −78 °C, and then the solution was allowed to warm to rt. The aqueous layer was extracted with EtOAc (2 x 0.003 L), and combined organic layer was dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography using gradient hexane / ethyl acetate for elution to afford the compound 2.5c as a colorless solid (0.155 g, 64%). ¹H NMR (CDCl₃, 400 MHz) δ 7.34–7.31 (m, 2 H), 7.25–7.23 (m, 1 H), 7.20–7.14 (m, 5 H), 4.19 (sept, J = 6.7 Hz, 2 H), 2.92 (sept, J = 6.9 Hz, 1 H), 2.78–2.74 (m, 2 H), 2.43–2.39 (m, 2 H), 2.01 (br, 1 H), 1.67–1.60 (m, 5 H), 1.27 (d, J = 6.7 Hz, 12 H), 1.26 (d,
\[ J = 6.9 \text{ Hz, } 6 \text{ H}, 1.19-1.11 \text{ (m, } 5 \text{ H) ppm. } ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz}) \delta 162.3, 153.3, 151.6, 140.5, 131.7, 128.9, 128.3, 126.8, 123.7, 45.8, 34.4, 31.2, 30.6, 30.5, 30.1, 26.2, 25.1, 23.8 \text{ ppm. IR (film) 3236, 2959, 2928, 2866, 1601, 1454, 1383, 1323, 1163, 1153, 941, 881, 746, 700, 660 cm}^{-1}\text{. HRMS (ESI, } m/z): \text{ calcd for C}_{30}\text{H}_{44}\text{N}_{2}\text{O}_{2}\text{SNa }\left[\text{M+Na}\right]^+ 519.3021, \text{ found 519.3018. mp 135–136 °C.}

\text{Preparation of Trisyl Hydrazone 2.5e}

\text{(S)-1-benzyl-N-methoxy-N-methylpyrrolidine-2-carboxamide (2.5e″) }

\text{(L)-N-Benzyl–proline (2.98 g, 15.5 mmol) was suspended in CH}_2\text{Cl}_2 \text{ (0.070 L), and HN(OMe)Me•HCl (1.42 g, 14.5 mmol), diisopropylethylamine (2.40 mL, 14.5 mmol) and EDCI (2.78 g, 14.5 mmol) were added into the reaction mixture sequentially at 0 °C. The resulting reaction solution was stirred at 0 °C for 2 h, and then water was added to quench the reaction. The organic layer was collected, and the aqueous layer was extracted further with CH}_2\text{Cl}_2 \text{ (2 x 0.030 L). The combined organic layer was dried over anhydrous Na}_2\text{SO}_4\text{, concentrated, and the residue was purified by column chromatography using gradient MeOH in CH}_2\text{Cl}_2 \text{ (2% to 5%) for elution to offer 2.5e″ as a liquid (1.41 g, 39%). } ^{1}\text{H NMR (CDCl}_3, 400 \text{ MHz}) \delta 7.36-7.22 \text{ (m, } 5 \text{ H), 3.94 (d, } J = 12.8 \text{ Hz, } 1 \text{ H), 3.57-3.56 \text{ (m, } 4 \text{ H), 3.55 (d, } J = 12.8 \text{ Hz, } 1 \text{ H), 3.17 (s, } 3 \text{ H), 3.13-3.08 \text{ (m, } 1 \text{ H), 2.44 (q, } J = 8.2 \text{ Hz, } 1 \text{ H), 2.19–2.10 \text{ (m, } 1 \text{ H), 1.96–1.75 \text{ (m, } 3 \text{ H) ppm. IR (film) 2964, 2939, 2874, 2359, 2341, 1663, 1454, 1387, 1312, 1177, 999, 745, 700 cm}^{-1}\text{. HRMS (ESI, } m/z): \text{ calcd for C}_{14}\text{H}_{21}\text{N}_{2}\text{O}_{2} [\text{M+H}]^+ 249.1603, \text{ found 249.1591.}}

\text{(S)-1-(1-benzylpyrrolidin-2-yl)ethanone (2.5e′)8} 

\text{2.5e″ (1.34 g, 5.40 mmol) was dissolved in dry ether (0.050 L) and cooled to 0 °C. Methylmagnesium bromide (2.52 mL, 7.56 mmol) was added dropwise into the solution over 10 min at 0 °C. The solution was stirred at this temperature for 1 h and quenched with NH}_4\text{Cl (sat'd). The organic layer was collected}
and the aqueous layer was extracted further with EtOAc (2 x 0.025 L). The combined organic layer was
dried over anhydrous Na₂SO₄, concentrated, and the residue was purified by column chromatography
using gradient MeOH in CH₂Cl₂ (2% to 4%) for elution to offer 2.5e' as a liquid (0.930 g, 85%). ¹H NMR
(CDCl₃, 400 MHz) δ 7.35–7.24 (m, 5 H), 3.82 (d, J = 13.0 Hz, 1 H), 3.45 (d, J = 13.0 Hz, 1 H), 3.13–3.07
(m, 2 H), 2.33–2.27 (m, 1 H), 2.15 (s, 3 H), 2.13–2.06 (m, 1 H), 1.90–1.76 (m, 3 H) ppm. HRMS (ESI,
m/z): calcd for C₁₃H₁₈NO [M+H]⁺ 204.1388, found 204.1392.

(S,E)-N'-(1-(1-benzylpyrrolidin-2-yl)ethylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.5e)
The general procedure was followed using TPSH (1.39 g, 4.65 mmol), 2.5e' (0.860 g, 4.23 mmol) with
THF (4.5 mL) as solvent for 4.0 h at rt. Workup B followed by chromatographic purification
(CH₂Cl₂/MeOH) provided the title compound 2.5e as a colorless solid (1.79 g, 88%). ¹H NMR (CDCl₃,
400 MHz) δ 7.34 (s, 1 H), 7.23–7.18 (m, 3 H), 7.14 (s, 2 H), 7.06 (dd, J = 7.6, 2.1 Hz, 2 H), 4.26 (sept, J
= 6.7 Hz, 2 H), 3.44 (d, J = 13.4 Hz, 1 H), 3.04–3.01 (m, 2 H), 2.93–2.88 (m, 1 H), 2.84 (sept, J = 6.9 Hz,
1 H), 2.12 (q, J = 8.4 Hz, 1 H), 1.92–1.82 (m, 1 H), 1.76 (s, 3 H), 1.75–1.61 (m, 3 H), 1.30 (d, J = 6.7 Hz,
6 H), 1.25 (d, J = 6.8 Hz, 6 H), 1.18 (t, J = 6.7 Hz, 6 H) ppm. ¹³C NMR (CDCl₃, 125 MHz) δ 157.3, 153.3,
151.4, 138.9, 131.5, 129.0, 128.2, 126.9, 123.8, 69.6, 57.6, 53.2, 34.3, 30.0, 28.7, 25.1, 25.0, 23.6, 23.3,
10.7 ppm. IR (film) 3231, 2959, 2868, 2359, 2341, 1599, 1458, 1425, 1383, 1364, 1323, 1165, 1153,
1038, 912, 739, 698, 667 cm⁻¹. HRMS (ESI, m/z): calcd for C₂₈H₄₁N₃O₂SNa [M+Na]⁺ 506.2817, found
506.2793. mp 134–135 °C.

Preparation of Trisyl Hydrazone 2.5f

![Chemical structure](image)

(3S,10R,13S)-3-((tert-butyldiphenylsilyl)oxy)-10,13-dimethyl-3,4,7,8,9,10,11,12,13,14,15,16-
dodecahydro-1H-cyclopenta[a]phenanthren-17(2H)-one (2.5f)⁹
(+)-Dehydroepiandrosterone (0.300 g, 1.04 mmol) was dissolved in dry DMF (0.010 L) at rt, and then imidazole (177 mg, 2.60 mmol) was added at 0 °C. The resulting solution was stirred at 0 °C for 15 min, and then TBDPSCl (0.540 mL, 2.08 mmol) was added dropwise. The solution was stirred at 50 °C overnight. A solution of saturated NH₄Cl (5.0 mL) was added at rt and stirred for additional 30 min. DMF was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layer was dried over anhydrous NaSO₄, concentrated and purified by column chromatography using gradient elution (EtOAc/hexanes) to furnish 2.5f⁻ as a colorless foam (500 mg, 91%). ¹H NMR (CDCl₃, 400 MHz) δ 7.71–7.68 (m, 4 H), 7.42–7.38 (m, 6 H), 5.17 (d, J = 5.3 Hz, 1 H), 3.59–3.52 (m, 1 H), 1.48–2.45 (m, 17 H), 1.27–1.19 (m, 2 H), 1.08 (s, 9 H), 1.03 (s, 3 H), 0.87 (s, 3 H) ppm. HRMS (ESI, m/z): calcd for C₃₅H₄₇O₂Si [M+H]+ 527.3345, found 527.3337.

(E)-N’-((3S,10R,13S)-3-((tert-butyldiphenylsilyl)oxy)-10,13-dimethyl-3,4,7,8,9,11,12,13,15,16-decahydro-1H-cyclopenta[a]phenanthren-17(2H,10H,14H)-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (2.5f)

The general procedure was followed using TPSH (401 mg, 1.34 mmol), 2.5f⁻ (590 mg, 1.12 mmol) with THF (1.0 mL) as solvent for 6.0 h at 40 °C. Workup C followed by chromatographic purification (EtOAc / hexanes) provided the title compound 2.5f as a colorless solid (230 mg, 25%). ¹H NMR (CDCl₃, 400 MHz) δ 7.69–7.66 (m, 4 H), 7.44–7.35 (m, 6 H), 7.15 (s, 2 H), 6.92 (s, 1 H), 5.12–5.11 (m, 1 H), 4.19 (sept, J = 6.7 Hz, 2 H), 3.54–3.48 (m, 1 H), 3.90 (sept, J = 6.9 Hz, 1 H), 2.19–2.35 (m, 2 H), 2.04–2.15 (m, 2 H), 1.94–1.96 (m, 1 H), 1.76–1.86 (m, 2 H), 1.69–1.36 (m, 8 H), 1.27–1.24 (m, 19 H), 1.06–0.97 (m, 13 H), 0.86–0.80 (m, 2 H), 0.73 (s, 3 H) ppm. ¹³C NMR (CDCl₃, 125 MHz) δ 169.8, 153.2, 151.5, 141.7, 136.0, 135.0, 131.7, 129.7, 127.7, 123.7, 120.6, 73.3, 53.9, 50.4, 44.8, 42.6, 37.3, 36.8, 34.3, 33.8, 32.0, 31.5, 31.4, 30.1, 27.2, 26.0, 25.1, 25.0, 23.8, 23.6, 20.6, 19.6, 19.3, 16.8 ppm. IR (film) 3441, 2959, 2932, 2359, 1653, 1636, 1427, 1381, 1325, 1165, 1153, 1109, 1086, 741, 702, 667 cm⁻¹. HRMS (ESI, m/z): calcd for C₅₀H₇₄N₃O₃SSi [M+NH₄]+ 824.5220, found 824.5190. mp 117–118 °C.
General Procedure for the Shapiro Fluorination of Trisyl Hydrazones 2.1a, 2.3a–i, 2.5a–f

An oven-dried round bottom flask was charged with the trisylhydrazone 2.1a, 2.3a–i, and 2.5a–f (1.0 equiv) and a magnetic stir bar. The reaction vessel was equipped with a three-way valve, evacuated and backfilled with nitrogen. Dry THF (c = 0.20 M) was added and the mixture was stirred at room temperature until the trisylhydrazone dissolved. The solution was cooled to –78 °C, and then base (2.2 equiv) was added dropwise to the stirred solution. The resulting solution was stirred at –78 °C for 30 min to generate the dianion, and then at 0 °C for 20 min to release N₂. Subsequently, the reaction was cooled to –78 °C, and then a solution of NFSI (1.5 equiv, c = 0.49 ~ 0.5 M in THF) was added dropwise over 2 min. Additional THF (0.1 mL) was used to wash the vial, and added successively. The resulting solution was stirred at –78 °C for 30 min, and then at rt for 2 h. A 1 N solution of α,α,α-trifluorotoluene in EtOAc (100 µL, 0.10 mmol) was added as an internal standard, and the resulting mixture was stirred at rt for 5 min. After standing for 3 min, an aliquot of the upper clear solution was removed and subjected to ¹⁹F NMR analysis to determine the yield of fluoroalkene 2.2a, 2.4a–i, and 2.6a–f. After the ¹⁹F NMR analysis, the NRM sample was returned to the bulk of the reaction mixture, and the combined mixture was concentrated under reduced pressure. The resulting residue was added to a solution of NaHCO₃ (1.0 mL), stirred, and extracted with ether (3 x 5 mL). (In some cases, EtOAc was used for extraction.) The organic layers were dried over anhydrous Na₂SO₄, and concentrated. Purification by flash chromatography provided the desired product.

4-(1-fluorovinyl)-1,1'-biphenyl (2.2a)

The general procedure was followed using 2.1a (119 mg, 0.250 mmol), n-BuLi (0.240 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided the title compound 2.2a as a colorless solid (38.4 mg, 75%). ¹H NMR (CDCl₃, 400 MHz) δ 7.67–7.62 (m, 6 H),
7.50–7.46 (m, 2 H), 7.41–7.38 (m, 1 H), 5.10 (dd, \( J = 49.7 \), 3.5 Hz, 1 H), 4.90 (dd, \( J = 17.8 \), 3.5 Hz, 1 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 163 (d, \( J = 248.5 \) Hz), 142.3, 140.5, 131.1 (\( J = 29.3 \) Hz), 129.1, 127.9, 127.4, 127.2, 125.3 (\( J = 6.9 \) Hz), 89.8 (\( J = 22.3 \) Hz) ppm. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –107.9 (dd, \( J_{F-H} = 49.6, 18.1 \) Hz, 1 F) ppm. IR (film) 2359, 2341, 1647, 1404, 1292, 843, 766, 689 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{14}\)H\(_{11}\)FNa [M+Na]\(^+\) 221.0742, found 221.0748. mp 120–121 °C.

### 4-(4-(1-fluorovinyl)phenyl)morpholine (2.4a)

The general procedure was followed using 2.3a (121 mg, 0.250 mmol), n-BuLi (0.240 mL, 0.550 mmol), and NFSI (86.7 mg, 0.275 mmol). Workup and chromatographic purification (2% EtOAc in hexanes) provided the title compound 2.4a as a colorless solid (35.0 mg, 68%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.48 (d, \( J = 8.8 \) Hz, 2 H), 6.89 (d, \( J = 8.5 \) Hz, 2 H), 4.87 (dd, \( J = 50.4 \), 3.4 Hz, 1 H), 4.71 (dd, \( J = 18.2 \), 3.4 Hz, 1 H), 3.87 (t, \( J = 4.9 \) Hz, 4 H), 3.22 (t, \( J = 4.9 \) Hz, 4 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 163.3 (d, \( J = 247.1 \) Hz), 152.0, 125.9 (d, \( J = 7.0 \) Hz), 123.4 (d, \( J = 29.8 \) Hz), 114.9 (d, \( J = 1.5 \) Hz), 87.2 (d, \( J = 22.8 \) Hz), 66.9, 48.8 ppm. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –107.7 (dd, \( J_{F-H} = 50.4, 18.1 \) Hz, 1 F) ppm. IR (film) 2856, 2359, 1645, 1518, 1279, 1265, 1123, 920, 849, 822 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{12}\)H\(_{15}\)FNO [M+H]\(^+\) 208.1138, found 208.1129. mp 111–112 °C.

![Image 2.4a](image)

### (4-(1-fluorovinyl)phenyl)(methyl)sulfane (2.4b)

The general procedure was followed using 2.3b (223 mg, 0.500 mmol), n-BuLi (0.470 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound 2.4b as a light yellow solid (60.0 mg, 67%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.48 (d, \( J = 8.4 \) Hz, 2 H), 6.86 (d, \( J = 7.8 \) Hz, 2 H), 4.77 (dd, \( J = 3.4 \), 3.4 Hz, 1 H), 3.88 (t, \( J = 4.9 \) Hz, 4 H), 3.24 (t, \( J = 4.9 \) Hz, 4 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 163.3 (d, \( J = 247.1 \) Hz), 152.0, 125.9 (d, \( J = 7.0 \) Hz), 123.4 (d, \( J = 29.8 \) Hz), 114.9 (d, \( J = 1.5 \) Hz), 87.2 (d, \( J = 22.8 \) Hz), 66.9, 48.8 ppm. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –107.7 (dd, \( J_{F-H} = 50.4, 18.1 \) Hz, 1 F) ppm. IR (film) 2856, 2359, 1645, 1518, 1279, 1265, 1123, 920, 849, 822 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{12}\)H\(_{15}\)FNO [M+H]\(^+\) 208.1138, found 208.1129. mp 111–112 °C.

![Image 2.4b](image)
2 H), 7.24 (d, J = 8.4 Hz, 2 H), 4.99 (dd, J = 49.9, 3.5 Hz, 1 H), 4.82 (dd, J = 17.9, 3.5 Hz, 1 H), 2.51 (s, 3 H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 162.8 (d, J = 248 Hz), 140.6, 128.8 (d, J = 29.6 Hz), 126.1 (d, J = 1.5 Hz), 125.1 (d, J = 7.0 Hz), 89.1 (d, J= 22.6 Hz), 15.6 ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –108.1 (dd, $^3$J$_{F-H}$ = 50.0, 18.1 Hz, 1 F) ppm. IR (film) 2922, 2361, 1647, 1493, 1396, 1288, 1107, 922, 821, 739 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_9$H$_9$FSNa [M+Na]$^+$ 191.0307, found 191.0316. mp 48–49 °C.

![2.4c](image)

**1-(1-fluorovinyl)-4-methoxybenzene (2.4c)$^{10}$**

The general procedure was followed using 2.3c (215 mg, 0.500 mmol), n-BuLi (0.490 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound 2.4c as a colorless liquid (41.0 mg, 54%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.50 (d, J = 8.8 Hz, 2 H), 6.90 (d, J = 8.7 Hz, 2 H), 4.89 (dd, J = 50.2, 3.4 Hz, 1 H), 4.74 (dd, J = 18.1, 3.4 Hz, 1 H), 3.84 (s, 3 H) ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –107.2 (dd, $^3$J$_{F-H}$ = 50.0, 18.1 Hz, 1 F) ppm. HRMS (ESI, m/z): calcd for C$_9$H$_{13}$FON [M+NH$_4$]$^+$ 170.0981, found 170.0977.

![2.4d](image)

**1-(1-fluorovinyl)-3-methoxybenzene (2.4d)$^{11}$**

The general procedure was followed using 2.3d (86.1 mg, 0.200 mmol), n-BuLi (0.220 mL, 0.500 mmol), and NFSI (110 mg, 0.350 mmol). Workup and chromatographic purification (hexanes) provided the title compound 2.4d as a colorless liquid (13.0 mg, 43%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.32–7.28 (m, 1 H), 7.17 (d, J = 7.8 Hz, 1 H), 7.10–7.09 (m, 1 H), 6.92 (dd, J = 8.2, 2.6 Hz, 1 H), 5.04 (dd, J = 49.6, 3.5 Hz, 1 H), 4.87 (dd, J = 17.8, 3.5 Hz, 1 H), 3.84 (s, 3 H) ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –107.4 (dd, $^3$J$_{F-H}$ = 49.6, 18.1 Hz, 1 F) ppm. HRMS (ESI, m/z): calcd for C$_9$H$_{10}$FO [M+H]$^+$ 153.0716, found 153.0720.
1-chloro-4-(1-fluorovinyl)benzene (2.4e)\textsuperscript{12}

The general procedure was followed using \textbf{2.3e} (218 mg, 0.500 mmol), \textit{n}-BuLi (0.470 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound \textbf{2.4e} as a colorless liquid (60.0 mg, 67\%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.50 (d, \(J = 8.7\) Hz, 2 H), 7.36 (d, \(J = 8.7\) Hz, 2 H), 5.03 (dd, \(J = 49.4\), 3.6 Hz, 1 H), 4.89 (dd, \(J = 17.8\), 3.6 Hz, 1 H) ppm. \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 376 MHz) \(\delta\) –107.9 (dd, \(3^J_{F-H} = 49.3\), 17.7 Hz, 1 F) ppm. HRMS (ESI, \(m/z\)): calcd for C\textsubscript{8}H\textsubscript{6}ClFNa [M+Na]\textsuperscript{+} 179.0040, found 179.0032.

4-fluoro-1,2-dihydronaphthalene (2.4f)\textsuperscript{13}

The general procedure was followed using \textbf{2.3f} (213 mg, 0.500 mmol), \textit{n}-BuLi (0.470 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound \textbf{2.4f} as a colorless liquid (37.0 mg, 50\%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.39–7.37 (m, 1 H), 7.26–7.20 (m, 2 H), 7.17–7.15 (m, 1 H), 5.49 (dt, \(J = 14.0\), 4.6 Hz, 1 H), 2.84 (t, \(J = 8.1\) Hz, 2 H), 2.44–2.37 (m, 2 H) ppm. \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 376 MHz) \(\delta\) –127.0 (ddt, \(3^J_{F-H} = 13.9\) Hz, \(4^J_{F-H} = 5.1\), 2.1 Hz, 1 F) ppm. HRMS (ESI, \(m/z\)): calcd for C\textsubscript{10}H\textsubscript{9}FNa [M+Na]\textsuperscript{+} 171.0586, found 171.0593.

\((Z)-(1\text{-fluoroethene-1,2-diyl})\text{dibenzene} \ (2.4g)\textsuperscript{14}\)
The general procedure was followed using 2.3g (238 mg, 0.500 mmol), s-BuLi (1.00 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound 2.4g as a colorless solid (82.3 mg, 83%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.69–7.67 (m, 4 H), 7.46–7.37 (m, 5 H), 7.31–7.27 (m, 1 H), 6.34 (d, $J$ = 39.5 Hz, 1 H) ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –114.2 (d, $^3J_{F-H}$ = 39.9 Hz, 1 F) ppm. HRMS (ESI, m/z): calcd for C$_{14}$H$_{11}$FNa [M+Na]$^+$ 221.0742, found 221.0749.

\[ \text{(Z)-(1-fluoronon-1-en-1-yl)benzene (2.4h)} \]

The general procedure was followed using 2.3h (249 mg, 0.500 mmol), n-BuLi (0.45 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound 2.4h as a colorless liquid (85.3 mg, 77%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.52–7.50 (m, 2 H), 7.38–7.28 (m, 3 H), 5.41 (dt, $J$ = 37.6, 7.6 Hz, 1 H), 2.32–2.26 (m, 2 H), 1.50–1.23 (m, 10 H), 0.90 (t, $J$ = 6.8 Hz, 3 H) ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –121.5 (d, $^3J_{F-H}$ (trans) = 37.2 Hz, 1 F, Z isomer), –102.8 (d, $^3J_{F-H}$ (cis) = 22.9 Hz, 1 F, E isomer) ppm. HRMS (ESI, m/z): calcd for C$_{15}$H$_{21}$FNa [M+Na]$^+$ 243.1525, found 243.1531.

\[ \text{(Z)-(1-fluoroprop-1-ene-1,3-diyl)dibenzene (2.4i)} \]

The general procedure was followed using 2.3i (245 mg, 0.500 mmol), n-BuLi (0.49 mL, 1.10 mmol), and NFSI (237 mg, 0.750 mmol). Workup and chromatographic purification (hexanes) provided the title compound 2.4i as a colorless liquid (46.0 mg, 43%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.56–7.22 (m, 10 H), 5.61 (dt, $J$ = 36.3, 7.7 Hz, 1 H), 3.66 (dd, $J$ = 7.7, 1.4 Hz, 2 H) ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –
121.0 (d, \( J_{F-H}^{\text{trans}} = 36.5 \text{ Hz}, 1 \ F, Z \text{ isomer} \)), \(-100.1 \ (d, \ J_{F-H}^{\text{cis}} = 21.4 \text{ Hz}, 1 \ F, E \text{ isomer}) \) ppm. HRMS (ESI, \( m/z \)): calcd for C\(_{12}\)H\(_{13}\)FNa [M+Na]\(^+\) 235.0899, found 235.0891.

6-fluoro-2,3,4,5-tetrahydro-1,1’-biphenyl (2.6aA)

The general procedure was followed using 2.5a (114 mg, 0.250 mmol), \( t-\text{BuLi} \) (0.400 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided compound 2.6aA as a colorless liquid (29.0 mg, 61%). \( ^1\text{H NMR (CDCl}_3, 400 \text{ MHz)} \delta 7.43–7.41 \) (m, 2 H), 7.37–7.32 (m, 1 H), 7.26–7.21 (m, 2 H), 2.46–2.40 (m, 2 H), 2.39–2.34 (m, 2 H), 1.87–1.80 (m, 2 H), 1.78–1.71 (m, 2 H) ppm. \( ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)} \delta 155.8 \) (d, 257 Hz), 137.8, 128.2, 127.9 (d, 6.9 Hz), 126.8, 113.7 (d, 6.9 Hz), 128.9 (d, 6.9 Hz), 23.0 (d, 9.5 Hz), 22.9 ppm. \( ^{19}\text{F NMR (CDCl}_3, 376 \text{ MHz)} \delta -104.0 \) (s, 1 F) ppm. IR (film) 2934, 1686, 1493, 1445, 1360, 1117, 760, 696 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{12}\)H\(_{14}\)F [M+H]\(^+\) 177.1080, found 177.1078.

(1S,4S)-2-fluoro-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (2.6b)

The general procedure was followed using 2.5b (433 mg, 1.00 mmol), \( s-\text{BuLi} \) (1.64 mL, 2.20 mmol), and NFSI (473 mg, 1.50 mmol). Workup and chromatographic purification (pentane) provided compound 2.6b as a colorless liquid (68.0 mg, 44%). \( ^1\text{H NMR (CDCl}_3, 500 \text{ MHz)} \delta 4.96 \) (d, 3.6 Hz, 1 H), 2.32–2.28 (m, 1 H), 1.91–1.85 (m, 1 H), 1.64–1.59 (m, 1 H), 1.34–1.29 (m, 1 H), 1.16–1.11 (m, 1 H), 0.94 (s, 3 H), 0.76 (s, 3 H) ppm. \( ^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz)} \delta 168.4 \) (d, 293.6 Hz), 103.2 (d, 2.1 Hz), 56.3 (d, 6.0 Hz), 52.2 (d, 17.6 Hz), 49.0 (d, 6.0 Hz), 31.5 (d, 4.1 Hz), 26.7 (d, 4.1 Hz), 22.9 ppm. IR (film) 2934, 1686, 1493, 1445, 1360, 1117, 760, 696 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{12}\)H\(_{14}\)F [M+H]\(^+\) 177.1080, found 177.1078.
3.5 Hz), 20.0, 19.6, 9.3 ppm. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta -131.7\) (s, 1 F) ppm. HRMS (ESI, \(m/z\)):
calcd for C\(_{16}\)H\(_{15}\)FNa [M+Na]\(^+\) 177.1055, found 177.1053.

\((E)-(3\text{-cyclohexyl-3-fluoroallyl})\text{benzene (2.6c)}\)

The general procedure was followed using 2.5c (124 mg, 0.250 mmol), \(n\)-BuLi (0.240 mL, 0.550 mmol),
and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided
compound 2.6c (\(E\)) as a colorless liquid (25.0 mg, 46%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 7.33–7.29\) (m, 2 H),
7.24–7.19 (m, 3 H), 5.12 (dt, \(J = 22.000, 8.2\) Hz, 1 H), 3.33 (d, \(J = 8.2\) Hz, 2 H), 2.51 (dtt, \(J = 30.8,
11.9, 3.4\) Hz, 1 H), 1.84–1.80 (m, 2 H), 1.74–1.70 (m, 3 H), 1.59–1.49 (m, 2 H), 1.34–1.15 (m, 3 H) ppm.
\(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 164\) (d, \(J = 249.6\) Hz), 140.8, 128.7, 128.3, 126.3, 102.8 (d, \(J = 24.4\) Hz),
37.4 (d, \(J = 26\) Hz), 31.4 (d, \(J = 10.1\) Hz), 29.6, 26.3, 25.9 ppm. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta -114.6\)
(dd, \(J = 30.8, 22.2\) Hz, 1 F, \(E\) isomer), \(-113.8\) (dd, \(J = 38.0, 13.9\) Hz, 1 F, \(Z\) isomer) ppm. IR (film) 2930,
2855, 1693, 1493, 1450, 1148, 1130, 735, 696 cm\(^{-1}\). HRMS (ESI, \(m/z\)):
calcd for C\(_{15}\)H\(_{19}\)FNa [M+Na]\(^+\) 241.1368, found 241.1366.

\(1\text{-benzyl-4-fluoro-1,2,3,6-tetrahydropyridine (2.6d)}\)

The general procedure was followed using 2.5d (117 mg, 0.250 mmol), \(n\)-BuLi (0.240 mL, 0.550 mmol),
and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (10% ether in hexanes)
provided compound 2.6d as a colorless liquid (11.0 mg, 23%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 7.36–7.28\)
(m, 5 H), 5.17 (dtt, \(J = 15.0, 7.1, 1.2\) Hz, 1 H), 3.63 (s, 2 H), 3.04–3.01 (m, 2 H), 2.69 (td, \(J = 5.8, 2.1\) Hz,
2 H), 2.34–2.31 (m, 2 H) ppm. \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 158.4\) (d, \(J = 256\) Hz), 138.4, 129.2, 128.5,
127.4, 100.5 (d, \( J = 14.6 \) Hz), 62.0 (d, \( J = 2.5 \) Hz), 50.3 (d, \( J = 9.1 \) Hz), 49.5 (d, \( J = 10.1 \) Hz), 26.7 (d, \( J = 22.4 \) Hz) ppm. \(^{19}\)F NMR (CDCl3, 376 MHz) \( \delta -104.3 \) (d, \( J = 15.4 \) Hz, 1 F) ppm. IR (film) 2928, 2802, 1713, 1454, 1375, 1119, 1028, 741, 700 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for \( \text{C}_{12}\text{H}_{15}\text{FN} \) [M+H]\(^+\) 192.1189, found 192.1186.

(S)-1-benzyl-2-(1-fluorovinyl)pyrrolidine (2.6e)

The general procedure was followed using \( 2.5e \) (121 mg, 0.250 mmol), \( n\)-BuLi (0.230 mL, 0.550 mmol), and NFSI (118 mg, 0.375 mmol). Workup and chromatographic purification (hexanes) provided compound \( 2.6e \) as a colorless liquid (37.0 mg, 72%). \(^1\)H NMR (CDCl3, 400 MHz) \( \delta 7.26-7.17 \) (m, 5 H), 4.60 (dd, \( J = 17.1, 2.5 \) Hz, 1 H), 4.52 (dd, \( J = 49.7, 2.5 \) Hz, 1 H), 4.02 (d, \( J = 13.1 \) Hz, 1 H), 3.25 (d, \( J = 13.1 \) Hz, 1 H), 3.07–2.99 (m, 1 H), 2.91 (t, \( J = 7.9 \) Hz, 1 H), 2.18 (q, \( J = 8.6 \) Hz, 1 H), 2.01–1.84 (m, 2 H), 1.80–1.66 (m, 2 H) ppm. \(^{13}\)C NMR (CDCl3, 125 MHz) \( \delta 166.8 \) (d, \( J = 258.8 \) Hz), 139.4, 129.0, 128.4, 127.1, 91.1 (d, \( J = 18.8 \) Hz), 64.5 (d, \( J = 29.1 \) Hz), 58.3, 53.4, 29.3, 23.0 ppm. \(^{19}\)F NMR (CDCl3, 376 MHz) \( \delta -108.3 \) (dt, \( J = 49.6, 17.7 \) Hz, 1 F) ppm. IR (film) 2970, 2797, 1672, 1495, 1454, 1277, 1202, 910, 854, 739, 698 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for \( \text{C}_{13}\text{H}_{16}\text{FNNa} \) [M+Na]\(^+\) 228.1164, found 228.1158.

\textit{tert}-butyl((3S,10R,13S)-17-fluoro-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)diphenylsilane (2.6f)

The general procedure was followed using \( 2.5f \) (121 mg, 0.150 mmol), \( n\)-BuLi (0.150 mL, 0.330 mmol), and NFSI (71 mg, 0.225 mmol). Workup and chromatographic purification (hexanes) provided compound \( 2.6f \) as a colorless liquid (29.0 mg, 38%). \(^1\)H NMR (CDCl3, 400 MHz) \( \delta 7.70-7.67 \) (m, 4 H), 7.45 –7.35
(m, 6 H), 5.15 (d, J = 5.3 Hz, 1 H), 4.88–4.87 (m, 1 H), 3.58–3.50 (m, 1 H), 2.38–2.32 (m, 1 H), 2.18–2.13 (m, 1 H), 2.06–1.99 (m, 1 H), 1.97–1.80 (m, 2 H), 1.77–1.67 (m, 3 H), 1.65–1.57 (m, 2 H), 1.52–1.46 (m, 2 H), 1.41–1.34 (m, 1 H), 1.27 (br, 1 H), 1.07 (s, 9 H), 1.03 (s, 3 H), 0.97 (s, 3 H), 0.96–0.83 (m, 3 H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 172.0 (d, $J = 287.1$ Hz), 141.9, 136.0, 135.0, 129.7 (d, $J = 2.3$ Hz), 127.7 (d, $J = 2.8$ Hz), 120.8, 100.7 (d, $J = 10.1$ Hz), 73.4, 54.8 (d, $J = 5.6$ Hz), 50.9, 42.7, 42.5, 37.3, 36.9, 33.0, 32.1, 30.8, 30.1, 27.2, 27.1 (d, $J = 7.0$ Hz), 20.4, 19.5, 19.4, 15.3 (d, $J = 4.0$ Hz) ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –131.9 (d, $J = 4.5$ Hz, 1 F) ppm. IR (film) 2932, 2856, 1651, 1462, 1427, 1371, 1109, 799, 739, 702, 613, 509 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{35}$H$_{45}$FOSiNa $[M+Na]^+$ 551.3121, found 551.3145.

**One-Pot Sequence Converting Ketones to Fluoroalkenes 2.8a–c**

An oven-dried round flask (25 mL) was charged with ketone 2.7a–c (0.50 mmol), TPSH (0.50 mmol) and a magnetic stir bar. The reaction vessel was equipped with a three-way valve, evacuated and backfilled with nitrogen. A pre-prepared stock solution of TFA (0.050 mmol) in THF (1.0 mL) was added and the reaction mixture was stirred at rt for 1.5 h. Then, the reaction solution was diluted with additional THF (1.5 mL) followed by the addition of activated 4Å molecular sieves (400 mg) and stirred at rt for 10 min. The solution was cooled to –78 °C, and then n-BuLi (1.5 mmol) was added dropwise into the pre-cooled and stirred solution at –78 °C. The resulting solution was stirred at –78 °C for 30 min to generate the dianion and at 0 °C for 20 min to release N$_2$. Subsequently, the reaction solution was cooled to –78 °C, and then a solution of NFSI (0.75 mmol, $c = 0.50$ M in THF) was added dropwise over 4 min. Additional THF (0.1 mL) was used to wash the vial, and added successively. The resulting solution was stirred at –78 °C for 30 min, and then at rt for 2 h. 0.50 N $\alpha,\alpha,\alpha$-trifluorotoluene in EtOAc (200 µL, 0.10 mmol) was added as an internal standard and the resulting mixture was stirred at rt for 5 min. After standing for 3 min, an aliquot of the upper clear solution was removed and subjected to $^{19}$F NMR analysis to determine yields of fluoroalkene 2.8a–c.
References for Chapter 2 Experimental Section


16. The ratio of Z to E isomers was determined by 19F NMR of crude product. After column purification, the minor isomer was removed mostly. From 1H and 13C NMR, the minor isomer was not observed apparently, thus only peaks for the major isomer were assigned. However, the minor isomer still was seen in 19F NMR.

Chapter 3. Palladium-Catalyzed Decarboxylative Benzylation of α,α-Difluoroketone Enolates

3.1 Introduction to α,α-Difluoroketones

The α,α-difluoroketone represents a privileged substructure in medicinal chemistry, and serves as inhibitors to many hydrolytic enzymes, such as serine and aspartyl proteases. For this substructure, the electron-withdrawing difluorinated group increases electrophilicity of the carbonyl group and encourages rehybridization of the sp²-hybridized C=O to form sp³-hybridized hydrates or hemi-hydrates (Figure 3.1). In the hydrates, sp³-hybridized carbon forms more stable bonding with electron-deficient fluorinated groups based on Bent’s rule, which requires that an atom uses more p-character in forming a bond with an electronegative substituent. Thus, the equilibrium constant shifts toward the direction of hydrates. The stabilized tetrahedral hydrate intermediates mimic the transition state of hydrolytic processes catalyzed by proteases and inhibit enzymes from acting on their peptide substrates. This tendency of favorable rehybridization to generate stabilized tetrahedral intermediates enables α,α-difluoroketones an important motif in the design of protease inhibitors.

Figure 3.1. Stabilized Tetrahedral Form of α,α-Difluoroketones

<table>
<thead>
<tr>
<th>sp² (more electronegative)</th>
<th>sp³ (less electronegative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α,α-Difluoroketone</td>
<td>α,α-Difluoroketone</td>
</tr>
<tr>
<td>R¹ CF₂R</td>
<td>R² OH</td>
</tr>
<tr>
<td>EWG</td>
<td>EWG</td>
</tr>
<tr>
<td>connected to 2 EWG groups</td>
<td>more stable bonding mode</td>
</tr>
</tbody>
</table>

80
In serine proteases, the hydroxyl group of serine amino acids attacks the carbonyl group of an amide bond on the substrates to form a tetrahedral intermediate, and then the collapse of the intermediate cleaves an amide bond and regenerates the enzymes (Figure 3.2A). Similarly, α,α-difluoroketone-bearing inhibitors react with the nucleophilic hydroxyl residue of serine proteases to covalently form a stabilized intermediate that is trapped in the active site through interactions with surrounding residues of the proteases, and inhibit the enzymes through reversible covalent interactions (Figure 3.2B).1,3

In aspartyl proteases, a water molecule activated by two aspartyl residues in the active site of the enzymes attacks carbonyl group of an amide bond on the substrates to form a tetrahedral intermediate, and then the collapse of the intermediate cleaves an amide bond and releases the water molecule (Figure 3.3A). For α,α-difluoroketone inhibitors, the activated water molecule reacts with the carbonyl group of α,α-difluoroketones to form a long-lasting stabilized adduct, which occupies in the active site of aspartyl proteases and prevents the peptide substrates from entering the hydrolytic site. Herein, α,α-difluoroketones react with a water molecule and inhibit aspartyl proteases via non-covalent H-bonding networks (Figure 3.3B).1,3a
Based on these mechanisms, $\alpha,\alpha$-difluoroketones serve as inhibitors of hydrolytic enzymes, some of which exhibit subnanomolar $K_i$ constants, including inhibitors of HIV proteases, human renin, and acetylcholinesterases (Figure 3.4).3,4
Furthermore, this substructure can be introduced into natural products,\textsuperscript{5a} and in inhibitors of non-protease targets that provide distinct pharmacological profiles (Figure 3.5).\textsuperscript{5b–f} Additionally, this substructure can serve as an intermediate for further functionalization; for example, olefination reaction to generate $\alpha,\alpha$-difluoroalkenes in the structure of arginine vasopressin antagonists (Figure 3.5).\textsuperscript{5g}

![Figure 3.5. Representative Examples of Bioactive Molecules Bearing $\alpha,\alpha$-Difluoroketone Motifs](image)

**3.2 Literature Review to Access $\alpha,\alpha$-Difluoroketones**

Few efficient methods have been developed for introducing the $\alpha,\alpha$-difluoroketone motif on the molecules. Current methods to access $\alpha,\alpha$-difluoroketones focus on the manipulation of building blocks, deoxyfluorination and electrophilic fluorination, and most of them possess several limitations, including long synthetic sequences, the use of harsh reagents, and narrow substrate scope, which impede their universal applications in accessing therapeutic candidates.

**3.2.1 Building Block Strategy**

The building block strategy is a common method to access $\alpha,\alpha$-difluoroketone derivatives in medicinal chemistry. This method uses commercially available halodifluoroacetates as difluoromethyl synthons to access the final $\alpha,\alpha$-difluoroketone targets \textit{via} multistep synthetic transformations (Scheme 3.1).\textsuperscript{5f,6} However, these conversions of functional groups cause a time- and labor-consuming process, which is a major disadvantage of this method.
Difluoroenoxy silanes and difluorinated enol ethers are important reactants that enable access to α,α-difluoroketone derivatives through a variety of reactions (Scheme 3.2). For example, difluoroenoxy silanes serve as nucleophiles and react with protons (path a, Scheme 3.2), carbonyl groups (path b, Scheme 3.2), imines (path b, Scheme 3.2), and carbon-based electrophiles in the presence of Lewis acids (path c, Scheme 3.2), to provide α,α-difluoroketone derivatives. On the other hand, difluorinated enol ethers act as electrophiles and undergo SN2′ attack by Grignard reagents to generate enol ethers, which afford the α,α-difluoroketone products after acidic hydrolysis (path d, Scheme 3.2). Additionally, difluoroenoxy silanes are used as coupling components in transition metal-mediated coupling reactions (path e, Scheme 3.2), in which difluoroenoxy silanes act as nucleophiles to react with electrophiles, or to couple with nucleophiles in the presence of oxidants to form α-substituted α,α-difluoroketones. Moreover, difluoroenoxy silanes serve as fluorinated Danishefsky’s dienes in hetero Diels-Alder reactions and react with aldehydes and imines to generate N- and O-containing six-membered α,α-difluoroketones (path f, Scheme 3.2). A recent report demonstrates the participation of difluoroenoxy silanes in radical addition reactions (path g, Scheme 3.2). In the reactions, difluoroenoxy silanes play a role of electron sink and receive a aryl radical generated from arene diazonium salts via a photo-initiated nitrogen-releasing process. Subsequent oxidation of the resulting radicals followed by removal of a TMS group produce α-arylated α,α-difluoroketones. Conclusively, these versatile synthetic transformations, based on difluorinated enol (silyl) ethers, provide a variety of α,α-difluoroketone-bearing molecules.
3.2.2 Deoxyfluorination Strategy

This method utilizes deoxyfluorinating reagents to convert the carbonyl group C=O of 2-oxoacetic acid derivatives to the difluoromethylene CF$_2$ group. Subsequent addition of organolithium or Grignard reagents to the resulting $\alpha,\alpha$-difluoracetic acid derivatives provides $\alpha,\alpha$-difluoroketone products (Scheme 3.3).$^{5d-e,8}$ However, the reactions require the use of strong deoxyfluorinating reagents, which are not compatible with many important functional groups and suffer from side reactions, such as eliminations, thus leading to limited substrate scope.

3.2.3 Electrophilic Fluorination Strategy

Electrophilic fluorination has been developed for synthesizing $\alpha,\alpha$-difluoroketones from carbonyl compounds,$^{9a,b}$ imines,$^{9c}$ alkynes$^{9d-f}$ and activated aromatics$^{9f-g}$ using Selectfluor®, N-fluorosulfonimides,
CF$_3$OF and FOSO$_2$OCs as fluorinating reagents (Scheme 3.4). However, most of the reactions require the use of strong bases to facilitate difluorination of less reactive mono-carbonyl substrates (Scheme 3.4A), which are not suitable for base-sensitive and highly functionalized molecules. Although the use of imines and benzophenol derivatives provides $\alpha,\alpha$-difluoroketones under mild conditions, extra synthetic steps are required to acquire these pre-functionalized precursors (Scheme 3.4B and 3.4D). These drawbacks detract its wide application in the late stage fluorination to access $\alpha,\alpha$-difluoroketones.

### 3.2.4 Miscellaneous Strategies

Other methods, including nucleophilic fluorination of $\alpha$-diazo- and $\alpha$-hydrazone ketones (path a, Scheme 3.5),$^{10a,b}$ Brook rearrangement of the $\alpha,\alpha$-difluoroacylsilanes with primary diazoalkanes (path b, Scheme 3.5),$^{10c}$ radical addition of halodifluoroketone to alkenes (path c, Scheme 3.5),$^{10d}$ and Claisen rearrangement of the vinylsilanes or -stannanes followed by fluoride-mediated alkylation or Stille
coupling (path d, Scheme 3.5)\textsuperscript{10e} provided a variety of \(\alpha,\alpha\)-difluoroketone products. Recently, different types of reactions have been created for accessing \(\alpha\)-aryl and \(\alpha\)-alkyl substituted \(\alpha,\alpha\)-difluoroketones, such as desulfurization-fluorination (path e, Scheme 3.5),\textsuperscript{10f} transition metal-catalyzed coupling reactions of the difluoromethyl ketones with aryl halides (path f, Scheme 3.5),\textsuperscript{10g,h} difluorohomologation of ketones (path g, Scheme 3.5),\textsuperscript{10i} and addition of difluoroalkyl anions to esters (path h, Scheme 3.5).\textsuperscript{10} However, most of these reactions are illustrated by the limited examples, characterized by a narrow range of substrates, thus they are not extensively applied in preparing \(\alpha,\alpha\)-difluoroketone derivatives.

\textbf{Scheme 3.5. Alternative Methods to Access \(\alpha,\alpha\)-Difluoroketone Products}

3.2.5 Strategies to Access \(\alpha\)-Benzyl-\(\alpha,\alpha\)-difluoroketones

Despite the many methods described above that have been reported in synthesizing \(\alpha,\alpha\)-difluoroketones, most of them rely on multiple transformations to access the final targets, which are not convergent strategies. Furthermore, efficient methods to generate \(\alpha\)-alkyl-\(\alpha,\alpha\)-difluoroketones are less explored. Several alternative strategies for accessing \(\alpha\)-benzyl-\(\alpha,\alpha\)-difluoroketones have been developed,
including: 1) deoxyfluorination of $\alpha$-ketoesters using strong fluorinating reagents, followed by addition of organolithium or Grignard reagents to the resulting $\alpha,\alpha$-difluorooester (Scheme 3.6A), for which the strong bases and harsh reagents destroy many functional groups;\textsuperscript{5d} 2) 1,2-addition of $\alpha$-lithio-$\alpha,\alpha$-difluorovinyl ethers to aldehydes/ketones followed by cyclization of the resulting alcohol (Scheme 3.6B), which only accesses a small subset of products;\textsuperscript{11a} 3) 1,2-addition of ethyl halodifluoroacetate to aldehydes followed by deoxygenation (Scheme 3.6C);\textsuperscript{5f} 4) a single radical addition reaction of an aldehyde to a (2,2-difluorovinyl)benzene (Scheme 3.6D);\textsuperscript{11b} and 5) a late-stage electrophilic difluorination of prefunctionalized imines using Selectfluor/NFSI followed by acid-mediated hydrolysis (Scheme 3.6E)-not a convergent strategy,\textsuperscript{9c} which also generates a mixture of fluorinated products for substrates bearing two sites capable of undergoing imine-enamine isomerization. However, none of these reactions convergently generate the $\alpha$-benzyl-$\alpha,\alpha$-difluoroketones.
3.3 Challenges to Access α-Alkyl-α,α-Difluoroketones

A convergent preparation of α-alkyl-α,α-difluoroketones would involve a transformation capable of generating a C(α)–C(sp³) bond, presumably by reacting a nucleophilic α,α-difluoroketone enolate with an sp³-hybridized electrophile (Scheme 3.7).

Alkylation of ketone enolates with sp³-based electrophiles is a fundamental transformation for accessing a broad spectrum of α-functionalized ketones. However, nucleophilic substitution reactions of α,α-difluorinated ketone enolates with sp³-based electrophiles have not been generally developed, because of two problems. First, chemoselective formation of α,α-difluoroketone enolates presents challenges, because deprotonation of α,α-difluoromethyl ketones produces enolates at the nonfluorinated position under both thermodynamic and kinetic conditions (Scheme 3.8A), and upon trapping, cannot afford α-functionalized-α,α-difluoroketones. Second, α,α-difluoroketone enolates possess unique physicochemical properties that preclude formation of the C(α)–C(sp³) bond. Specifically, the strong inductive effect of the two fluorine atoms decreases the charge density of an enolate at the α-position, and thus reduces the nucleophilicity of the anion and disfavors reactions with sp³-based electrophiles (Scheme 3.8B). As a result, α,α-difluoroketone enolates react by S_N2 reactions at the O to generate difluorovinyl ethers, instead of at C(α) (Scheme 3.8C).
Because of these two factors, only two manuscripts describe $S_N1$- or $S_N2$-like alkylation reactions of $\alpha,\alpha$-difluoroketones, and both require stoichiometric amount of metal reagents to promote the reactions (Scheme 3.9).\textsuperscript{16}

3.4 Palladium-Catalyzed Decarboxylative Difluoroalkylation to Access $\alpha$-Benzyl-$\alpha,\alpha$-difluoroketones

Because of the previously discussed challenges with forming $\alpha,\alpha$-difluoroketone enolates by conventional base deprotonation and alkylation, an alternative strategy is necessary for accessing the reactive enolates. It has been reported that non-fluorinated ketone enolates can be generated \textit{in situ} via a decarboxylative coupling process, which enables the regioselective formation of reactive enolate
nucleophiles that might be difficult to access otherwise, followed by a C–C bond-forming event. Thus, we predicted that a decarboxylative protocol could generate \(\alpha,\alpha\)-difluoroketone enolates. Moreover, we assumed the low reactivity of \(\alpha,\alpha\)-difluoroketone enolates could be overcome by a transition metal mediator that can link the nucleophilic enolate with the electrophile and facilitate the reaction. Combining these thoughts, a Pd-catalyzed decarboxylative strategy was explored to address two major challenges associated with alkylation reactions of \(\alpha,\alpha\)-difluoroketone enolates, and to generate \(\alpha\)-alkyl-\(\alpha,\alpha\)-difluoroketones (Scheme 3.10). Although recently reported reactions have coupled \(\alpha,\alpha\)-difluoroketone enolates with aryl halides, rarely has a Pd-based catalytic system effectively promoted the alkylation reaction of \(\alpha,\alpha\)-difluoroketone enolates. In this proposed reaction, a decarboxylative strategy would chemoselectively generate the appropriate \(\alpha,\alpha\)-difluoroketone enolate, and the critical C(\(\alpha\))–C(sp\(^3\)) bond would form by reductive elimination from a high-energy \([L_n\text{Pd}(\text{benzyl})(\alpha,\alpha\text{-difluoroenolate})]\) intermediate (Scheme 3.10).

![Scheme 3.10, Proposed Decarboxylative Strategy to Access \(\alpha\)-Alky-\(\alpha,\alpha\)-difluoroketones](image)

To begin the study, benzylic electrophiles were selected because they possess higher reactivity compared to alkyl electrophiles, and the \(\alpha,\alpha\)-difluoroketone enolates would be generated \textit{in situ} via decarboxylation of \(\alpha,\alpha\)-difluoro-\(\beta\)-keto-esters. Thus, benzyl \(\alpha,\alpha\)-difluoro-\(\beta\)-keto-esters were identified as test substrates, and they were prepared through four steps, comprising 1) Reformatsky addition of ethyl bromodifluoroacetate to aldehydes; 2) oxidation of alcohols to ketones; 3) basic hydrolysis of ethyl esters; and 4) esterification of \(\beta\)-keto-\(\alpha,\alpha\)-difluoroacetate with benzyl alcohols (Scheme 3.11).
Initial screening was performed by Niusha Sharifi, who focused on the identification of appropriate ligands that form metal catalysts to activate the substrate, stabilize the \([\text{LnPd}({\text{benzyl}})(\alpha,\alpha\text{-difluoroenolate})]\) intermediate, and facilitate the C–C bond formation. Our screening identified certain biarylmonophosphine-based ligands derived from RuPhos, SPhos, PhXPhos, XPhos and BrettPhos scaffolds, and bidentate phosphine ligands such as Xantphos and DPEPhos that could generate the coupled product 3.2a in modest yields (Scheme 3.12A). Other ligands failed to produce at least 15% of the coupled product 3.2a (Scheme 3.12B).
Subsequent thorough and systematic screening of palladium-based catalysts and precatalysts identified Pd(PPh₃)₄ as an efficient catalyst for the present transformation that afforded comparable yields as other systems containing Pd/ligands (entry 8, Table 3.1). After further optimization of solvent, temperature, Pd loading, and concentration, the final conditions [2.5% [Pd(PPh₃)₄] / o-xylene / 120 °C] readily generated the desired α-benzyl-α,α-difluoroketone (entry 15, Table 3.2), thus confirming our hypothesis that transition metal catalysis should form the critical C(α)–C(sp³) bond.
### Table 3.1. Preliminary Screening of Pd Sources for Pd-Catalyzed Decarboxylative Difluorobenzylation

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd</th>
<th>XPhos (%)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>conv. (%)</th>
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<tr>
<td>1</td>
<td>Pd&lt;sub&gt;2&lt;/sub&gt;dba&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10</td>
<td>43</td>
<td>100</td>
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<td>2</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15</td>
<td>7</td>
<td>56</td>
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<tr>
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<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15</td>
<td>43</td>
<td>100</td>
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<tr>
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<td>Pd(TFA)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15</td>
<td>21</td>
<td>95</td>
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<tr>
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<td>Pd(CH&lt;sub&gt;2&lt;/sub&gt;CN)xCl&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>23</td>
<td>78</td>
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<td>15</td>
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</tr>
<tr>
<td>7</td>
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<td>15</td>
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<td>100</td>
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<tr>
<td>8</td>
<td>Pd(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>0</td>
<td>45</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pd (5 mol%) indicates dimeric Pd (2.5 mol%) and monomeric Pd (5 mol%).

<sup>b</sup> Yields were determined by GC using dodecane as an internal standard.

<sup>c</sup> We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed difluorobenzylation.

### Table 3.2. Optimization of Pd(PPh<sub>3</sub>)<sub>4</sub>-Catalyzed Decarboxylative Difluorobenzylation

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd (%)</th>
<th>solvent</th>
<th>conc. (M)</th>
<th>T (°C)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>conv. (%)</th>
</tr>
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<td>45</td>
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<tr>
<td>2</td>
<td>5</td>
<td>DME</td>
<td>0.2</td>
<td>100</td>
<td>4</td>
<td>100</td>
</tr>
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<td>5</td>
<td>2-Me-THF</td>
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<td>80</td>
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<td>5</td>
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<td>6</td>
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<td>o-xylene</td>
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<tr>
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<td>120</td>
<td>(66)</td>
<td>100</td>
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<td>100</td>
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<td>120</td>
<td>(87)</td>
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</table>

<sup>a</sup> Yields were determined by GC using dodecane as an internal standard. The value in parentheses was 19F NMR yields using <sup>19</sup>F-trifluorotoluene as an internal standard.

<sup>b</sup> We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed difluorobenzylation.
As previously noted, alkylation reactions of \( \alpha,\alpha \)-difluoroketone enolates suffer from two classical problems, namely, generation of the appropriate enolate\(^{13}\) and alkylation at C(\( \alpha \)) instead of at O.\(^{15}\) Although the example 3.2a (Table 3.2) confirms the ability of the palladium-catalyzed system to generate the C(\( \alpha \))–C(sp\(^3\)) bond, the substrate 3.1a does not bear enolizable H-atoms at the nonfluorinated \( \alpha \)-position of the ketone, and therefore cannot form a nonfluorinated enolate. As such, 3.1a does not confirm whether the Pd-catalyzed decarboxylative protocol would selectively generate the fluorinated ketone enolate. To address this concern, the reaction of aliphatic substrate 3.1b, which could theoretically decarboxylate and isomerize to generate the undesired enolate 3.1ba at nonfluorinated position (Scheme 3.13), was explored. Subjection of 3.1b to \([\text{Pd(PPh}_3\text{)}_4]\) at 140 °C, generated product 3.2b in 53% isolated yield, with no detectable products arising from alkylation at the nonfluorinated position (Scheme 3.13). Thus, the present decarboxylative reaction overcomes both previously presented challenges associated with alkylation reactions of \( \alpha,\alpha \)-difluoroketone enolates.

![Scheme 3.13. Decarboxylative Strategy Chemoselectively Generated the Desired Enolate and Enabled the Formation of the Key C(\( \alpha \))–C(sp\(^3\)) Bond](image)

A variety of substrates bearing electron-rich, -neutral, and -deficient benzylic moieties underwent the decarboxylative reaction to generate \( \alpha \)-benzyl-\( \alpha,\alpha \)-difluoroketones (Scheme 3.14). Generally, the optimized conditions converted electron-rich, and -neutral substrates into products 3.4a–b and 3.2a in high yields. However, moderately electron-deficient substrates required higher catalyst loading and/or reaction temperatures to provide good yields of products 3.4c–d. Further, substrates bearing strong
electron-withdrawing groups were less active, and generated products 3.4e–f in lower yields, even after optimization. This trend implicates the intermediacy of [Pd-(π-benzyl)(α,α-difluoroenoate)], as electron-donating groups stabilize the intermediate and facilitate the reaction, and electron-withdrawing groups destabilize the intermediate and retard the reaction (Scheme 3.15). While the electronic nature of substrates affected the outcome of the reaction, steric effects did not impede the reaction. Reactions of ortho-substituted benzyl esters afforded products in comparably high yields to the analogous para-substituted substrates (3.4g–h versus 3.4a–b).

![Scheme 3.14. Decarboxylative Difluorobenzylolation of Substrates Bearing Distinct Benzyl Moieties](image)

<table>
<thead>
<tr>
<th>R</th>
<th>F_2</th>
<th>Ph</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td></td>
<td></td>
<td>3.4a, 94% (63%)</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td>3.4b, 95% (85%)</td>
</tr>
<tr>
<td>MeO-C</td>
<td></td>
<td></td>
<td>3.4c, 88% (80%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>F:C</td>
<td></td>
<td></td>
<td>3.4d, 66% (60%)&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>NC</td>
<td></td>
<td></td>
<td>3.4e, 35% (31%)&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>O:N</td>
<td></td>
<td></td>
<td>3.4f, 28% (22%)&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>3.4g, 96% (89%)</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td>3.4h, 97% (87%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Standard reaction conditions: 3.3a–h (1.0 equiv), Pd(PPh₃)₄ (2.5 mol%), o-xylene (0.05 M), 120 °C, 15 h. <sup>b</sup>19F NMR Yields were determined using α,α,α',α'-trifluorobenzene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs). <sup>c</sup>Pd(PPh₃)₄ (5.0 mol%).<sup>d</sup> Pd(PPh₃)₄ (5.0 mol%), 140 °C. <sup>e</sup>Pd(PPh₃)₄ (20 mol%), 140 °C, o-xylene (0.01 M), 24 h. <sup>f</sup>Pd(PPh₃)₄ (5.0 mol%), 140 °C, 24 h.

![Scheme 3.15. Pd-α-Benzyl Complex Was Involved in the Reactions](image)
The decarboxylative reaction also successfully produced products bearing a variety of aryl- and alkyl \(\alpha,\alpha\)-difluoroketone moieties (Scheme 3.16). Reactions of substrates bearing electron-rich, neutral and withdrawing aryl \(\alpha,\alpha\)-difluoroketones provided the corresponding products 3.6a–c in high yields under the standard conditions. Further, both \(S\)- and \(N\)-containing heteroaryl \(\alpha,\alpha\)-difluoroketone moieties were tolerated (3.6d–e), and at an increased temperature, the reaction of an aliphatic \(\alpha,\alpha\)-difluoroketone substrate afforded product 3.6f in reasonable yield.

This catalyst system only coupled the \(\alpha,\alpha\)-difluorinated substrate (entry 1, Table 3.3), while the mono- and nonfluorinated substrates did not provide the expected products (entries 2–3, Table 3.3). This dramatic fluorine effect facilitated the present reaction with neutral and even electron-deficient benzyl esters, while some other transformations involving oxidative addition of \(\text{Pd(PPh}_3\text{)}_4\) into nonfluorinated benzyl esters typically require an extended conjugated system or an electron-rich benzylic moiety.\(^{21}\) This phenomenon likely reflects the strong \(\sigma\)-withdrawing inductive effect of the two fluorine atoms, which increases the electrophilicity of the substrate, and accelerates the oxidative addition step to generate the high-energy dearomatized \(\pi\)-benzyl intermediate (\(\text{A},^{22}\) Table 3.3).\(^{17\text{a},23}\) In contrast, we believe that the
fluorine substituents likely do not accelerate the decarboxylation step of the reaction. Despite the increased stability of the \(\alpha,\alpha\)-difluorinated enolate (ketone-C\(\text{F}_2\)H \(pK_a = 20.2\); ketone-C\(\text{FH}_2\) \(pK_a = 21.7\); ketone-\(\text{CH}_3\) \(pK_a = 24.7\)),\(^{24}\) rehybridization of \(\alpha,\alpha\)-difluorinated enolate carbanions from C(sp\(^3\)) to C(sp\(^2\)) actually occurs more slowly than nonfluorinated enolates,\(^{25}\) which contradicts the trend observed (Table 3.3).

<table>
<thead>
<tr>
<th>Table 3.3. Fluorine Atoms Increased Reactivity of Substrate toward Pd-Catalyzed Decarboxylative Benzylation of (\alpha,\alpha)-Difluoroketone Enolates.(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>entry</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

\(^a\) Standard reaction conditions: 3.1a-a" (1.0 equiv), Pd\((\text{PPPh}_3)_2\) (2.5 mol%), \(\alpha\)-xylene (0.05 M), 120 °C, 15 h. The reported data represents an average of two independent experiments.\(^b\) The yields were determined by \(^{19}\)F NMR using \(\alpha,\alpha\)-difluorobenzene and fluoroanisole (3.1a and 3.1a") and by \(^1\)H NMR using \(\text{CH}_2\text{Br}_2\) (3.1a") as an internal standard.\(^c\) Yield of isolated product.

3.5 Conclusion

A palladium-catalyzed decarboxylative coupling reaction generated an unfavourable enolate and formed a key C(\(\alpha\))–C(sp\(^3\)) bond. Compared to building block and deoxyfluorination strategies, this method 1) facilitated the preparation of \(\alpha\)-benzyl-\(\alpha,\alpha\)-difluoroketones under neutral conditions; 2) tolerated molecules bearing sensitive functional groups and \(N\)-containing heterocycles on both of benzylic and \(\alpha,\alpha\)-difluoroketone moieties;\(^{26}\) and 3) avoided multistep synthetic manipulations. Moreover, this strategy should not only provide a straightforward route to access biologically important \(\alpha\)-benzyl-\(\alpha,\alpha\)-difluoroketone-based compounds, but also enable the development of additional transition metal-catalyzed coupling reactions of functionalized fluoroalkyl anions with sp\(^3\)-based electrophiles.
3.6 References for Chapter 3


We acknowledged Niusha Sharifi for the initial screening of decarboxylative benzyla
tion reactions of \( \alpha,\alpha \)-difluoroketone enolates.


Substrates bearing heterocycle-type benzylic moieties, such as pyrazoles and indoles, are not included in this thesis. Please see *Angew. Chem. Int. Ed.* **2016**, *55*, 9080–9083 for the details.
Chapter 3 Appendix

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General Information

Unless otherwise noted, reactions were performed under an atmosphere of N₂ using oven-dried glassware. Palladium-catalyzed reactions were performed in 20 mL pressure-resistant scintillation vials, which were sealed with PTFE-lined silicone septa, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing by quenching of fluorescence, or by staining with KMnO₄, anisaldehyde or iodine. Column chromatography was conducted using an automated system. ¹⁹F NMR yields and isolated yields reported in the manuscript represent an average of at least two independent runs of material deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment.

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. o-Xylene (anhydrous) and Pd(PPh₃)₄ (reagent grade, 99%) were purchased from Sigma Aldrich. Solvents including DMF, PhMe, CH₂Cl₂, THF, MeOH were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon.

Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual CHCl₃ in the NMR solvent (CDCl₃: δ = 7.27 ppm or DMSO-d₆: δ = 2.50 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak (CDCl₃: δ = 77.23 ppm or DMSO-d₆: δ = 39.51 ppm). Fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz). ¹⁹F NMR chemical shifts (δ) are reported in ppm upfield from trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity
(s = singlet, d = doublet, t = triplet, q = quartet, p = pent, m = multiplet), coupling constant in Hertz (Hz), integration. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier™ mass spectrometer or by atmospheric-pressure chemical ionization (APCI–hexane/PhMe) on a Waters Q-Tof Premier™, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as ionization solvent. Infrared spectra were measured at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on Thomas Hoover Capillary Melting Point apparatus.

**Preparation of Compound 3.1a**

[Diagram showing the reaction steps involving zinc, benzaldehyde, 1,2-dibromoethane, ethyl bromodifluoroacetate, potassium hydroxide, and benzyl alcohol.]

**ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (3.1a-3)**

An oven-dried three-neck flask was charged with activated Zn (6.4 g, 98.4 mmol). The reaction vessel was equipped with a reflux condenser and two rubber septa, evacuated and backfilled with N_2(g) three times. Dry THF (0.10 L) was added, followed by addition of the initiator 1,2-dibromoethane (0.50 mL, 5.8 mmol) under N_2(g). To activate the Zn, the reaction mixture was heated with a heat gun until the THF boiled suddenly. Heating was stopped, and the mixture was cooled to rt. This heating/cooling sequence for activation of Zn was repeated four more times (5 total). Subsequently, the reaction mixture was heated to 70 °C (oil-bath), and a solution of aldehyde (5.0 mL, 49 mmol) and ethyl bromodifluoroacetate (6.4 mL, 49 mmol) was added dropwise at a rate that maintained a gentle reflux. The resulting reaction mixture was stirred at 70 °C for 1 h, and then cooled to 50 °C and stirred overnight. The reaction mixture was cooled to 0 °C, and 1 N HCl(aq) was added until the residual Zn was consumed (roughly 100 mL). The reaction mixture was warmed to rt, and transferred to a separation funnel. The phases were separated, and
the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (10% to 15%) for elution to provide the compound 3.1a-3 as a colorless oil (10.5 g, 93%). ¹H NMR (CDCl₃, 400 MHz) δ 7.47–7.39 (m, 5 H), 5.18 (ddd, J = 15.6, 8.0, 5.2 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 2.66 (d, J = 5.2 Hz, 1 H), 1.30 (t, J = 7.2 Hz, 3 H). ¹⁹F NMR (CDCl₃, 376 MHz) δ −120.4 (dd, J = 263.2, 15.4 Hz, 1 F), −113.9 (dd, J = 263.2, 7.9 Hz, 1 F). HRMS (ESI, m/z): calcd for C₁₁H₁₂F₂O₃Na [M+Na]⁺ 253.0652, found 253.0663. Spectroscopic data matched that from the previous report.¹

**ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.1a-2)**

An oven-dried three-neck flask was equipped with a liquid addition funnel, a three-way valve and two rubber septa, evacuated and backfilled with N₂(g) three times. Dry CH₂Cl₂ (130 mL) and oxalyl chloride (6.1 mL, 71 mmol) were added sequentially at rt, and the reaction solution was cooled to −78 °C. A solution of anhydrous DMSO (6.7 mL, 94 mmol) in dry CH₂Cl₂ (13 mL) was added dropwise at −78 °C, and then the reaction solution was stirred at this temperature for 1 h. Next, a solution of 3.1a-3 (5.42 g, 23.5 mmol) dissolved in dry CH₂Cl₂ (13 mL) was added dropwise at −78 °C, and then the resulting reaction solution was stirred at this temperature for 1 h. Et₃N (0.020 L, 0.14 mol) was added dropwise at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. The reaction mixture was gradually warmed to rt, and stirred at rt for 2 h. H₂O (100 mL) was added to quench the reaction, and CH₂Cl₂ was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 100 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to afford the compound 3.1a-2 as a as a light yellow oil (4.40 g, 82%). ¹H NMR (CDCl₃, 400 MHz) δ 8.09 (d, J = 7.6 Hz, 2 H), 7.71–7.67 (m, 1 H), 7.56–7.52 (m, 2 H), 4.40 (q, J = 7.2 Hz, 2 H), 1.33 (t, J = 7.2 Hz, 3 H). ¹⁹F NMR (CDCl₃, 376 MHz) δ −107.6 (s, 2 F). HRMS (ESI, m/z): calcd for
C_{11}H_{10}F_{2}O_{3}Na \ [M+Na]^+ 251.0496, found 251.0490. Spectroscopic data matched that from the previous report.\(^2\)

**potassium 2,2-difluoro-3-oxo-3-phenylpropanoate (3.1a-1)**

A one-neck round-bottom flask was charged with 3.1a-2 (3.10 g, 13.6 mmol), and MeOH (7.0 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (0.760 g, 13.6 mmol) dissolved in MeOH (7.0 mL) was added dropwise, and then the reaction solution was warmed to rt, and stirred at rt for 6 h. MeOH was removed under reduced pressure. EtOAc (5 mL) and ether (5 mL) were added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried \textit{in vacuo} to give the compound 3.1a-1 as a colorless solid (2.72 g, 84%). \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\) 8.00 (d, \(J = 8.0\) Hz, 2 H), 7.65 (t, \(J = 7.6\) Hz, 1 H), 7.52 (t, \(J = 7.6\) Hz, 2 H).

\(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz) \(\delta\) 189.6 (t, \(J = 27.5\) Hz), 162.4 (t, \(J = 23.8\) Hz), 133.8, 132.6, 129.2, 128.5, 111.3 (t, \(J = 261.9\) Hz). \(^{19}\)F NMR (DMSO-\(d_6\), 376 MHz) \(\delta\) –105.2 (s, 2 F). IR (film) 3061, 1720, 1697, 1682, 1645, 1599, 1450, 1412, 1381, 1281, 1169, 1132, 1101, 922, 912, 816, 729, 708, 685, 584 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C_{9}H_{5}F_{2}K_{2}O_{3} \ [M+K]^+ 276.9481, found 276.9492. mp 154–155 °C decomposed.

**benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.1a)**

An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (4.3 g, 18 mmol), and the system was evacuated and backfilled with N\(_2\)(g) three times. Dry CH\(_2\)Cl\(_2\) (0.090 L) and DMF (0.46 mL) were added via a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (1.4 mL, 17 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. Next, benzyl alcohol (1.5 mL, 15 mmol) was added dropwise at 0 °C followed by dropwise addition of Et\(_3\)N (4.2 mL, 30 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. H\(_2\)O (15 mL) was added to quench the reaction, and CH\(_2\)Cl\(_2\) was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 15 mL), and the combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The
crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound 3.1a as a colorless oil (3.5 g, 80%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.04 (d, $J = 8.0$ Hz, 2 H), 7.67 (t, $J = 7.4$ Hz, 1 H), 7.49 (t, $J = 7.6$ Hz, 2 H), 7.36–7.30 (m, 5 H), 5.35 (s, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.4 (t, $J = 27.5$ Hz), 161.9 (t, $J = 30.6$ Hz), 135.3, 133.9, 131.1 (t, $J = 2.5$ Hz), 130.1 (t, $J = 2.5$ Hz), 129.2, 129.1, 128.9, 128.6, 110.0 (t, $J = 263.1$ Hz), 69.2. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.4 (s, 2 F). IR (film) 3068, 3036, 1778, 1715, 1699, 1597, 1499, 1450, 1381, 1308, 1259, 1157, 1101, 1080, 920, 798, 746, 712, 696, 687, 579 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{12}$F$_2$O$_3$Na [M+Na]$^+$ 313.0652, found 313.0666.

**Initial Screening and Optimization of Reaction Conditions**

An oven-dried 1 dram vial was charged with substrate 3.1a (0.100 mmol), Pd catalysts or precatalysts, ligand, and a magnetic stir bar. The dry solvent was added via a syringe. Subsequently, the vial was transferred out of the glove box and placed on a pre-heated reaction block at the indicated temperature, and stirred for the indicated time. The vial was cooled to rt, and the mixture was diluted with EtOAc. An internal standard $\alpha,\alpha,\alpha$-trifluorotoluene (for $^{19}$F NMR analysis) or dodecane (for GC analysis) was added, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing in prior to $^{19}$F NMR or GC analysis.
Table S1. Screening Conditions of Pd$_2$dba$_3$-Catalyzed Decarboxylative Difluorobenzylation:

<table>
<thead>
<tr>
<th>Ligands$^{a,b,c}$</th>
<th>Pd$_2$dba$_3$ (5 mol%)</th>
<th>Ligand (10 mol%)</th>
<th>toluene (0.2 M)</th>
<th>110 °C, 15 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>66%</td>
<td>RuPhos</td>
<td>69%</td>
<td>SPhos</td>
<td>66%</td>
</tr>
</tbody>
</table>

$^a$ Yields were determined by $^{19}$F NMR using $\alpha,\alpha,\alpha$-trifluorotoluene as an internal standard.

$^b$ The conversion for all reactions above was more than 99%.

Other ligands screened that produced < 15% product by GC are shown below.

We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed difluorobenzylation reactions.
Table S2. Screening Conditions of Pd-Catalyzed Decarboxylative Difluorobenzylation: Pd Sources, Temperature and Concentration

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd Source</th>
<th>XPhos (%)</th>
<th>T (°C)</th>
<th>conc. (M)</th>
<th>yield (%)(^b)</th>
<th>conv (%)</th>
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</thead>
<tbody>
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<td>Pd(_2\text{dba}_3)</td>
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<td>43</td>
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<tr>
<td>2</td>
<td>PdCl(_2)</td>
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<tr>
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<td>Pd(OAc)(_2)</td>
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<td>23</td>
<td>78</td>
</tr>
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<td>6</td>
<td>Pd(acac)(_2)</td>
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<td>110</td>
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<td>8</td>
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<td>11(^d)</td>
<td>Pd(OAc)(_2)</td>
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<td>110</td>
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\(^a\) Pd (5 mol%) indicates dimeric Pd (2.5 mol%) and monomeric Pd (5 mol%).

\(^b\) Yields were determined by GC using dodecane as an internal standard.

\(^c\) Solvent: 1,4-dioxane

\(^d\) Solvent: DMF
Table S3. Screening Conditions of PdCp(1-η³-1-Ph-C₃H₄)-Catalyzed Decarboxylative Difluorobenzylaition: Catalyst Loading, Temperature and Reaction Time

<table>
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<th>Pd (%)</th>
<th>XPhos (%)</th>
<th>T (°C)</th>
<th>time (h)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>conv (%)</th>
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<sup>a</sup> Yields were determined by <sup>19</sup>F NMR using α,α,α-trifluorotoluene as an internal standard.
Table S4. Screening Conditions of PdCp(1-η^3-1-Ph-C_3H_4)-Catalyzed Decarboxylative Difluorobenzylolation: Concentration and Ligands

![Chemical structure](image)

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<th>yield (%)</th>
<th>conv (%)</th>
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<td>PCy₃ (2)</td>
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* Yields were determined by ^19F NMR using α,α,α-trifluorotoluene as an internal standard.
Table S5. Optimization of Pd(PPh₃)₄-Catalyzed Decarboxylative Difluorobenzylolation-Screening

Conditions: Catalyst Loading, Solvent and Temperature

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² Yields were determined by GC using dodecane as an internal standard. The value in parentheses was ¹⁹F NMR yields using α,α,α-trifluorotoluene as an internal standard.
Table S6. Optimization of Pd(PPh₃)₄-Catalyzed Decarboxylative Difluorobenzylation-Screening

**Conditions: Concentration and Reaction Time**

![Diagram of reaction](image)

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<th>yield (%)</th>
<th>conv (%)</th>
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*a* Yields were determined by ¹⁹F NMR using α,α,α-trifluorotoluene as an internal standard.

Characterization of Compound 3.2a

![Compound 3.2a](image)

**2,2-difluoro-1,3-diphenylpropan-1-one (3.2a)**

¹H NMR (CDCl₃, 400 MHz) δ 8.04 (d, J = 7.6 Hz, 2 H), 7.62 (t, J = 7.6 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.32 (br, 5 H), 3.53 (t, J = 17.8 Hz, 2 H). ¹³C NMR (CDCl₃, 125 MHz) δ 189.7 (t, J = 30.6 Hz), 134.4, 132.3 (t, J = 2.5 Hz), 131.5 (t, J = 3.1 Hz), 131.1, 130.3 (t, J = 3.7 Hz), 128.8, 128.6, 127.8, 118.6 (t, J = 253.1 Hz), 40.3 (t, J = 23.1 Hz). ¹⁹F NMR (CDCl₃, 376 MHz) δ –98.6 (t, J = 16.9 Hz, 2 H). IR (film) 3063, 3032, 2937, 1701, 1597, 1497, 1450, 1279, 1173, 1115, 1084, 1049, 1032, 943, 901, 727, 715, 698, 669, 600 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₅H₁₂F₂ONa [M+Na]⁺ 269.0754, found 269.0742. m.p. 45 °C. Spectroscopic data matched that from the previous report."
Experimental Procedures and Characterization of Compounds in Scheme 3.13

**ethyl 2,2-difluoro-3-hydroxyundecanoate (3.1b-3)**

An oven-dried three-neck flask was charged with activated Zn (3.20 g, 49.2 mmol). The reaction vessel was equipped with a reflux condenser and two rubber septa, evacuated and backfilled with N\(_2\)\(_{\text{(g)}}\) three times. Dry THF (0.05 L) was added, followed by addition of the initiator 1,2-dibromoethane (0.25 mL, 2.9 mmol) under N\(_2\)\(_{\text{(g)}}\). To activate the Zn, the reaction mixture was heated with a heat gun until the THF boiled suddenly. Heating was stopped, and the mixture was cooled to rt. This heating/cooling sequence for activation of Zn was repeated four more times (5 total). Subsequently, the reaction mixture was heated to 70 °C (oil-bath), and a solution of nonyl aldehyde (4.3 mL, 25 mmol) and ethyl bromodifluoroacetate (3.2 mL, 25 mmol) was added dropwise at a rate that maintained a gentle reflux. The resulting reaction mixture was stirred at 70 °C for 1 h, and then cooled to 50 °C and stirred overnight. The reaction mixture was cooled to rt, and the residual Zn was filtered through a pad of celite and washed with EtOAc. The filtrate was acidified with 1 N HCl\(_{\text{(aq)}}\) to pH 3–4, and the solution was transferred to a separation funnel. The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (5% to 10%) for elution to provide the compound **3.1b-3** as a colorless liquid (4.0 g, 61%).

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 4.37\) (q, \(J = 7.2\) Hz, 2 H), 4.08–3.97 (m, 1 H), 1.98 (d, \(J = 7.2\) Hz, 1 H), 1.72–1.65 (m, 1 H), 1.64–1.50 (m, 2 H), 1.43–1.27 (m, 14 H), 0.89 (t, \(J = 6.6\) Hz, 3 H). \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 163.9\) (t, \(J = 31.9\) Hz), 114.9 (dd, \(J = 255.0, 252.5\) Hz), 72.0 (dd, \(J = 26.2, 25.0\) Hz), 63.2, 32.0, 29.6, 29.5, 29.4, 29.3, 25.4, 22.9,
14.3, 14.1. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ $-122.4$ (dd, $J = 267.0$, 15.0 Hz, 1 F), $-115.0$ (dd, $J = 267.0$, 7.5 Hz, 1 F). IR (film) 3477, 2957, 2928, 2856, 1759, 1396, 1375, 1315, 1217, 1122, 1092, 856, 783, 721 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{13}$H$_{24}$F$_2$O$_3$Na [M+Na]$^+$ 289.1591, found 289.1581.

**ethyl 2,2-difluoro-3-oxoundecanoate (3.1b-2)**

Dess-Martin periodinane (7.38 g, 17.4 mmol) was added into a solution of compound 3.1b-3 (3.56 g, 13.4 mmol) dissolved in CH$_2$Cl$_2$ (0.100 L) at 0 °C, and the solution was stirred at rt for 2 h. The solvent was removed under reduced pressure, and the residue was stirred in EtOAc / hexanes (1:10, 100 mL) and sonicated. The white solid was filtered through a pad of celite, and washed with EtOAc / hexanes (1:10). The filtrate was concentrated to provide the title compound 3.1b-2 as a colorless liquid (3.49 g, 98%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 4.38 (q, $J = 7.2$ Hz, 2 H), 2.74 (t, $J = 7.2$ Hz, 2 H), 1.66 (p, $J = 7.0$ Hz, 2 H), 1.38–1.28 (m, 13 H), 0.89 (t, $J = 6.8$ Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 197.7 (t, $J = 27.5$ Hz), 161.7 (t, $J = 30.0$ Hz), 108.4 (t, $J = 262.5$ Hz), 63.9, 36.8, 32.0, 29.4, 29.2, 29.0, 22.8, 22.6, 14.3, 14.1. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ $-113.9$ (s, 2 F). IR (film) 2957, 2930, 2858, 1782, 1747, 1468, 1402, 1373, 1313, 1203, 1140, 1014, 959 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{13}$H$_{22}$F$_2$O$_3$Na [M+Na]$^+$ 287.1435, found 287.1421.

**potassium 2,2-difluoro-3-oxoundecanoate (3.1b-1)**

A one-neck round-bottom flask was charged with 3.1b-2 (2.84 g, 10.7 mmol), and MeOH (18 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (0.600 g, 10.7 mmol) dissolved in MeOH (5.0 mL) was added dropwise, and then the reaction solution was warmed to rt, and stirred for 6 h. The solvent was removed under reduced pressure. Ether (15 mL) was added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried in vacuo to give the compound 3.1b-1 as an off-white solid (2.4 g, 82%). $^1$H NMR (DMSO-d$_6$, 400 MHz) δ 2.57 (t, $J = 7.2$ Hz, 2 H), 1.46 (p, $J = 7.0$ Hz, 2 H), 1.29–1.23 (m, 10 H), 0.85 (t, $J = 6.6$ Hz, 3 H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz) δ 201.6 (t, $J = 26.9$ Hz), 162.1 (t, $J = 25.0$ Hz), 111.0 (t, $J = 262.5$ Hz), 36.6, 31.3, 28.8, 28.6, 28.4, 22.5, 22.1, 14.0. $^{19}$F NMR (DMSO-d$_6$, 376 MHz) δ $-111.4$ (s,
2 F). IR (film) 2955, 2922, 2854, 1742, 1661, 1468, 1398, 1194, 1124, 1082, 818 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₁H₁₇F₂O₃K₂ [M+K]⁺ 313.0420, found 313.0435. mp 155 °C (decomposed).

3,5-dimethoxybenzyl 2,2-difluoro-3-oxoundecanoate (3.1b)

An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxoundecanoate 3.1b-1 (1.6 g, 6.0 mmol), and the system was evacuated and backfilled with N₂ three times. Dry CH₂Cl₂ (0.030 L) and DMF (0.17 mL) were added via a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (0.50 mL, 5.8 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. Next, 3,5-dimethoxybenzyl alcohol (0.92 g, 5.5 mmol) was added dropwise at 0 °C followed by dropwise addition of Et₃N (1.5 mL, 11 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 3.0 h. H₂O (15 mL) was added to quench the reaction, and CH₂Cl₂ was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 30 mL), and the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (5% to 10%) for elution to furnish the compound 3.1b as a colorless oil (1.5 g, 71%). ¹H NMR (CDCl₃, 400 MHz) δ 6.49 (d, J = 2.0 Hz, 2 H), 6.45 (t, J = 2.2 Hz, 1 H), 5.26 (s, 2 H), 3.80 (s, 6 H), 2.71 (t, J = 7.2 Hz, 2 H), 1.63 (p, J = 7.0 Hz, 2 H), 1.32–1.23 (m, 10 H), 0.89 (t, J = 6.6 Hz, 3 H). ¹³C NMR (CDCl₃, 125 MHz) δ 197.5 (t, J = 28.1 Hz), 161.5 (t, J = 31.2 Hz), 161.2, 136.1, 108.5 (t, J = 262.5 Hz), 106.2, 101.0, 68.9, 55.6, 36.8, 32.0, 29.4, 29.2, 29.0, 22.8, 22.6, 14.3. ¹⁹F NMR (CDCl₃, 376 MHz) δ –113.6 (s, 2 F). IR (film) 2953, 2930, 2856, 1780, 1747, 1599, 1464, 1431, 1379, 1346, 1302, 1207, 1155, 1068, 991, 947, 920, 837, 696 cm⁻¹. HRMS (ESI, m/z): calcd for C₂₀H₂₉F₂O₅ [M+H]⁺ 387.1983, found 387.1981.

1-(3,5-dimethoxyphenyl)-2,2-difluoroundecan-3-one (3.2b)
An oven-dried 20 mL scintillation vial was charged with substrate 3.1b (193 mg, 0.500 mmol), Pd(PPh3)4 (20.2 mg, 0.0175 mmol), and a magnetic stir bar. Dry o-xylene (0.010 L) was added via a syringe. Subsequently, the vial was transferred out of the glove box and placed on a pre-heated reaction block at 140 °C, and stirred for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). α,α,α-Trifluorotoluene (30 µL, 0.2443 mmol) was added as an internal standard, and the reaction mixture was stirred at rt at least 20 min to ensure thorough mixing. An aliquot was taken from the vial for 19F NMR analysis. After determining the 19F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. Removal of the solvents in vacuo and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.2b as a colorless oil (95 mg, 55%). 1H NMR (CDCl3, 400 MHz) δ 6.39 (s, 3 H), 3.78 (s, 6 H), 3.24 (t, J = 16.8 Hz, 2 H), 2.48 (t, J = 7.2 Hz, 2 H), 1.56–1.48 (m, 2 H), 1.30–1.19 (m, 10 H), 0.89 (t, J = 6.8 Hz, 3 H). 13C NMR (CDCl3, 125 MHz) δ 202.1 (t, J = 30.6 Hz), 160.9, 133.3 (t, J = 4.4 Hz), 117.3 (t, J = 253.1 Hz), 108.8, 99.9, 55.5, 39.8 (t, J = 23.7 Hz), 37.4, 32.0, 29.4, 29.3, 29.0, 22.8, 22.6, 14.3. 19F NMR (CDCl3, 376 MHz) δ –105.2 (t, J = 16.9 Hz, 2 F). IR (film) 2928, 2854, 1742, 1599, 1462, 1431, 1294, 1205, 1153, 1070, 835 cm⁻¹. HRMS (ESI, m/z): calcd for C19H28F2O3Na [M+Na]⁺ 365.1904, found 365.1920.

**Experimental Procedures and Characterization of Compounds in Scheme 3.14**

**General Procedure A:** An oven-dried one-neck round-bottom flask was charged with aldehyde (14 mmol). Methanol (30 mL) was added as solvent, followed by the addition of NaBH₄ (21 mmol) as solid portion. The reaction mixture was stirred at 0 °C for 30 min. H₂O was added to quench the reaction, and methanol was removed under reduced pressure. The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL) three times and the combined organic phases were dried over anhydrous MgSO₄ or Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (0% to 30%) for elution to afford the desired benzyl alcohol.
**General Procedure B:** An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (7.2 mmol), and the system was evacuated and backfilled with \( \text{N}_2(g) \) three times. Dry CH\(_2\)Cl\(_2\) (35 mL) and DMF (0.19 mL) were added via a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (6.9 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. Next, a solution of benzyl alcohol derivative (6.0 mmol) dissolved in dry CH\(_2\)Cl\(_2\) (3.0 mL) was added dropwise at 0 °C, followed by dropwise addition of Et\(_3\)N (12 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. H\(_2\)O (10 mL) was added to quench the reaction, and the CH\(_2\)Cl\(_2\) was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 25 mL), and the combined organic layers were dried over anhydrous MgSO\(_4\) or Na\(_2\)SO\(_4\), filtered, and concentrated. Purification by flash chromatography provided the desired product.

**General Procedure C:** An oven-dried 20 mL scintillation vial was charged with substrate 3.3a-h (0.500 mmol), Pd(PPh\(_3\))\(_4\) (14.4 mg, 0.0125 mmol), and a magnetic stir bar. Dry o-xylene (0.010 L) was added via a syringe. Subsequently, the vial was transferred out of the glove box and placed on a pre-heated reaction block at 120 °C, and stirred for 15 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). \( \alpha,\alpha,\alpha \)-Trifluorotoluene (30 \( \mu \)L, 0.2443 mmol) or 2,2,2-trifluoroethanol (20 \( \mu \)L, 0.2745 mmol) was added as an internal standard, and the reaction mixture was stirred at rt at least 20 min to ensure thorough mixing. An aliquot was taken from the vial for \( ^{19}\text{F} \) NMR analysis. After determining the \( ^{19}\text{F} \) yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. Removal of the solvents in \textit{vacuo} and chromatographic purification provided the desired product 3.4a-h.

![3.3a-1](image)

\((4\text{-methoxyphenyl})\text{methanol (3.3a-1)}\)
General procedure A was followed using \( p \)-anisaldehyde (3.6 mL, 30 mmol), NaBH\(_4\) (1.7 g, 45 mmol), and MeOH (75 mL). Workup and chromatographic purification (20% to 30% EtOAc in hexanes) afforded the title compound 3.3a-1 as a colorless solid (4.1 g, 99%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.29 (d, \( J = 8.8 \) Hz, 2 H), 6.90 (d, \( J = 8.8 \) Hz, 2 H), 4.61 (s, 2 H), 3.82 (s, 3 H), 1.77 (br, 1 H). Spectroscopic data matched that from the previous report.\(^5\) mp 25–26 °C (lit.\(^6\) 25 °C).

4-methoxybenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3a)

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), 3.3a-1 (0.97 g, 7.0 mmol), Et\(_3\)N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH\(_2\)Cl\(_2\) (45 mL). Workup and chromatographic purification (0% to 10% EtOAc in hexanes) afforded the title compound 3.3a as a colorless oil (1.67 g, 74%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.02 (d, \( J = 7.6 \) Hz, 2 H), 7.66 (t, \( J = 7.4 \) Hz, 1 H), 7.48 (t, \( J = 7.8 \) Hz, 2 H), 7.25 (d, \( J = 8.4 \) Hz, 2 H), 6.85 (d, \( J = 8.4 \) Hz, 2 H), 5.28 (s, 2 H), 3.81 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 185.4 (t, \( J = 26.9 \) Hz), 161.9 (t, \( J = 30.6 \) Hz), 160.3, 135.2, 131.1, 130.7, 130.1 (t, \( J = 2.5 \) Hz), 129.1, 126.0, 114.2, 109.9 (t, \( J = 263.1 \) Hz), 69.2, 55.5. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) −107.5 (s, 2 F). IR (film) 2945, 2908, 2835, 1770, 1699, 1597, 1502, 1464, 1450, 1290, 1250, 1159, 1124, 1034, 920, 987, 816, 771, 715, 685, 667 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{17}\)H\(_{14}\)F\(_2\)O\(_4\)Na [M+Na]\(^+\) 343.0758, found 343.0765.

2,2-difluoro-3-(4-methoxyphenyl)-1-phenylpropan-1-one (3.4a)

General procedure C was followed using 3.3a (160 mg, 0.500 mmol), Pd(PPh\(_3\))\(_4\) (14.4 mg, 0.0125 mmol), and \( o \)-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes)
afforded the title compound 3.4a as an off-white solid (116 mg, 84%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.04 (dd, $J = 8.4, 1.6$ Hz, 2 H), 7.62 (t, $J = 7.4$ Hz, 1 H), 7.47 (t, $J = 7.8$ Hz, 2 H), 7.23 (d, $J = 8.4$ Hz, 2 H), 6.86 (d, $J = 8.0$ Hz, 2 H), 3.80 (s, 3 H), 3.47 (t, $J = 17.6$ Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 189.9 (t, $J = 31.2$ Hz), 159.3, 134.4, 132.4 (t, $J = 1.9$ Hz), 132.1, 130.3 (t, $J = 3.1$ Hz), 128.8, 123.3 (t, $J = 3.7$ Hz), 118.6 (t, $J = 252.5$ Hz), 114.1, 55.4, 39.6 (t, $J = 23.1$ Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –98.9 (t, $J = 16.9$ Hz, 2 F). IR (film) 3003, 2935, 2837, 1699, 1612, 1599, 1514, 1448, 1279, 1252, 1178, 1115, 1034, 945, 845, 822, 779, 714, 687, 663, 598 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{14}$F$_2$O$_2$Na [M+Na]$^+$ 299.0860, found 299.0847. mp 49–50 °C.

![p-tolylmethanol (3.3b-1)](image)

$p$-tolylmethanol (3.3b-1)

General procedure A was followed using $p$-tolualdehyde (3.5 mL, 30 mmol), NaBH$_4$ (1.7 g, 45 mmol), and MeOH (75 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound 3.3b-1 as an off-white solid (3.3 g, 90%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.27 (d, $J = 8.0$ Hz, 2 H), 7.19 (d, $J = 8.0$ Hz, 2 H), 4.66 (d, $J = 5.6$ Hz, 2 H), 2.37 (s, 3 H), 1.66 (t, $J = 5.8$ Hz, 1 H). Spectroscopic data matched that from the previous report.$^5$ mp 57–58 °C (lit.$^7$ 59 °C).

![4-methylbenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3b)](image)

4-methylbenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3b)

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), 3.3b-1 (0.85 g, 7.0 mmol), Et$_3$N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH$_2$Cl$_2$ (45 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 3.3b as a colorless oil (1.57 g, 74%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$
8.03 (d, $J = 8.0$ Hz, 2 H), 7.68–7.64 (m, 1 H), 7.49 (t, $J = 8.0$ Hz, 2 H), 7.20 (d, $J = 8.0$ Hz, 2 H), 7.14 (d, $J = 8.0$ Hz, 2 H), 5.30 (s, 2 H), 2.35 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.5 (t, $J = 27.5$ Hz), 161.9 (t, $J = 30.6$ Hz), 139.1, 135.2, 131.2 (t, $J = 1.9$ Hz), 130.9, 130.1 (t, $J = 2.5$ Hz), 129.5, 129.1, 128.8, 110.0 (t, $J = 263.7$ Hz), 69.3, 21.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.5 (s, 2 F). IR (film) 3032, 2960, 1776, 1715, 1699, 1599, 1520, 1450, 1379, 1306, 1257, 1157, 1126, 1101, 1080, 922, 810, 754, 714, 685 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{14}$F$_2$O$_3$Na [M+Na]$^+$ 327.0809, found 327.0794.

![3.4b](image)

**2,2-difluoro-1-phenyl-3-(p-tolyl)propan-1-one (3.4b)**

General procedure C was followed using 3.3b (152 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.4b as an off-white solid (110 mg, 85%). $^{1}$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.04 (d, $J = 8.0$ Hz, 2 H), 7.62 (t, $J = 7.4$ Hz, 1 H), 7.47 (t, $J = 7.6$ Hz, 2 H), 7.20 (d, $J = 8.0$ Hz, 2 H), 7.14 (d, $J = 7.6$ Hz, 2 H), 3.49 (t, $J = 17.8$ Hz, 2 H), 2.34 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 189.8 (t, $J = 31.2$ Hz), 137.5, 134.4, 132.4 (t, $J = 3.1$ Hz), 130.9, 130.3 (t, $J = 3.1$ Hz), 129.4, 128.8, 128.3 (t, $J = 3.7$ Hz), 118.6 (t, $J = 252.5$ Hz), 40.0 (t, $J = 23.1$ Hz), 21.3. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –98.8 (t, $J = 18.8$ Hz, 2 F). IR (film) 3028, 2924, 1703, 1599, 1516, 1448, 1279, 1171, 1115, 1040, 937, 903, 769, 714, 687, 663, 600 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{14}$F$_2$ONa [M+Na]$^+$ 283.0910, found 283.0901. mp 67–68 °C.

![3.3c-1](image)

**methyl 3-(hydroxymethyl)benzoate (3.3c-1)**
The preparation was followed according to literature report using 3-(methoxycarbonyl)benzoic acid (1.8 g, 0.010 mol), BH₃·SMe₂ (0.020 L, 0.020 mol), and THF (20 mL). Workup and chromatographic purification (20% to 50% EtOAc in hexanes) afforded the title compound as a colorless liquid (1.55 g, 93%). \(^1\)H NMR (CDCl₃, 400 MHz) \(\delta\) 8.04 (t, \(J = 1.6\) Hz, 1 H), 7.97 (dt, \(J = 7.6, 1.2\) Hz, 1 H), 7.58 (d, \(J = 7.6\) Hz, 1 H), 7.44 (t, \(J = 7.6\) Hz, 1 H), 4.76 (s, 2 H), 3.93 (s, 3 H), 1.91 (br, 1 H). HRMS (ESI, \(m/z\)): calcd for C₉H₁₁O₃ \([M+H]^+\) 167.0708, found 167.0705. Spectroscopic data matched that from the previous report.³

\[ \text{methyl 3-}((2,2\text{-difluoro-3-oxo-3-phenylpropanoyl)}\text{oxy)methyl} \text{benzoate (3.3c)} \]

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (1.4 g, 6.0 mmol), oxalyl chloride (0.46 mL, 5.5 mmol), 3.3c-1 (0.83 g, 5.0 mmol), Et₃N (1.4 mL, 0.010 mol), DMF (0.15 mL), and CH₂Cl₂ (30 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound as a colorless oil (1.17 g, 67%). \(^1\)H NMR (CDCl₃, 400 MHz) \(\delta\) 8.05–7.99 (m, 4 H), 7.66 (tt, \(J = 7.4, 1.2\) Hz, 1 H), 7.53–7.46 (m, 3 H), 7.43 (td, \(J = 7.6, 0.4\) Hz, 1 H), 5.38 (s, 2 H), 3.93 (s, 3 H). \(^13\)C NMR (CDCl₃, 125 MHz) \(\delta\) 185.4 (t, \(J = 26.9\) Hz), 166.6, 161.8 (t, \(J = 31.2\) Hz), 135.4, 134.3, 133.0, 131.0, 130.9, 130.3, 130.1 (t, \(J = 2.5\) Hz), 129.8, 129.2, 129.1, 110.0 (t, \(J = 263.7\) Hz), 68.5, 52.5. \(^19\)F NMR (CDCl₃, 376 MHz) \(\delta\) –107.3 (s, 2 F). IR (film) 2955, 1778, 1722, 1597, 1450, 1435, 1308, 1290, 1207, 1159, 1103, 922, 750, 712, 687 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C₁₈H₁₄F₂O₅Na \([M+Na]^+\) 371.0707, found 371.0706.

\[ \text{methyl 3-}((2,2\text{-difluoro-3-oxo-3-phenylpropyl})\text{benzoate (3.4c)} \]
General procedure C was followed using 3.3c (174 mg, 0.500 mmol), Pd(PPh₃)₄ (28.9 mg, 0.0250 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.4c as an off-white solid (123 mg, 81%).¹H NMR (CDCl₃, 400 MHz) δ 8.07 (dd, J = 8.8, 1.6 Hz, 2 H), 8.02 (s, 1 H), 7.99 (dd, J = 7.8, 1.4 Hz, 1 H), 7.65–7.61 (m, 1 H), 7.54 (d, J = 7.6 Hz, 2 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.42 (t, J = 7.6 Hz, 1 H), 3.93 (s, 3 H), 3.58 (t, J = 17.8 Hz, 2 H).¹³C NMR (CDCl₃, 125 MHz) δ 189.2 (t, J = 30.6 Hz), 167.0, 135.6, 134.6, 132.2, 132.1 (t, J = 2.5 Hz), 132.0 (t, J = 3.1 Hz), 130.6, 130.4 (t, J = 3.1 Hz), 129.1, 128.9, 128.7, 118.3 (t, J = 253.1 Hz), 52.4, 39.9 (t, J = 22.5 Hz).¹⁹F NMR (CDCl₃, 376 MHz) δ −98.6 (t, J = 16.9 Hz, 2 F). IR (film) 3065, 2953, 1724, 1703, 1597, 1448, 1435, 1288, 1203, 1173, 1111, 1086, 1040, 908, 741, 715, 694, 665, 604 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₇H₁₄F₂O₃Na [M+Na]⁺ 327.0809, found 327.0800. mp 44–45 °C.

(3-(trifluoromethyl)phenyl)methanol (3.3d-1)

General procedure A was followed using 3-(trifluoromethyl)benzaldehyde (1.3 mL, 10 mmol), NaBH₄ (0.57 g, 15 mmol), and MeOH (25 mL). Workup and chromatographic purification (10% to 30% EtOAc in hexanes) afforded the title compound 3.3d-1 as a colorless oil (1.73 g, 98%).¹H NMR (CDCl₃, 400 MHz) δ 7.65 (s, 1 H), 7.57–7.55 (m, 2 H), 7.49 (dd, J = 8.4, 6.8 Hz, 1 H), 4.78 (d, J = 5.6 Hz, 2 H), 1.83–1.79 (m, 1 H).¹⁹F NMR (CDCl₃, 376 MHz) δ −62.6 (s, 3 F). HRMS (ESI, m/z): calcd for C₈H₆F₃O [M-H]⁺ 175.0371, found 175.0372. Spectroscopic data matched that from the previous report.⁹
General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), 3.3d-1 (1.2 g, 7.0 mmol), Et₃N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH₂Cl₂ (45 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound 3.3d as a colorless oil (1.58 g, 63%). ¹H NMR (CDCl₃, 400 MHz) δ 8.05 (d, J = 8.0 Hz, 2 H), 7.70–7.65 (m, 1 H), 7.61 (d, J = 7.2 Hz, 1 H), 7.57 (s, 1 H), 7.53–7.46 (m, 4 H), 5.40 (s, 2 H). ¹³C NMR (CDCl₃, 125 MHz) δ 185.4 (t, J = 27.5 Hz), 161.8 (t, J = 30.6 Hz), 135.5, 134.9, 131.8, 131.4 (q, J = 32.5 Hz), 131.0 (t, J = 2.5 Hz), 130.1 (t, J = 2.5 Hz), 129.5, 129.2, 125.9 (q, J = 3.7 Hz), 125.3 (q, J = 3.7 Hz), 123.9 (q, J = 271.2 Hz), 110.1 (t, J = 264.4 Hz), 68.1. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.3 (s, 2 F), –62.7 (s, 3 F). IR (film) 3070, 1780, 1715, 1701, 1599, 1450, 1333, 1310, 1205, 1165, 1128, 1099, 1074, 920, 885, 802, 700, 685, 661, 588 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₇H₁₂F₅O₃ [M+H]⁺ 359.0707, found 359.0704.

2,2-difluoro-1-phenyl-3-(3-(trifluoromethyl)phenyl)propan-1-one (3.4d)

General procedure C was followed using 3.3d (179 mg, 0.500 mmol), Pd(PPh₃)₄ (28.9 mg, 0.0250 mmol), and o-xylene (0.010 L). The reaction was run at 140 °C. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.4d as an off-white solid (95.0 mg, 60%). ¹H NMR (CDCl₃, 400 MHz) δ 8.07 (d, J = 7.6 Hz, 2 H), 7.64 (t, J = 7.6 Hz, 1 H), 7.60–7.44 (m, 6 H), 3.59 (t, J = 17.6 Hz, 2 H). ¹³C NMR (CDCl₃, 125 MHz) δ 189.1 (t, J = 30.6 Hz), 134.7, 134.5, 132.6 (t, J = 3.7 Hz), 132.0 (t, J = 3.1 Hz), 131.0 (q, J = 32.5 Hz), 130.4 (t, J = 3.1 Hz), 129.1, 128.9, 127.8 (q, J = 3.7 Hz), 124.7 (q, J = 3.4 Hz), 124.2 (q, J = 270.9 Hz), 118.2 (t, J = 253.7 Hz), 39.9 (t, J = 23.1 Hz). ¹⁹F NMR (CDCl₃, 376 MHz) δ –98.5 (t, J = 16.9 Hz, 2 F), –62.7 (s, 3 F). IR (film) 3068, 2928, 1699, 1599, 1450, 1329, 1279, 1169, 1126, 1076, 1040, 920, 771, 715, 702, 658 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₆H₁₂F₃O [M+H]⁺ 315.0808, found 315.0794. mp 49–50 °C.
4-(hydroxymethyl)benzonitrile (3.3e-1)

General procedure A was followed using 4-cyanobenzaldehyde (3.0 g, 23 mmol), NaBH₄ (1.3 g, 34 mmol), and MeOH (60 mL). Workup and chromatographic purification (20% to 50% EtOAc in hexanes) afforded the title compound 3.3e-1 as an off-white solid (2.8 g, 91%). ¹H NMR (CDCl₃, 400 MHz) δ 7.65 (d, J = 8.0 Hz, 2 H), 7.48 (d, J = 8.0 Hz, 2 H), 4.79 (d, J = 3.6 Hz, 2 H), 2.05–2.01 (m, 1 H). Spectroscopic data matched that from the previous report.¹⁰a mp 41–42 °C (lit.¹⁰b 41–42 °C).

4-cyanobenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3e)

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (2.0 g, 8.4 mmol), oxalyl chloride (0.68 mL, 8.0 mmol), 3.3e-1 (0.93 g, 7.0 mmol), Et₃N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH₂Cl₂ (45 mL). Workup and chromatographic purification (10% to 30% EtOAc in hexanes) afforded the title compound 3.3e as a pale yellow solid (1.3 g, 59%). ¹H NMR (CDCl₃, 400 MHz) δ 8.06 (d, J = 8.0 Hz, 2 H), 7.70 (t, J = 7.6 Hz, 1 H), 7.64 (d, J = 8.0 Hz, 2 H), 7.52 (t, J = 7.6 Hz, 2 H), 7.43 (d, J = 8.0 Hz, 2 H), 5.40 (s, 2 H).¹³C NMR (CDCl₃, 125 MHz) δ 185.4 (t, J = 27.5 Hz), 161.7 (t, J = 30.6 Hz), 139.1, 135.6, 132.7, 130.9 (t, J = 2.5 Hz), 130.1 (t, J = 2.5 Hz), 129.3, 128.7, 118.5, 112.9, 110.1 (t, J = 264.4 Hz), 67.7.¹⁹F NMR (CDCl₃, 376 MHz) δ −107.0 (s, 2 F). IR (film) 3068, 2231, 1778, 1715, 1699, 1597, 1450, 1308, 1159, 1099, 926, 823, 714, 685, 669 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₇H₁₂F₂NO₃ [M+H]⁺ 316.0785, found 316.0778. mp 79–80 °C.
4-(2,2-difluoro-3-oxo-3-phenylpropyl)benzonitrile (3.4e)

General procedure C was followed using 3.3e (157.6 mg, 0.500 mmol), Pd(PPh₃)₄ (116 mg, 0.100 mmol), and α-xylene (0.050 L) in 100 mL Schlenk tube. The reaction was run at 140 °C for 24 h. Workup and chromatographic purification (20% to 50% CH₂Cl₂ in hexanes) afforded the title compound 3.4e as a pale yellow solid (44.0 mg, 32%). ¹H NMR (CDCl₃, 400 MHz) δ 8.07 (d, J = 8.0 Hz, 2 H), 7.67–7.62 (m, 3 H), 7.52–7.45 (m, 4 H), 3.59 (t, J = 15.6 Hz, 2 H). ¹³C NMR (CDCl₃, 125 MHz) δ 188.7 (t, J = 31.2 Hz), 137.2 (t, J = 3.7 Hz), 134.8, 132.3, 131.9, 131.7 (t, J = 2.5 Hz), 130.4 (t, J = 3.1 Hz), 129.0, 118.8, 118.1 (t, J = 254.4 Hz), 111.9, 40.1 (t, J = 23.1 Hz). ¹⁹F NMR (CDCl₃, 376 MHz) δ –97.9 (t, J = 18.8 Hz, 2 F). IR (film) 3068, 2926, 2230, 1703, 1597, 1506, 1448, 1279, 1209, 1171, 1115, 1038, 943, 904, 777, 714, 656, 602, 552 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₆H₁₂F₂NO [M+H]⁺ 272.0887, found 272.0875. mp 79 °C.

4-nitrobenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3f)

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (1.7 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), 4-nitrobenzyl alcohol (0.92 g, 6.0 mmol), Et₃N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH₂Cl₂ (35 mL). Workup and chromatographic purification (10% to 30% EtOAc in hexanes) afforded the title compound 3.3f as an off-white solid (1.03 g, 51%). ¹H NMR (CDCl₃, 400 MHz) δ 8.21 (d, J = 8.4 Hz, 2 H), 8.07 (dd, J = 8.6, 1.4 Hz, 2 H), 7.70 (tt, J = 7.4, 1.5 Hz, 1 H), 7.54–7.48 (m, 4 H), 5.45 (s, 2 H). ¹³C NMR (CDCl₃, 125 MHz) δ 185.4 (t, J = 31.2 Hz), 148.2, 141.0, 135.6, 130.9, 130.2 (t, J = 2.5 Hz), 129.3, 128.8, 124.1, 110.2 (t, J = 265.0 Hz), 67.4. ¹⁹F
NMR (CDCl$_3$, 376 MHz) $\delta$ –107.0 (s, 2 F). IR (film) 3080, 1778, 1715, 1699, 1599, 1526, 1450, 1348, 1310, 1257, 1159, 1128, 1101, 926, 843, 791, 739, 714, 687 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{12}$F$_2$NO$_5$ [M+H]$^+$ 336.0684, found 336.0683. mp 53–54 °C.

**2,2-difluoro-3-(4-nitrophenyl)-1-phenylpropan-1-one (3.4f)**

General procedure C was followed using 3.3f (167.6 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (28.9 mg, 0.0250 mmol), and o-xylene (0.010 L). The reaction was run at 140 °C for 24 h. Workup and chromatographic purification (20% to 50% CH$_2$Cl$_2$ in hexanes) afforded the title compound 3.4f as an off-white solid (34.2 mg, 23%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.20 (d, $J$ = 8.0 Hz, 2 H), 8.08 (d, $J$ = 8.0 Hz, 2 H), 7.66 (t, $J$ = 7.4 Hz, 1 H), 7.54–7.48 (m, 4 H), 3.64 (t, $J$ = 17.4 Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 188.7 (t, $J$ = 30.6 Hz), 147.7, 139.2 (t, $J$ = 3.1 Hz), 134.9, 132.1, 131.7 (t, $J$ = 2.5 Hz), 130.4 (t, $J$ = 3.1 Hz), 129.0, 123.7, 118.1 (t, $J$ = 254.4 Hz), 39.8 (t, $J$ = 23.1 Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –97.8 (t, $J$ = 16.9 Hz, 2 F). IR (film) 3080, 2928, 1699, 1599, 1520, 1450, 1348, 1279, 1171, 1115, 1055, 1040, 904, 856, 773, 733, 715, 694, 669, 600 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{15}$H$_{12}$F$_2$NO$_3$ [M+H]$^+$ 292.0785, found 292.0786. mp 89–90 °C.

(2-methoxyphenyl)methanol (3.3g-1)

General procedure A was followed using o-anisaldehyde (2.7 g, 20 mmol), NaBH$_4$ (1.1 g, 30 mmol), and MeOH (50 mL). Workup and chromatographic purification (20% to 50% EtOAc in hexanes) afforded the title compound 3.3g-1 as a colorless oil (2.3 g, 83%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.31–7.28 (m, 2 H), 6.96 (t, $J$ = 7.4 Hz, 1 H), 6.90 (d, $J$ = 8.4 Hz, 1 H), 4.70 (d, $J$ = 6.0 Hz, 2 H), 3.88 (s, 3 H), 2.32 (t, $J$ = 6.4
Hz, 1 H). HRMS (ESI, m/z): calcd for C₈H₉O₂ [M–H]⁺ 137.0603, found 137.0587. Spectroscopic data matched that from the previous report.¹¹

**2-methoxybenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3g)**

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (1.7 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), 3.3g-1 (0.83 g, 6.0 mmol), Et₃N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH₂Cl₂ (35 mL). Workup and chromatographic purification (2% to 10% EtOAc in hexanes) afforded the title compound 3.3g as a colorless oil (1.51 g, 79%). ¹H NMR (CDCl₃, 400 MHz) δ 8.05 (d, J = 8.0 Hz, 2 H), 7.66 (t, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.6 Hz, 2 H), 7.32 (t, J = 8.0 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 1 H), 6.91 (t, J = 7.4 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 5.40 (s, 2 H), 3.73 (s, 3 H). ¹³C NMR (CDCl₃, 125 MHz) δ 185.4 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 157.8, 135.2, 131.3, 130.6, 130.3, 130.1 (t, J = 2.5 Hz), 129.1, 122.2, 120.6, 110.6, 109.9 (t, J = 263.1 Hz), 65.1, 55.5. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.6 (s, 2 F). IR (film) 3070, 2964, 2841, 1770, 1715, 1699, 1599, 1497, 1466, 1450, 1381, 1308, 1254, 1157, 1124, 1101, 1028, 922, 808, 756, 712, 687, 586 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₇H₁₄F₂O₄Na [M+Na]⁺ 343.0758, found 343.0746.

**2,2-difluoro-3-(2-methoxyphenyl)-1-phenylpropan-1-one (3.4g)**

General procedure C was followed using 3.3g (160 mg, 0.500 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.4g as a colorless oil (124 mg, 90%). ¹H NMR (CDCl₃, 400 MHz) δ 8.03 (d, J = 7.6 Hz, 2 H), 7.60 (t, J = 7.2 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 2 H), 7.32–7.29 (m, 1 H), 7.28–7.25 (m, 1
H), 6.95 (t, \( J = 7.6 \) Hz, 1 H), 6.79 (d, \( J = 8.0 \) Hz, 1 H), 3.60 (t, \( J = 17.4 \) Hz, 2 H), 3.58 (s, 3 H).\(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 189.7 (t, \( J = 29.4 \) Hz), 158.1, 134.1, 132.6, 132.5, 130.2 (t, \( J = 3.7 \) Hz), 129.4, 128.6, 120.7, 120.0 (t, \( J = 4.4 \) Hz), 118.8 (t, \( J = 251.9 \) Hz), 110.6, 55.1, 35.2 (t, \( J = 23.7 \) Hz).\(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –98.8 (t, \( J = 18.8 \) Hz, 2 F). IR (film) 2939, 2839, 1703, 1599, 1497, 1464, 1450, 1290, 1252, 1176, 1124, 1051, 1026, 933, 754, 714, 687, 667 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{16}\)H\(_{14}\)F\(_2\)O\(_2\)Na [M+Na]\(^+\) 299.0860, found 299.0847.

\( o\)-tolylmethanol (3.3h-1)

General procedure A was followed using \( o\)-tolualdehyde (1.7 g, 15 mmol), NaBH\(_4\) (0.87 g, 23 mmol), and MeOH (38 mL). Workup and chromatographic purification (15% to 35% EtOAc in hexanes) afforded the title compound 3.3h-1 as a colorless solid (1.73 g, 94%).\(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.38–7.36 (m, 1 H), 7.24–7.18 (m, 3 H), 4.71 (d, \( J = 2.8 \) Hz, 2 H), 2.38 (s, 3 H), 1.58 (br, 1 H). Spectroscopic data matched that from the previous report.\(^5\) mp 35–36 °C (lit.\(^5\) 37–38 °C).

\( 2\)-methylbenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.3h)

General procedure B was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate 3.1a-1 (1.7 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), 3.3h-1 (0.73 g, 6.0 mmol), Et\(_3\)N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH\(_2\)Cl\(_2\) (35 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 3.3h as a colorless oil (1.48 g, 81%).\(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.03 (d, \( J = 7.6 \) Hz, 2 H), 7.66 (t, \( J = 7.4 \) Hz, 1 H), 7.48 (t, \( J = 7.6 \) Hz, 2 H), 7.30–7.25 (m, 2 H), 7.18 (t, \( J = 6.8 \) Hz, 2 H), 5.36 (s, 2 H), 2.28 (s, 3 H).\(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 185.4 (t, \( J = 27.5 \) Hz), 161.9 (t,
$J = 30.6 \text{ Hz}$, 137.6, 135.3, 131.9, 131.1, 130.7, 130.1 (t, $J = 2.5 \text{ Hz}$), 129.5, 129.1, 126.3, 110.0 (t, $J = 263.1 \text{ Hz}$), 67.9, 18.9. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ −107.3 (s, 2 F). IR (film) 3068, 2974, 1776, 1715, 1697, 1599, 1450, 1310, 1257, 1157, 1101, 1078, 922, 804, 762, 744, 712, 685, 584 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{17}$H$_{14}$F$_2$O$_3$Na [M+Na]$^+$ 327.0809, found 327.0801.

**2,2-difluoro-1-phenyl-3-(o-tolyl)propan-1-one (3.4h)**

General procedure C was followed using 3.3h (152 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.4h as a colorless oil (114 mg, 88%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.05 (d, $J = 7.6 \text{ Hz}$, 2 H), 7.63 (t, $J = 7.4 \text{ Hz}$, 1 H), 7.48 (t, $J = 7.8 \text{ Hz}$, 2 H), 7.28–7.26 (m, 1 H), 7.22–7.15 (m, 3 H), 3.56 (t, $J = 18.4 \text{ Hz}$, 2 H), 2.37 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 190.0 (t, $J = 31.2 \text{ Hz}$), 138.3, 134.5, 132.3, 131.9, 130.8, 130.4 (t, $J = 3.1 \text{ Hz}$), 130.0 (t, $J = 2.5 \text{ Hz}$), 128.8, 128.0, 126.1, 119.1 (t, $J = 252.5 \text{ Hz}$), 36.9 (t, $J = 23.1 \text{ Hz}$), 20.2 (t, $J = 1.9 \text{ Hz}$). $^{19}$F NMR (CDCl$_3$, 376 MHz) δ −98.6 (t, $J = 18.8 \text{ Hz}$, 2 F). IR (film) 3063, 3024, 1703, 1597, 1497, 1448, 1275, 1184, 1171, 1115, 1057, 1028, 904, 744, 714, 687, 665, 602 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{14}$F$_2$ONa [M+Na]$^+$ 283.0910, found 283.0905.

**Experimental Procedures and Characterization of Compounds in Scheme 3.16**
**General Procedure D:** An oven-dried three-neck flask was charged with activated Zn (3.2 g, 49 mmol). The reaction vessel was equipped with a reflux condenser and two rubber septa, evacuated and backfilled with \( \text{N}_2(\text{g}) \) three times. Dry THF (0.050 L) was added, followed by addition of the initiator 1,2-dibromoethane (0.25 mL, 2.9 mmol) under \( \text{N}_2(\text{g}) \). To activate the Zn, the reaction mixture was heated with a heat gun until the THF boiled suddenly. Heating was stopped, and the mixture was cooled to rt. This heating/cooling sequence for activation of Zn was repeated four more times (5 total). Subsequently, the reaction mixture was heated to 70 °C (oil-bath), and a solution of aldehyde (25 mmol) and ethyl bromodifluoroacetate (25 mmol) was added dropwise at a rate that maintained a gentle reflux. The resulting reaction mixture was stirred at 70 °C for 1 h, and then cooled to 50 °C and stirred overnight. The reaction mixture was cooled to 0 °C, and 1 N HCl(aq) was added until the residual Zn was consumed (roughly 100 mL). The reaction mixture was warmed to rt, and transferred to a separation funnel. The phases were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated. Purification by flash chromatography provided the desired product.

**General Procedure E:** An oven-dried three-neck flask was equipped with a liquid addition funnel, three-way valve and two rubber septa, evacuated and backfilled with \( \text{N}_2(\text{g}) \) three times. Dry \( \text{CH}_2\text{Cl}_2 \) (0.10 L) and oxalyl chloride (59 mmol) were added sequentially at rt, and the reaction solution was cooled to –78 °C. A solution of anhydrous DMSO (78 mmol) in dry \( \text{CH}_2\text{Cl}_2 \) (0.010 L) was added dropwise at –78 °C, and then the reaction solution was stirred continually at this temperature for 1 h. Next, a solution of alcohol (19.5 mmol) dissolved in dry \( \text{CH}_2\text{Cl}_2 \) (0.010 L) was added dropwise at –78 °C, and then the resulting reaction solution was stirred continually at this temperature for 1 h. Et3N (117 mmol) was added dropwise at –78 °C, and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was gradually warmed to rt, and stirred at rt for 2 h. \( \text{H}_2\text{O} \) (0100 mL) was added to quench the reaction, and \( \text{CH}_2\text{Cl}_2 \) was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 100 mL), and the combined organic layers were dried over anhydrous \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated. Purification by flash chromatography provided the desired product.
General Procedure F: A one-neck round-bottom flask was charged with β-keto ester (16 mmol), and MeOH (8.0 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (16 mmol) dissolved in MeOH (8.0 mL) was added dropwise, and then the reaction solution was warmed to rt, and stirred at rt for 7 h. MeOH was removed under reduced pressure. EtOAc (8.0 mL) and ether (8.0 mL) were added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried in vacuo to give potassium salt.

General Procedure G: An oven-dried one-neck round-bottom flask was charged with potassium salt (5.0 mmol), and the system was evacuated and backfilled with N2(g) three times. Dry CH2Cl2 (15 mL) and DMF (0.75 mL) were added via a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (5.0 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. Next, a solution of cinnamyl alcohol (6.5 mmol) dissolved in dry CH2Cl2 (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et3N (6.0 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. H2O (8.0 mL) was added to quench the reaction, and CH2Cl2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 15 mL), and the combined organic layers were dried over anhydrous Na2SO4, filtered, and concentrated. Purification by flash chromatography provided the desired product.

ethyl 2,2-difluoro-3-hydroxy-3-(4-methoxyphenyl)propanoate (3.5a-3)

General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), p-anisaldehyde (3.0 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 3.5a-3 as a colorless oil (5.4 g, 84%). 1H NMR (CDCl3, 400 MHz) δ 7.37 (d, J = 8.8 Hz, 2 H), 6.92 (d, J = 8.8 Hz, 2 H), 5.12 (ddd, J = 15.2, 8.0, 5.2 Hz, 1 H), 4.32 (q, J = 7.2 Hz, 2 H), 3.82 (s, 3 H),
2.63 (d, $J = 5.2$ Hz, 1 H), 1.31 (t, $J = 7.2$ Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 163.8 (t, $J = 31.2$ Hz), 160.5, 129.2, 126.7, 114.1, 114.0 (dd, $J = 257.5, 252.5$ Hz), 73.6 (dd, $J = 26.2, 23.8$ Hz), 63.3, 55.5, 14.1. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ -120.4 (dd, $J = 259.4, 15.0$ Hz, 1 F), -114.2 (dd, $J = 259.4, 7.5$ Hz, 1 F). HRMS (ESI, $m/z$): calcd for C$_{12}$H$_{14}$F$_2$O$_4$Na $[M+Na]^+$ 283.0758, found 283.0746. Spectroscopic data matched that from the previous report.$^{12}$

ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (3.5a-2)

General procedure E was followed using oxalyl chloride (5.0 mL, 59 mmol), DMSO (5.5 mL, 78 mmol), 3.5a-3 (5.07 g, 19.5 mmol), Et$_3$N (16 mL, 120 mmol) and CH$_2$Cl$_2$ (120 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 3.5a-2 as a colorless oil (4.38 g, 87%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.08 (d, $J = 8.8$ Hz, 2 H), 6.99 (d, $J = 8.8$ Hz, 2 H), 4.39 (q, $J = 7.2$ Hz, 2 H), 3.91 (s, 3 H), 1.33 (t, $J = 7.2$ Hz, 3 H). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ -107.3 (s, 2 F). HRMS (ESI, $m/z$): calcd for C$_{12}$H$_{12}$F$_2$O$_4$Na $[M+Na]^+$ 281.0601, found 281.0587. Spectroscopic data matched that from the previous report.$^{13}$

potassium 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (3.5a-1)

General procedure F was followed using 3.5a-2 (4.08 g, 15.8 mmol), KOH (0.890 g, 15.8 mmol), and MeOH (16 mL). Workup afforded the title compound 3.5a-1 as a colorless solid (3.68 g, 87%). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.99 (d, $J = 8.8$ Hz, 2 H), 7.04 (t, $J = 8.8$ Hz, 2 H), 3.84 (s, 3 H). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 188.0 (t, $J = 27.5$ Hz), 163.5, 162.5 (t, $J = 23.8$ Hz), 131.6, 125.5, 113.8, 111.4 (t, $J = 261.2$ Hz), 55.6. $^{19}$F NMR (DMSO-$d_6$, 376 MHz) $\delta$ -104.9 (s, 2 F). IR (film) 2970, 2845, 1693, 1676,
3,5-dimethoxybenzyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (3.5a)

General procedure G was followed using potassium 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate 3.5a-1 (1.6 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.7 mmol), 3,5-dimethoxybenzyl alcohol (0.84 g, 5.0 mmol), Et₃N (1.4 mL, 10 mmol), DMF (0.19 mL), and CH₂Cl₂ (30 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound 3.5a as an off-white solid (1.5 g, 79%). ¹H NMR (CDCl₃, 400 MHz) δ 8.03 (d, J = 8.8 Hz, 2 H), 6.94 (dt, J = 9.2, 2.4 Hz, 2 H), 6.45 (d, J = 2.4 Hz, 2 H), 6.41 (t, J = 2.2 Hz, 1 H), 5.28 (s, 2 H), 3.90 (s, 3 H), 3.76 (s, 6 H). ¹³C NMR (CDCl₃, 125 MHz) δ 183.7 (t, J = 27.5 Hz), 165.3, 162.1 (t, J = 30.6 Hz), 161.1, 136.2, 132.7 (t, J = 2.5 Hz), 124.0 (t, J = 2.5 Hz), 114.5, 110.3 (t, J = 263.1 Hz), 106.1, 101.0, 68.9, 55.8, 55.5. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.0 (s, 2 F). IR (film) 2957, 2937, 2841, 1774, 1701, 1686, 1599, 1512, 1458, 1431, 1311, 1267, 1157, 1099, 1067, 1024, 922, 843, 791, 768, 696 cm⁻¹. HRMS (ESI, m/z): calcd for C₁⁹H₁₈F₂O₆Na [M+Na]⁺ 403.0969, found 403.0960. mp 52–53 °C.

3-(3,5-dimethoxyphenyl)-2,2-difluoro-1-(4-methoxyphenyl)propan-1-one (3.6a)

General procedure C was followed using 3.5a (190 mg, 0.500 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 3.6a as a colorless oil (128 mg, 76%). ¹H NMR (CDCl₃, 400 MHz) δ 8.06 (d, J = 8.4 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 6.46 (s, 2 H), 6.40 (t, J = 2.2 Hz, 1 H), 3.89 (s, 3 H), 3.77 (s, 6
H), 3.44 (t, J = 17.8 Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 188.0 (t, J = 30.0 Hz), 164.6, 160.8, 133.7 (t, J = 3.7 Hz), 132.9 (t, J = 3.1 Hz), 125.2 (t, J = 1.9 Hz), 118.7 (t, J = 253.7 Hz), 114.1, 109.1, 99.8, 55.7, 55.5, 40.7 (t, J = 23.1 Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –98.1 (t, J = 18.8 Hz, 2 F). IR (film) 3003, 2957, 2939, 2841, 1691, 1599, 1578, 1512, 1460, 1431, 1317, 1265, 1205, 1165, 1151, 1113, 1068, 1030, 947, 879, 843, 796, 769, 715, 696, 688, 594 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{18}$H$_{18}$F$_{2}$O$_4$Na [M+Na]$^+$ 359.1071, found 359.1056.

![3.5b-3](image)

**ethyl 2,2-difluoro-3-(4-fluorophenyl)-3-hydroxypropanoate (3.5b-3)**

General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), 4-fluorobenzaldehyde (2.6 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 3.5b-3 as a colorless oil (5.1 g, 82%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.46–7.42 (m, 2 H), 7.10 (t, J = 8.8 Hz, 2 H), 5.18 (ddd, J = 15.2, 8.0, 5.2 Hz, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 2.71 (d, J = 4.8 Hz, 1 H), 1.32 (t, J = 7.2 Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 163.7 (t, J = 31.2 Hz), 163.4 (d, J = 246.2 Hz), 130.4 (t, J = 2.5 Hz), 129.8 (d, J = 7.5 Hz), 115.6 (d, J = 21.2 Hz), 113.7 (dd, J = 257.5, 252.5 Hz), 73.3 (dd, J = 27.5, 23.8 Hz), 63.5, 14.0. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –120.6 (dd, J = 263.2, 15.0 Hz, 1 F), –113.8 (dd, J = 263.2, 7.5 Hz, 1 F), –112.2 (m, 1 F). HRMS (ESI, m/z): calcd for C$_{11}$H$_{11}$F$_{3}$O$_3$Li [M+Li]$^+$ 255.0820, found 255.0831. Spectroscopic data matched that from the previous report.$^{12}$

![3.5b-2](image)

**ethyl 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate (3.5b-2)**
General procedure E was followed using oxalyl chloride (5.0 mL, 58 mmol), DMSO (5.5 mL, 77 mmol), 3.5b-3 (4.76 g, 19.2 mmol), Et₃N (16 mL, 120 mmol) and CH₂Cl₂ (130 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 3.5b-2 as a colorless oil (3.93 g, 83%). ¹H NMR (CDCl₃, 400 MHz) δ 8.16–8.13 (m, 2 H), 7.21 (t, J = 8.6 Hz, 2 H), 4.40 (q, J = 7.2 Hz, 2 H), 1.34 (t, J = 7.2 Hz, 3 H). ¹³C NMR (CDCl₃, 125 MHz) δ 184.2 (t, J = 28.1 Hz), 167.1 (d, J = 257.5 Hz), 161.9 (t, J = 30.0 Hz), 133.2 (dt, J = 8.8, 3.1 Hz), 127.6 (m), 116.6 (d, J = 22.5 Hz), 110.0 (t, J = 262.5 Hz), 64.1, 14.0. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.5 (s, 2 F), –100.4 (m, 1 F). HRMS (ESI, m/z): calcd for C₁₁H₉F₃O₃Na [M+Na]⁺ 269.0401, found 269.0411. Spectroscopic data matched that from the previous report.¹⁴

![3.5b-1](image)

potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate (3.5b-1)

General procedure F was followed using 3.5b-2 (3.72 g, 15.1 mmol), KOH (0.850 g, 15.1 mmol), and MeOH (0.030 L). Workup afforded the title compound 3.5b-1 as a colorless solid (3.28 g, 85%). ¹H NMR (DMSO- d₆, 400 MHz) δ 8.09 (dd, J = 8.6, 5.4 Hz, 2 H), 7.37 (t, J = 9.0 Hz, 2 H). ¹³C NMR (DMSO- d₆, 125 MHz) δ 188.4 (t, J = 28.1 Hz), 165.3 (d, J = 252.5 Hz), 162.2 (t, J = 23.8 Hz), 132.3 (d, J = 10.0 Hz), 129.3 (d, J = 3.8 Hz), 115.8 (d, J = 21.2 Hz), 111.3 (t, J = 261.2 Hz). ¹⁹F NMR (DMSO- d₆, 376 MHz) δ –105.4 (s, 2 F), –104.5 (m, 1 F). IR (film) 3086, 1718, 1678, 1645, 1605, 1512, 1404, 1300, 1250, 1161, 1099, 912, 849, 816, 764, 717, 688, 573, 521, 480 cm⁻¹. HRMS (ESI, m/z): calcd for C₉H₄F₃K₂O₃ [M+K]⁺ 294.9387, found 294.9375. mp 173–174 °C decomposed.

![3.5](image)

3,5-dimethoxybenzyl 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate (3.5b)
General procedure G was followed using potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate 3.5b-1 (1.5 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.7 mmol), 3,5-dimethoxybenzyl alcohol (0.84 g, 5.0 mmol), Et$_3$N (1.4 mL, 10 mmol), DMF (0.19 mL), and CH$_2$Cl$_2$ (30 mL). Workup and chromatographic purification (5% to 15% EtOAc in hexanes) afforded the title compound 3.5b as a light yellow oil (1.3 g, 71%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.11–8.07 (m, 2 H), 7.16 (t, $J = 8.6$ Hz, 2 H), 6.44–6.42 (m, 3 H), 5.28 (s, 2 H), 3.77 (s, 6 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 184.0 (t, $J = 27.5$ Hz), 167.0 (d, $J = 257.5$ Hz), 161.7 (t, $J = 30.6$ Hz), 161.1, 136.0, 133.1 (dt, $J = 10.0$, 2.5 Hz), 127.5 (d, $J = 2.5$ Hz), 116.6 (d, $J = 21.2$ Hz), 110.0 (t, $J = 263.7$ Hz), 106.3, 100.9, 69.1, 55.6. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –100.4 (m, 1 F), –107.3 (s, 2 F). IR (film) 2959, 1774, 1701, 1599, 1508, 1473, 1431, 1304, 1244, 1207, 1159, 1101, 922, 850, 766, 715, 690, 615, 575 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{15}$F$_3$O$_5$Na$^{+}$ 391.0769, found 391.0762.

![Image](image_url)

3-(3,5-dimethoxyphenyl)-2,2-difluoro-1-(4-fluorophenyl)propan-1-one (3.6b)

General procedure C was followed using 3.5b (184 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.6b as a colorless oil (133 mg, 82%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.11–8.07 (m, 2 H), 7.15 (t, $J = 8.8$ Hz, 2 H), 6.45 (d, $J = 2.4$ Hz, 2 H), 6.40 (t, $J = 2.2$ Hz, 1 H), 3.77 (s, 6 H), 3.45 (t, $J = 17.8$ Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 188.1 (t, $J = 31.2$ Hz), 166.5 (d, $J = 256.2$ Hz), 160.8, 133.4 (t, $J = 3.7$ Hz), 133.3 (dt, $J = 10.0$, 3.7 Hz), 128.7 (q, $J = 2.5$ Hz), 118.5 (t, $J = 253.1$ Hz), 116.1 (d, $J = 22.5$ Hz), 109.1, 99.8, 55.5, 40.4 (t, $J = 23.1$ Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –102.3 (m, 1 F), –98.1 (t, $J = 16.9$ Hz, 2 F). IR (film) 3001, 2939, 2839, 1701, 1599, 1508, 1466, 1458, 1431, 1412, 1319, 1277, 1242, 1205, 1161, 1111, 1070, 947, 879, 849, 771, 712, 688, 613, 596, 586 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{15}$F$_3$O$_3$ [M+H]$^+$ 325.1052, found 325.1061.
ethyl 2,2-difluoro-3-hydroxy-3-(3-(trifluoromethyl)phenyl)propanoate (3.5c-3)

General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), 3-(trifluoromethyl)benzaldehyde (3.3 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 3.5c-3 as a colorless oil (5.7 g, 78%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.74 (s, 1 H), 7.66 (d, \(J = 7.6\) Hz, 2 H), 7.53 (t, \(J = 7.8\) Hz, 1 H), 5.29–5.23 (m, 1 H), 4.33 (q, \(J = 7.2\) Hz, 2 H), 2.95 (d, \(J = 4.8\) Hz, 1 H), 1.31 (t, \(J = 7.2\) Hz, 3 H). \(^1\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 163.5 (t, \(J = 31.2\) Hz), 135.7, 131.3, 131.0 (q, \(J = 32.1\) Hz), 129.1, 126.2 (q, \(J = 3.7\) Hz), 124.7 (q, \(J = 4.1\) Hz), 124.1 (q, \(J = 270.9\) Hz), 113.6 (dd, \(J = 258.7\) Hz, 253.7 Hz), 73.3 (dd, \(J = 28.1\) Hz, 24.4 Hz), 63.6, 14.0. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –120.3 (dd, \(J = 263.2\), 15.0 Hz, 1 F), –113.0 (dd, \(J = 263.2\), 7.5 Hz, 1 F), –62.7 (s, 3 F). IR (film) 3493, 2989, 2945, 1759, 1452, 1377, 1331, 1169, 1128, 1074, 854, 783, 729, 702, 667 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{12}\)H\(_{11}\)F\(_5\)O\(_3\)Na [M+Na]\(^+\) 321.0526, found 321.0533.

ethyl 2,2-difluoro-3-oxo-3-(3-(trifluoromethyl)phenyl)propanoate (3.5c-2)

Dess-Martin periodinane (8.53 g, 20.1 mmol) was added into a solution of compound 3.5c-3 (4.61 g, 15.5 mmol) dissolved in CH\(_2\)Cl\(_2\) (0.120 L) at 0 °C, and the solution was stirred at rt for 3 h. CH\(_2\)Cl\(_2\) was removed under reduced pressure, and the residue was charged with ether (170 mL). Next, the mixture was cooled to 0 °C, and Na\(_2\)S\(_2\)O\(_3\) (sat’d), water and NaHCO\(_3\) (sat’d, 75 mL each) were added into the mixture and stirred until the two phases were generated. The solution was transferred to a separation funnel, and the organic layer was collected. The aqueous layer was extracted with ether (2 x 170 mL), and the
combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated to provide the title compound 3.5c-2 as a colorless liquid (4.5g, 98%). Occasionally, a small amount of the hydrate form of the ketone was observed by $^{19}$F NMR [(CDCl$_3$, 376 MHz) $\delta$ -117.2 (s, 2 F)]. To convert the hydrate form to keto form, the crude product was stirred together with activated 4Å molecular sieves in dry toluene for several hours. The molecular sieves were removed by filtration and washed with dry toluene. The filtrate was concentrated, and the product was dried in vacuo. The colorless liquid product was used in the next step without further purification. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.35 (s, 1 H), 8.28 (d, $J$ = 7.6 Hz, 1 H), 7.95 (d, $J$ = 8.0 Hz, 1 H), 7.70 (t, $J$ = 7.8 Hz, 1 H), 4.42 (q, $J$ = 7.2 Hz, 2 H), 1.35 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 184.8 (t, $J$ = 28.1 Hz), 161.5 (t, $J$ = 30.6 Hz), 133.3 (t, $J$ = 2.5 Hz), 132.1, 131.8 (t, $J$ = 1.9 Hz), 131.6 (q, $J$ = 3.3 Hz), 127.0 (q, $J$ = 3.2 Hz), 123.5 (q, $J$ = 270.9 Hz), 109.8 (t, $J$ = 263.1 Hz), 64.3, 14.0. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ -107.7 (s, 2 F), -63.1 (s, 3 F). IR (film) 2989, 1778, 1713, 1614, 1375, 1269, 1161, 1134, 1076, 1009, 941, 785, 692, 651 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{12}$H$_{10}$F$_5$O$_3$ [M+H]$^+$ 297.0550, found 297.0538.

![3.5c-1](image)

potassium 2,2-difluoro-3-oxo-3-(3-(trifluoromethyl)phenyl)propanoate (3.5c-1)

A one-neck round-bottom flask was charged with 3.5c-2 (4.80 g, 16.2 mmol), and MeOH (35 mL) was added at rt. The resulting solution was cooled to 0 °C. A pre-cooled solution of KOH (0.910 g, 16.2 mmol) dissolved in MeOH (20 mL) was added dropwise, and then the reaction solution was warmed to rt. The reaction mixture was stirred at rt for 12 h, after which the solvent was removed under reduced pressure. Ether (20 mL) and hexanes (5 mL) were added, and the mixture was sonicated at rt until fine solids formed. The solid was collected by filtration, washed with ether, and dried in vacuo to give the compound 3.5c-1 as an off-white solid (4.1 g, 83%). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 8.30 (s, 1 H), 8.28 (d, $J$ = 8.0 Hz, 1 H), 8.05 (d, $J$ = 7.6 Hz, 1 H), 7.80 (t, $J$ = 8.0 Hz, 1 H). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 189.1 (t, $J$
= 28.1 Hz), 162.8 (t, \( J = 23.7 \) Hz), 133.4, 133.2, 130.3, 130.2, 129.6 (q, \( J = 32.1 \) Hz), 125.7, 123.8 (q, \( J = 270.9 \) Hz) 111.4 (t, \( J = 261.9 \) Hz). \( ^{19} \)F NMR (DMSO-\( d_6 \), 376 MHz) \( \delta -105.7 \) (s, 2 F), \( -61.5 \) (s, 3 F). IR (film) 1701, 1670, 1389, 1333, 1269, 1128, 1074, 920, 814, 692 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{10}\)H\(_5\)F\(_5\)KO\(_3\) [M+H]\(^+\) 306.9796, found 306.9783. mp 145 °C decomposed.

2,2-difluoro-3-oxo-3-(3-(trifluoromethyl)phenyl)propanoic acid (3.5c-1')

A one-neck round-bottom flask was charged with 3.5c-1 (1.4 g, 4.6 mmol), and CHCl\(_3\) (25 mL) was added at rt. The resulting suspension was cooled to 0 °C, and then a pre-cooled solution of HCl in 1,4-dioxane (4 N, 1.5 mL) was added dropwise. The mixture solution was stirred at 0 °C until the thick white suspension disappeared, leaving a translucent turbid suspension of KCl. Then, the mixture was filtered through a pad of anhydrous Na\(_2\)SO\(_4\), and the solid portion was washed with CHCl\(_3\). The filtrate was concentrated under reduced pressure, and the residue was dried in vacuo to give the compound 3.5c-1' as a slightly pink solid (1.2 g, 97%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta 8.37 \) (s, 1 H), 8.31 (d, \( J = 7.6 \) Hz, 1 H), 7.97 (d, \( J = 7.6 \) Hz, 1 H), 7.72 (t, \( J = 7.8 \) Hz, 1 H), 6.80 (br, 1 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta 184.7 \) (t, \( J = 28.7 \) Hz), 165.0 (t, \( J = 30.6 \) Hz), 133.4, 132.1 (q, \( J = 33.4 \) Hz), 132.0 (t, \( J = 3.7 \) Hz), 131.4, 130.1, 127.1 (q, \( J = 3.4 \) Hz), 123.4 (q, \( J = 270.9 \) Hz), 110.0 (t, \( J = 264.4 \) Hz). \( ^{19} \)F NMR (CDCl\(_3\), 376 MHz) \( \delta -107.6 \) (s, 2 F), \( -63.1 \) (s, 3 F). IR (film) 3088, 1769, 1709, 1612, 1439, 1335, 1271, 1167, 1130, 1074, 935, 916, 818, 793, 758, 690 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{10}\)H\(_6\)F\(_5\)O\(_3\) [M+H]\(^+\) 269.0237, found 269.0242. mp 81–82 °C.

3,5-dimethoxybenzyl 2,2-difluoro-3-oxo-3-(3-(trifluoromethyl)phenyl)propanoate (3.5c)

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General procedure G was followed using 3.5c-1' (1.1 g, 4.3 mmol), oxalyl chloride (0.35 mL, 4.1 mmol), 3,5-dimethoxybenzyl alcohol (0.69 g, 4.1 mmol), Et₃N (1.1 mL, 8.2 mmol), DMF (0.12 mL), and CH₂Cl₂ (25 mL). Workup and chromatographic purification (30% to 60% CH₂Cl₂ in hexanes) afforded the title compound 3.5c as a light yellow oil (1.2 g, 70%). ¹H NMR (CDCl₃, 400 MHz) δ 8.32 (s, 1 H), 8.22 (d, J = 8.0 Hz, 1 H), 7.65 (t, J = 8.0 Hz, 1 H), 6.45–6.42 (m, 3 H), 5.29 (s, 2 H), 3.77 (s, 6 H). ¹³C NMR (CDCl₃, 125 MHz) δ 184.6 (t, J = 28.1 Hz), 161.4 (t, J = 30.0 Hz), 161.2, 135.9, 133.2, 132.0 (q, J = 33.7 Hz), 131.6 (m), 129.9, 126.9 (q, J = 3.3 Hz), 123.4 (q, J = 271.2 Hz), 109.8 (t, J = 263.7 Hz), 106.3, 101.0, 69.3, 55.5. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.5 (s, 2 F), –63.1 (s, 3 F). IR (film) 2962, 2843, 1778, 1713, 1610, 1597, 1464, 1431, 1335, 1259, 1205, 1165, 1132, 1074, 837, 816, 766, 692 cm⁻¹. HRMS (ESI, m/z): calced for C₁₉H₁₅F₅O₅ [M]+ 418.0840, found 418.0838.

3-(3,5-dimethoxyphenyl)-2,2-difluoro-1-(3-(trifluoromethyl)phenyl)propan-1-one (3.6c)

General procedure C was followed using 3.5c (209 mg, 0.500 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). The reaction was run at 130 °C for 24 h. Workup and chromatographic purification (1% to 10% CH₂Cl₂ in hexanes) afforded the title compound 3.6c as a colorless oil (144 mg, 77%). ¹H NMR (CDCl₃, 400 MHz) δ 8.23 (s, 1 H), 8.20 (d, J = 8.4 Hz, 1 H), 7.86 (d, J = 7.6 Hz, 1 H), 7.61 (t, J = 7.8 Hz, 1 H), 6.45 (d, J = 2.0 Hz, 2 H), 6.40 (t, J = 2.2 Hz, 1 H), 3.77 (s, 6 H), 3.47 (t, J = 17.6 Hz, 2 H). ¹³C NMR (CDCl₃, 125 MHz) δ 188.8 (t, J = 31.2 Hz), 160.9, 133.3 (t, J = 3.7 Hz), 133.0 (t, J = 3.1 Hz), 132.9 (t, J = 2.5 Hz), 131.5 (t, J = 32.9 Hz), 130.7 (q, J = 3.3 Hz), 129.5, 127.1 (h, J = 3.7 Hz), 123.6 (q, J = 270.9 Hz), 118.4 (t, J = 253.1 Hz), 109.1, 99.9, 55.5, 40.4 (t, J = 22.5 Hz). ¹⁹F NMR (CDCl₃, 376 MHz) δ –98.2 (t, J = 16.9 Hz, 2 F), –63.0 (s, 3 F). IR (film) 3003, 2941, 2841, 1713, 1610, 1597, 1464, 1431, 1335, 1259, 1205, 1165, 1132, 1074, 837, 816, 766, 692 cm⁻¹. HRMS (ESI, m/z): calced for C₁₈H₁₆F₅O₃ [M+H]⁺ 375.1020, found 375.1022.
ethyl 2,2-difluoro-3-hydroxy-3-(5-methylthiophen-2-yl)propanoate (3.5d-3)

General procedure D was followed using activated Zn (1.94 g, 29.6 mmol), 1,2-dibromoethane (0.15 mL, 1.8 mmol), 5-methyl-2-thiophenecarboxaldehyde (1.6 mL, 15 mmol), ethyl bromodifluoroacetate (1.9 mL, 15 mmol), and THF (0.030 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 3.5d-3 as a yellow oil (2.15 g, 58%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.96 (d, $J$ = 3.2 Hz, 1 H), 6.68 (dd, $J$ = 3.4, 1.4 Hz, 1 H), 5.33 (ddd, $J$ = 14.8, 8.0, 6.4 Hz, 1 H), 4.35 (q, $J$ = 7.2 Hz, 2 H), 2.60 (d, $J$ = 6.0 Hz, 1 H), 2.49 (s, 3 H), 1.34 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 163.4 (dd, $J$ = 32.5, 31.2 Hz), 142.2, 134.2, 128.0, 125.3, 113.4 (dd, $J$ = 257.5, 253.8 Hz), 70.6 (dd, $J$ = 27.5, 25.0 Hz), 63.5, 15.5, 14.1. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ -120.2 (dd, $J$ = 263.2, 15.0 Hz, 1 F), -114.2 (dd, $J$ = 263.2, 7.5 Hz, 1 F). IR (film) 3495, 2986, 2924, 1759, 1375, 1321, 1217, 1186, 1103, 1072, 1045, 854, 793, 669 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{10}$H$_{12}$F$_2$O$_3$SNa [M+Na]$^+$ 273.0373, found 273.0376.

ethyl 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate (3.5d-2)

General procedure E was followed using oxalyl chloride (3.9 mL, 46 mmol), DMSO (4.4 mL, 61 mmol), 3.5d-3 (3.8 g, 15 mmol), Et$_3$N (13 mL, 92 mmol) and CH$_2$Cl$_2$ (0.11 L). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 3.5d-2 as a yellow oil (3.2 g, 83%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.87–7.86 (m, 1 H), 6.90 (dd, $J$ = 4.2, 1.4 Hz, 1 H), 4.39 (q, $J$ = 7.2 Hz, 2 H), 2.60 (s, 3 H), 1.34 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 178.1 (t, $J$ = 27.5 Hz), 161.9 (t, $J$ = 30.6 Hz), 154.5, 137.4 (t, $J$ = 4.4 Hz), 135.3, 128.2, 109.7 (t, $J$ = 262.5 Hz), 64.0, 16.4, 14.1.

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$^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ −108.2 (s, 2 F). IR (film) 2988, 2941, 1774, 1666, 1313, 1267, 1126, 1053, 868, 816, 787, 675, 580 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{10}$H$_{10}$F$_2$O$_3$SNa [M+Na]$^+$ 271.0216, found 271.0221.

potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate (3.5d-1)

General procedure F was followed using 3.5d-2 (3.0 g, 12 mmol), KOH (0.67 g, 12 mmol), and MeOH (25 mL). Workup afforded the title compound 3.5d-1 as a colorless solid (2.6 g, 84%). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.78 (d, $J$ = 3.6 Hz, 1 H), 6.97 (dd, $J$ = 4.0, 1.4 Hz, 1 H), 2.52 (s, 3 H). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) $\delta$ 182.6 (t, $J$ = 28.8 Hz), 162.1 (t, $J$ = 23.8 Hz), 150.9, 136.8, 136.2 (t, $J$ = 2.5 Hz), 127.8, 111.3 (t, $J$ = 261.9 Hz), 15.6. $^{19}$F NMR (DMSO-$d_6$, 376 MHz) $\delta$ −105.2 (s, 2 F). IR (film) 1693, 1668, 1454, 1389, 1298, 1157, 1130, 1074, 1047, 860, 818, 806, 793, 706, 615, 590, 575, 511 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_8$H$_5$F$_2$K$_2$O$_3$S $[M+K]^+$ 296.9202, found 296.9193. mp 141–142 °C decomposed.

3,5-dimethoxybenzyl 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate (3.5d)

General procedure G was followed using potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate 3.5d-1 (1.1 g, 4.1 mmol), oxalyl chloride (0.33 mL, 3.9 mmol), 3,5-dimethoxybenzyl alcohol (0.66 g, 3.9 mmol), Et$_3$N (0.96 mL, 6.9 mmol), DMF (0.13 mL), and CH$_2$Cl$_2$ (22 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound 3.5d as a light yellow oil (0.49 g, 34%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.81 (dt, $J$ = 4.0, 1.6 Hz, 1 H), 6.86 (dd, $J$ = 4.0, 1.2 Hz, 1 H), 6.46 (d, $J$ = 2.0 Hz, 2 H), 6.42 (t, $J$ = 2.2 Hz, 1 H), 5.28 (s, 2 H), 3.78 (s, 6 H), 2.58 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 177.9 (t, $J$ = 28.1 Hz), 161.7 (t, $J$ = 30.6 Hz), 161.1, 154.6, 137.4 (t, $J$
= 4.4 Hz), 136.2, 135.1 (t, J = 1.9 Hz), 128.2, 109.7 (t, J = 263.7 Hz), 106.0, 101.1, 69.0, 55.6, 16.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –108.0 (s, 2 F). IR (film) 2960, 2939, 2841, 1774, 1670, 1599, 1448, 1302, 1205, 1155, 1053, 918, 837, 816, 750, 700, 677 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{17}$H$_{16}$F$_2$O$_5$SNa [M+Na]$^+$ 393.0584, found 393.0577.

3-(3,5-dimethoxyphenyl)-2,2-difluoro-1-(5-methylthiophen-2-yl)propan-1-one (3.6d)

General procedure C was followed using 3.5d (185 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.6d as an off-white solid (137 mg, 84%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.75–7.74 (m, 1 H), 6.83 (d, J = 4.0 Hz, 1 H), 6.44 (s, 2 H), 6.39 (t, J = 2.2 Hz, 1 H), 3.77 (s, 6 H), 3.41 (t, J = 17.4 Hz, 2 H), 2.56 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 182.4 (t, J = 30.6 Hz), 160.8, 153.2, 136.9 (t, J = 5.6 Hz), 136.5, 133.4 (t, J = 3.7 Hz), 127.9, 118.3 (t, J = 253.1 Hz), 109.0, 99.9, 55.5, 40.8 (t, J = 23.1 Hz), 16.2. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –99.7 (t, J = 18.8 Hz, 2 F). IR (film) 2939, 2839, 1668, 1597, 1446, 1319, 1288, 1205, 1153, 1067, 893, 837, 816, 766, 696, 602 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{16}$F$_2$O$_3$SNa [M+Na]$^+$ 349.0686, found 349.0699. mp 30–31 °C.

ethyl 2,2-difluoro-3-hydroxy-3-(1-phenyl-1H-pyrazol-4-yl)propanoate (3.5e-3)

General procedure D was followed using activated Zn (1.54 g, 23.6 mmol), 1,2-dibromoethane (0.16 mL, 1.9 mmol), 1-phenyl-1H-pyrazole-4-carbaldehyde$^{15}$ (2.70 g, 15.7 mmol), ethyl bromodifluoroacetate (2.0 mL, 15.7 mmol), and THF (80 mL). Workup and chromatographic purification (10% to 30% EtOAc in
hexanes) afforded the title compound 3.5e-3 as a colorless solid (3.8 g, 82%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.00 (s, 1 H), 7.74 (s, 1 H), 7.63 (dt, $J = 7.2$, 1.5 Hz, 2 H), 7.44 (t, $J = 8.0$ Hz, 2 H), 7.30 (tt, $J = 7.6$, 1.4 Hz, 1 H), 5.25 (ddd, $J = 16.0$, 7.8, 2.4 Hz, 1 H), 4.34 (q, $J = 7.2$ Hz, 2 H), 3.40 (br, 1 H), 1.32 (t, $J = 7.2$ Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 163.6 (t, $J = 31.2$ Hz), 140.3, 139.6, 129.6, 127.1, 127.0, 119.5, 118.2 (d, $J = 2.5$ Hz), 113.9 (dd, $J = 256.2$, 252.5 Hz), 66.9 (dd, $J = 29.4$, 24.4 Hz), 63.3, 13.9. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –120.7 (dd, $J = 263.2$, 15.0 Hz, 1 F), –114.1 (dd, $J = 263.2$, 7.5 Hz, 1 F). IR (film) 3325, 2986, 1759, 1599, 1568, 1504, 1406, 1321, 1213, 1074, 1007, 955, 856, 800, 758, 690 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{14}$H$_{14}$F$_2$N$_2$O$_3$Na [M+Na]$^+$ 319.0870, found 319.0865. mp 51–52 °C.

![3.5e-2](image)

**ethyl 2,2-difluoro-3-oxo-3-(1-phenyl-1H-pyrazol-4-yl)propanoate (3.5e-2)**

IBX (3.89 g, 13.9 mmol) was added into a solution of compound 3.5e-3 (1.65 g, 5.57 mmol) dissolved in DMSO (0.020 L), and the solution was stirred at rt for 20 h. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with saturated NaHCO$_3$(aq) (2 x 60 mL) and brine (2 x 60 mL), then dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Purification by flash chromatography (10% to 20% EtOAc in hexanes) provided the title compound 3.5e-2 as a colorless solid (1.45g, 88%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.61 (s, 1 H), 8.30 (s, 1 H), 7.76–7.73 (m, 2 H), 7.55–7.50 (m, 2 H), 7.43 (tt, $J = 7.6$, 1.5 Hz, 1 H), 4.40 (q, $J = 7.2$ Hz, 2 H), 1.36 (t, $J = 7.2$ Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 180.1 (t, $J = 28.8$ Hz), 161.8 (t, $J = 30.6$ Hz), 142.9 (t, $J = 2.5$ Hz), 139.0, 131.6 (t, $J = 4.4$ Hz), 129.9, 128.5, 120.2, 118.8 (t, $J = 2.5$ Hz), 109.5 (t, $J = 261.9$ Hz), 64.1, 14.0. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –110.8 (s, 2 F). IR (film) 3138, 2986, 1772, 1690, 1541, 1504, 1312, 1244, 1174, 1126, 1036, 951, 889, 824, 760, 688 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{14}$H$_{12}$F$_2$N$_2$O$_3$Na [M+Na]$^+$ 317.0714, found 317.0695. mp 28–29 °C.
potassium 2,2-difluoro-3-oxo-3-(1-phenyl-1H-pyrazol-4-yl)propanoate (3.5e-1)

General procedure F was followed using 3.5e-2 (1.31 g, 4.45 mmol), KOH (0.250 g, 4.45 mmol), and MeOH (0.020 L). Workup afforded the title compound 3.5e-1 as a colorless solid (1.2 g, 89%). 1H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\) 9.04 (s, 1 H), 8.20 (s, 1 H), 7.90 (dd, \(J = 7.6, 1.6\) Hz, 2 H), 7.55 (t, \(J = 8.0\) Hz, 2 H), 7.41 (t, \(J = 7.2\) Hz, 1 H). 13C NMR (DMSO-\(d_6\), 125 MHz) \(\delta\) 184.5 (t, \(J = 28.8\) Hz), 162.3 (t, \(J = 2.5\) Hz), 142.3, 138.7, 131.8, 129.7, 127.7, 120.4, 119.4, 111.3 (t, \(J = 261.2\) Hz). 19F NMR (DMSO-\(d_6\), 376 MHz) \(\delta\) –107.8 (s, 2 F). IR (film) 3126, 1693, 1682, 1543, 1506, 1385, 1267, 1167, 1126, 1084, 951, 883, 810, 752, 698, 683, 656 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{12}\)H\(_7\)F\(_2\)K\(_2\)N\(_2\)O\(_3\) [M+K]\(^+\) 342.9699, found 342.9707. mp 139–140 °C.

3,5-dimethoxybenzyl 2,2-difluoro-3-oxo-3-(1-phenyl-1H-pyrazol-4-yl)propanoate (3.5e)

General procedure G was followed using potassium 2,2-difluoro-3-oxo-3-(1-phenyl-1H-pyrazol-4-yl)propanoate 3.5e-1 (1.1 g, 3.7 mmol), oxalyl chloride (0.30 mL, 3.5 mmol), 3,5-dimethoxybenzyl alcohol (0.59 g, 3.5 mmol), Et\(_3\)N (0.97 mL, 7.0 mmol), DMF (0.13 mL), and CH\(_2\)Cl\(_2\) (20 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 3.5e as an off-white solid (0.42 g, 29%). 1H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.54 (s, 1 H), 8.28 (s, 1 H), 7.71–7.69 (m, 2 H), 7.52 (t, \(J = 8.0\) Hz, 2 H), 7.44–7.40 (m, 1 H), 6.46 (d, \(J = 2.4\) Hz, 2 H), 6.39 (t, \(J = 2.2\) Hz, 1 H), 5.28 (s, 2 H), 3.75 (s, 3 H). 13C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 179.8 (t, \(J = 29.4\) Hz), 161.6 (t, \(J = 31.2\) Hz), 161.2, 143.0 (t, \(J = 2.5\) Hz), 138.9, 136.0, 131.6 (t, \(J = 3.7\) Hz), 129.9, 128.6, 120.2, 118.7, 109.5 (t, \(J = 262.5\) Hz), 106.2, 101.0, 69.2, 55.5. 19F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –110.7 (s, 2 F). IR (film) 3132, 2959, 2941,
2841, 1774, 1686, 1599, 1541, 1502, 1466, 1431, 1381, 1302, 1242, 1205, 1157, 1068, 1036, 951, 881, 820, 760, 688, 660, 607 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{21}\)H\(_{18}\)F\(_2\)N\(_2\)O\(_5\)Na \([M+Na]^+\) 439.1081, found 439.1061. mp 66–67 °C.

3-(3,5-dimethoxyphenyl)-2,2-difluoro-1-(1-phenyl-1\(H\)-pyrazol-4-yl)propan-1-one (3.6e)

General procedure C was followed using 3.5e (208 mg, 0.500 mmol), Pd(PPh\(_3\))\(_4\) (14.4 mg, 0.0125 mmol), and \(o\)-xylene (0.010 L). The reaction was run at 120 °C for 24 h. Workup and chromatographic purification (2.5% to 5% EtOAc in hexanes) afforded the title compound 3.6e as an off-white solid (127 mg, 68%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.41 (s, 1 H), 8.21 (s, 1 H), 7.67 (d, \(J = 7.6\) Hz, 2 H), 7.50 (t, \(J = 8.0\) Hz, 2 H), 7.42–7.37 (m, 1 H), 6.46 (d, \(J = 2.0\) Hz, 2 H), 6.37 (t, \(J = 2.2\) Hz, 1 H), 3.76 (s, 6 H), 3.42 (t, \(J = 17.2\) Hz, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 184.5 (t, \(J = 31.9\) Hz), 160.9, 143.1 (t, \(J = 2.5\) Hz), 139.1, 133.3 (t, \(J = 3.7\) Hz), 131.5 (t, \(J = 5.0\) Hz), 129.9, 128.3, 120.1, 119.8 (t, \(J = 2.5\) Hz), 118.3 (t, \(J = 251.9\) Hz), 109.1, 99.8, 55.5, 40.4 (t, \(J = 23.7\) Hz). \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –101.8 (t, \(J = 16.9\) Hz, 2 F). IR (film) 2939, 2839, 1682, 1597, 1539, 1504, 1464, 1431, 1296, 1205, 1151, 1070, 1038, 951, 874, 845, 760, 688 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{20}\)H\(_{19}\)F\(_2\)N\(_2\)O\(_3\) \([M+H]^+\) 373.1364, found 373.1352. mp 58–59 °C.

ethyl 3-cyclohexyl-2,2-difluoro-3-hydroxypropanoate (3.5f-3)

General procedure D was followed using activated Zn (3.2 g, 49 mmol), 1,2-dibromoethane (0.25 mL, 2.9 mmol), cyclohexanecarboxaldehyde (3.0 mL, 25 mmol), ethyl bromodifluoroacetate (3.2 mL, 25 mmol), and THF (0.050 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded
the title compound 3.5f-3 as a colorless oil (3.7 g, 63%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 4.36 (q, $J = 7.2$ Hz, 2 H), 3.89–3.79 (m, 1 H), 1.99 (d, $J = 8.0$ Hz, 1 H), 1.94–1.91 (m, 1 H), 1.82–1.65 (m, 5 H), 1.37 (t, $J = 7.2$ Hz, 3 H), 1.32–1.08 (m, 5 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 164.1 (dd, $J = 32.5, 31.2$ Hz), 115.6 (dd, $J = 256.2, 253.8$ Hz), 75.4 (dd, $J = 26.2, 23.8$ Hz), 63.2, 38.4, 29.8, 27.5, 26.3, 26.2, 26.0, 14.2. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –120.1 (dd, $J = 263.2, 15.0$ Hz, 1 F), –111.6 (dd, $J = 263.2, 7.5$ Hz, 1 F). HRMS (ESI, $m/z$): calcd for C$_{11}$H$_{18}$F$_2$O$_3$Na [M+Na]$^+$ 259.1122, found 259.1128. Spectroscopic data matched that from the previous report.$^1$

![3.5f-2](image)

**ethyl 3-cyclohexyl-2,2-difluoro-3-oxopropanoate (3.5f-2)**

General procedure E was followed using oxalyl chloride (3.8 mL, 44 mmol), DMSO (4.2 mL, 59 mmol), 3.5f-3 (3.47 g, 14.7 mmol), Et$_3$N (12 mL, 88 mmol) and CH$_2$Cl$_2$ (95 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 3.5f-2 as a colorless oil (3.00 g, 87%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 4.37 (q, $J = 7.2$ Hz, 2 H), 2.94–2.88 (m, 1 H), 1.94–1.89 (m, 2 H), 1.85–1.80 (m, 2 H), 1.73–1.69 (m, 1 H), 1.36 (t, $J = 7.2$ Hz, 3 H), 1.47–1.19 (m, 5 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 200.4 (t, $J = 26.2$ Hz), 161.8 (t, $J = 30.6$ Hz), 108.8 (t, $J = 263.1$ Hz), 63.8, 45.5, 28.3, 25.7, 25.5, 14.1. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –113.1 (s, 2 F). HRMS (ESI, $m/z$): calcd for C$_{11}$H$_{18}$F$_2$O$_3$Na [M+Na]$^+$ 257.0965, found 257.0959. Spectroscopic data matched that from the previous report.$^1$

![3.5f-1](image)

**potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate (3.5f-1)**

General procedure F was followed using 3.5f-2 (2.8 g, 12 mmol), KOH (0.67 g, 12 mmol), and MeOH (12 mL). Workup afforded the title compound 3.5f-1 as a colorless solid (2.5 g, 85%). $^1$H NMR (DMSO-
$d_6$, 400 MHz) δ 2.72–2.66 (m, 1 H), 1.78–1.59 (m, 5 H), 1.27–1.11 (m, 5 H). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ 204.0 (t, $J = 26.2$ Hz), 162.2, 111.2 (t, $J = 263.8$ Hz), 44.8, 28.3, 25.4, 25.0. $^{19}$F NMR (DMSO-$d_6$, 376 MHz) δ –111.1 (s, 2 F). IR (film) 2935, 2864, 1732, 1690, 1674, 1446, 1373, 1329, 1248, 1207, 1174, 1140, 1070, 964, 820, 796, 739, 631, 584 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_9$H$_{11}$F$_2$K$_2$O$_3$ [M+K]$^+$ 282.9950, found 282.9948. mp 188 °C decomposed.

3,5-dimethoxybenzyl 3-cyclohexyl-2,2-difluoro-3-oxopropanoate (3.5f)

General procedure G was followed using potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate 3.5f-1 (0.93 g, 3.8 mmol), oxalyl chloride (0.31 mL, 3.7 mmol), 3,5-dimethoxybenzyl alcohol (0.54 g, 3.2 mmol), Et$_3$N (0.89 mL, 6.4 mmol), DMF (0.12 mL), and CH$_2$Cl$_2$ (20 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound 3.5f as a colorless oil (0.74 g, 65%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 6.49 (d, $J = 2.0$ Hz, 2 H), 6.45 (t, $J = 2.4$ Hz, 1 H), 5.26 (s, 2 H), 3.80 (s, 6 H), 2.90–2.84 (m, 1 H), 1.86 (dd, $J = 13.6, 2.8$ Hz, 2 H), 1.81–1.76 (m, 2 H), 1.71–1.66 (m, 1 H), 1.44–1.19 (m, 5 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 200.2 (t, $J = 26.9$ Hz), 161.7 (t, $J = 30.6$ Hz), 161.2, 136.2, 108.8 (t, $J = 263.1$ Hz), 106.2, 101.1, 68.9, 55.6, 45.5, 28.2, 25.6, 25.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –112.9 (s, 2 F). IR (film) 2937, 2856, 1780, 1736, 1599, 1458, 1431, 1379, 1302, 1207, 1155, 1068, 970, 955, 837, 702, 588 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{22}$F$_2$O$_5$Na [M+Na]$^+$ 379.1333, found 379.1324.

2-(methylthio)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (3.6f)
General procedure C was followed using 3.5f (178 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). The reaction was run at 130 °C for 24 h. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 3.6f as a colorless oil (92 mg, 59%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 6.39–6.37 (m, 3 H), 3.78 (s, 6 H), 3.25 (t, $J = 16.8$ Hz, 2 H), 2.73–2.67 (m, 1 H), 1.76–1.64 (m, 5 H), 1.29–1.19 (m, 5 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 204.6 (t, $J = 29.4$ Hz), 160.9, 133.3 (t, $J = 4.4$ Hz), 117.8 (t, $J = 253.7$ Hz), 108.9, 99.9, 55.5, 45.3, 39.9 (t, $J = 23.1$ Hz), 28.1, 25.8, 25.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ −104.5 (t, $J = 16.9$ Hz, 2 F). IR (film) 2935, 2856, 1732, 1608, 1599, 1462, 1431, 1310, 1296, 1205, 1153, 1070, 980, 930, 891, 837, 760 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{14}$F$_2$O$_3$SNa [M+Na]$^+$ 359.0529, found 359.0511.

Preparation of Compounds 3.1a′ and 3.1a″ in Table 3.3

benzyl 2-fluoro-3-oxo-3-phenylpropanoate (3.1a′)

Compound 3.1′ was prepared according to a previous report.$^{16}$ Compound 3.1a″ (1.87 g, 7.35 mmol) and CpTiCl$_3$ (81.0 mg, 0.370 mmol) were dissolved in CH$_3$CN (0.040 L) at rt, and selectfluor (2.86 g, 8.08 mmol) was added. The mixture was stirred at rt for 6 h, and filtered to remove solids. The filtrate was concentrated, and the crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound 3.1a′ as a colorless oil (1.71 g, 85%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.01 (dt, $J = 8.4$, 1.2 Hz, 2 H), 7.64 (tt, $J = 7.6$, 1.5 Hz, 1 H), 7.48 (t, $J = 7.8$ Hz, 2 H), 7.34–7.30 (m, 3 H), 7.28–7.25 (m, 2 H), 5.93 (d, $J = 48.8$ Hz, 1 H), 5.31–5.23 (m, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 189.5 (d, $J = 20.0$ Hz), 165.0 (d, $J = 25.0$ Hz), 134.8, 134.5, 133.5 (d, $J = 1.2$ Hz), 129.7 (d, $J = 2.5$ Hz), 129.0, 128.9, 128.8, 128.5, 90.2 (d, $J = 196.2$ Hz), 68.3. $^{19}$F NMR (CDCl$_3$, 376
benzyl 3-oxo-3-phenylpropanoate (3.1a’’)

Compound 3.1a’’ was prepared according to a previous report.17 A mixture of benzyl alcohol (1.0 mL, 10.0 mmol), ethyl benzoylacetate (1.73 g, 10.0 mmol), DMAP (1.22 g, 10.0 mmol) was stirred with oven-dried 4 Å molecular sieves (50 g) in dry toluene (0.080 L) at 100–105 °C for 36 h. The reaction mixture was cooled to rt, and filtered to remove the molecular sieves. The solvents were removed under reduced pressure, and EtOAc (60 mL) and water (60 mL) were added to the residue. The layers were separated, and the organic layer was dried over anhydrous Na2SO4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound 3.1a’’ as a yellow solid (2.1 g, 83%, ketone : enol = 4.4:1). 1H NMR (CDCl3, 400 MHz) δ 12.51 (s, 1 H, enol), 7.95–7.93 (m, 2 H, keto), 7.80–7.78 (m, 2 H, enol), 7.63–7.58 (m, 1 H, keto), 7.50–7.30 (m, 15 H, keto + enol), 5.75 (s, 1 H, enol), 5.27 (s, 2 H, enol), 5.21 (s, 2 H, keto), 4.06 (s, 2 H, keto). 13C NMR (CDCl3, 125 MHz) δ 192.5 (keto), 173.1 (enol), 172.0 (enol), 167.6 (keto), 136.1, 136.0, 135.5, 134.0, 133.5, 131.6, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 126.3, 87.4 (enol), 67.4 (keto), 66.3 (enol), 46.2 (keto). IR (film) 3063, 3032, 2957, 1742, 1688, 1637, 1497, 1450, 1410, 1325, 1267, 1211, 1186, 1144, 1078, 980, 775, 754, 688, 582 cm⁻¹. HRMS (ESI, m/z): calcd for C16H14O3Na [M+Na]⁺ 277.0841, found 277.0833. mp 39–40 °C.
Experimental Procedures and Characterization of Compounds for Table 3.3

General Procedure H: An oven-dried 20 mL scintillation vial was charged with substrate (3.1a, 3.1a’ or 3.1a”, 0.500 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), and a magnetic stir bar. Dry o-xylene (0.010 L) was added via a syringe. Subsequently, the vial was transferred out of the glove box and placed on a pre-heated reaction block at 120 °C, and stirred for 15 h. The vial was cooled to rt, and the mixture was diluted with EtOAc. An internal standard was added, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing in prior to ¹⁹F or ¹H NMR analysis.

2,2-difluoro-1,3-diphenylpropan-1-one (3.2a)

General procedure H was followed using 3.1a (145 mg, 0.500 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), and o-xylene (0.010 L). Workup and chromatographic purification (0% to 2% EtOAc in hexanes) afforded the title compound 3.2a as a colorless oil, which becomes a colorless solid in the fridge (100 mg, 81%). ¹H NMR (CDCl₃, 400 MHz) δ 8.04 (d, J = 7.6 Hz, 2 H), 7.62 (t, J = 7.6 Hz, 1 H), 7.48 (t, J = 7.6 Hz, 2 H), 7.32 (br, 5 H), 3.53 (t, J = 17.8 Hz, 2 H). ¹³C NMR (CDCl₃, 125 MHz) δ 189.7 (t, J = 30.6 Hz), 134.4, 132.3 (t, J = 2.5 Hz), 131.5 (t, J = 3.1 Hz), 131.1, 130.3 (t, J = 3.7 Hz), 128.8, 128.6, 127.8, 118.6 (t, J = 253.1 Hz), 40.3 (t, J = 23.1 Hz). ¹⁹F NMR (CDCl₃, 376 MHz) δ −98.6 (t, J = 16.9 Hz, 2 F). IR (film) 3063, 3032, 2937, 1701, 1597, 1497, 1450, 1279, 1173, 1115, 1084, 1049, 1032, 943, 901, 727, 715, 698, 669, 600 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₅H₁₂F₂ONa [M+Na]⁺ 269.0754, found 269.0742. mp 45 °C. Spectroscopic data matched that from the previous report.⁴
References for Chapter 3 Experimental Section

3 We acknowledged Niusha Sharifi for the initial screening of Pd-catalyzed decarboxylative difluorobenzylations reactions, including Table S1 to Table S6.
12 Zhou, H.; Xu, Q.; Chen, P. “Kinetic Resolution of 2,2-Difluoro-3-hydroxy-3-aryl-propionates Catalyzed by Organocatalyst (R)-Benztetramisole” Tetrahedron 2008, 64, 6494–6499.
Chapter 4. Ligand-Controlled Regiodivergent Palladium-Catalyzed Decarboxylative Allylation of α,α-Difluoroketone Enolates

4.1 Introduction to Transition Metal-Catalyzed Decarboxylative Allylation

Decarboxylative coupling is a powerful method for the construction of C–C bonds that generates reactive organometallic intermediates under mild conditions and releases CO₂ as the only byproduct.¹ Moreover, this strategy enables the formation of reactive nucleophiles bearing an acidic proton capable of undergoing deprotonation and regioselective coupling to provide products that might be difficult to access otherwise.² Among decarboxylative C–C coupling reactions, decarboxylative allylation reactions,¹b in which the allylic electrophile and the nucleophile are generated in situ from unimolecular decarboxylation of β-ketoesters, are broadly investigated because of their potential applications. These types of reaction play an important role in accessing chiral allylic products³ and are widely applied for the synthesis of natural products (Scheme 4.1).⁴

\[
\text{Scheme 4.1. General Mechanism of Transition Metal-Catalyzed Decarboxylative Allylation Reactions}
\]

Many transition metals participate in the allylation reactions with complementary regioselectivities. Metals such as Ru, Rh, Ir, Mo, and W afford the branched products,¹b,⁵ while Pd metal complexes predominately form the linear products.¹b,⁶ With the development of new ligands, Pd-catalyzed allylation reactions of monosubstituted allylic electrophiles with soft C-based (e.g. malonates, β-diketones, β-ketoesters) and heteroatom-based nucleophiles can enable to access branched products (Scheme 4.2).⁷
Pd-catalyzed allylation reactions of hard ketone enolate nucleophiles with monosubstituted allylic electrophiles almost exclusively provide linear products (Scheme 4.3),\textsuperscript{1b,3c,8} which arise from an outer-sphere attack of enolates on the less-hindered terminus of a Pd-\(\pi\)-allyl intermediate.

In a rare example, a Pd-catalyzed allylation reaction of a ketone enolate employed stoichiometric Li additives to generate the uncommon branched product (Scheme 4.4A), while the use of Cu(I) salts still favored the formation of linear products.\textsuperscript{9} In this reaction, the selectivity was believed to originate from the state of carbanion aggregation, which was affected by the addition of Li or Cu(I) additives. However
until recently, the ability of a ligand to control the regioselectivity for Pd-catalyzed allylation reactions of ketone enolates had not been reported. In 2016, the Hou lab demonstrated a ligand controlled Pd-catalyzed allylation reaction of the ketone enolates to generate the branched products, in which the use of achiral NHC ligands enables the formation of racemic anti/syn products along with other diastereoisomers (Scheme 4.4B).\textsuperscript{10} In their mechanistic studies, the branched products come from an inner-sphere [3,3′]-reductive elimination based on the experimental results and density functional theory (DFT) calculations.

### Scheme 4.4. Examples of Allylation Reactions of Ketone Enolates to Access Branched Products

**A) Branched Regioselectivity by Li Additive**

\[
\text{Ar} = \text{alkyl, aryl, alkylnyl} \\
\text{R}^1 = \text{alkyl, aryl, alkylnyl} \\
\text{R}^2 = \text{alkyl}
\]

**B) Branched Regioselectivity by Ligand**

\[
\text{Ar} = \text{alkyl, aryl, alkylnyl} \\
\text{R}^1 = \text{alkyl, aryl, alkylnyl} \\
\text{R}^2 = \text{alkyl}
\]

4.2 Development to Access \(\alpha\)-Allyl-\(\alpha\),\(\alpha\)-Difluoroketones

Current methods to access \(\alpha\)-allylated \(\alpha\),\(\alpha\)-difluoroketones focus on Aldol/Mannich condensation reactions of \(\alpha\),\(\alpha\)-difluoroenoxysilanes (Scheme 4.5A),\textsuperscript{11} which come from either Brook rearrangement of the intermediate A (path a) or trifluoroacetate-release-driven cleavage of a C–C bond of...
pentafluoroacetone hydrate B (path b). Other similar strategies involve Reformatsky-type reactions of halodifluoromethyl ketones with allylic aldehydes and imines using an excess of metal as a mediator (Scheme 4.5B). However, these reactions simultaneously introduce a heteroatom at the \( \alpha \)-position, while also incorporating the allyl group.

The Claisen rearrangement has also been utilized for generating \( \alpha \)-allyl-\( \alpha \)-difluoroketones, and the products including difluoroacylsilanes and difluoroacystannanes can couple with alkyl or aryl electrophiles to form complex \( \alpha \)-allyl-\( \alpha \)-difluoroketone derivatives (Scheme 4.6A). However, the preparation of the allyl vinyl ether starting materials requires the use of strong bases, which restrict the substrate scope of the entire reaction. Additionally, the Portella and Kobayashi labs demonstrated alkylation reactions of \( \alpha \)-difluoroenoxy silanes with allyl electrophiles; however, Lewis acids or stoichiometric amount of metal additives are required to promote the reactions, and the substrate scope of these reactions is similarly limited to simple alkyl substituents (Scheme 4.6B).
4.3 Palladium-Catalyzed Decarboxylative Difluoroalkylation to Access α-Allyl-α,α-difluoroketones

Based on our ongoing studies aimed at accessing privileged fluorinated motifs using decarboxylative strategies,15 and the successful example of decarboxylative benzylation of α,α-difluoroketone enolates,15c we envisioned that a decarboxylative strategy should afford α-allyl-α,α-difluoroketones from allylic alcohols. Decarboxylative allylation reactions of fluorine-containing nucleophiles are restricted to α-fluoroketones,16 and decarboxylative allylation reactions of α,α-difluoroketones have not been realized. Furthermore, even simple allylation reactions of α,α-difluoroketone enolates have remained restricted to a single reaction that uses stoichiometric amount of copper,14b and no catalytic allylation reactions generate this substructure.

To begin the study, cinnamyl alcohol-derived esters were used as the sp3-based electrophiles because they possess higher reactivity compared to other allylic electrophiles. The cinnamyl alcohols required were prepared by either reduction of corresponding esters or Pd-catalyzed coupling reactions (Scheme 4.7A). The α,α-difluoroketone enolates would be generated in situ via decarboxylation of α,α-difluoro-β-
Based on our previous successes with Cu-catalyzed decarboxylative coupling reactions of cinnamyl α-bromo-α,α-difluoro esters, we initially explored the use of Cu-based catalytic systems in decarboxylative allylation reactions of α,α-difluoroketone enolates (Scheme 4.8A). In some of the Cu-catalyzed reactions, full conversion was achieved; however, no or trace amounts of the desired coupling product 4.2a were detected by GC. Instead, the Cu-based catalysts typically provided difluoroacetophenone and various isomers of bicinnamyl. In contrast, the preliminary result that 5% of
Pd(OAc)$_2$/PPh$_3$ system provided 5% of the desired coupling product 4.2a revealed that a Pd-based catalyst could promote the desired transformation (Scheme 4.8B). Thus, Pd-based system was selected for further investigation.

4.4 An Orthogonal Set of Palladium-Catalyzed Allylation Reactions of α,α-Difluoroketone Enolates

A broad screen of P-based ligands identified biarylmonophosphines as privileged ligands for the present reaction. The biarylmonophosphine class of ligands demonstrated several notable relationships between ligand structure and catalytic activity (Scheme 4.9). First, substitution of the ortho-position of the right aromatic ring improved the yield and selectivity for the branched product (Scheme 4.9A). For example, only 2% of the branched product was generated with CyJohnPhos; however, the use of SPhos and XPhos improved the yield and selectivity of the transformation. This phenomenon might arise from increased steric hindrance of the ligands, or from inhibition of cyclometalation processes that deactivate the catalyst. Second, substituents on the phosphine atom control the selectivity for formation of branched and linear products (Scheme 4.9B). As a control, XPhos provided a 25:1 selectivity for...
formation of the branched product, and substitution of the cyclohexyl groups with phenyl groups, (PhXPhos)\textsuperscript{18} improved the yield and selectivity of the branched product. In contrast, substitution of the cyclohexyl groups with bulkier \textit{t}-butyl groups (\textit{t}-BuXPhos) unexpectedly inverted the regioselectivity and provided an orthogonal protocol for accessing the linear product. Third, relative to \textit{t}-BuXPhos, ligands bearing substituents on the left ring (Me\textsubscript{4}\textit{t}-BuXPhos and \textit{t}-BuBrettPhos\textsuperscript{19}) modulated the yield and selectivity for formation of the linear product (Scheme 4.9C). Additional optimization revealed that both linear and branched products formed in 1,4-dioxane and toluene, although distinct temperatures and concentrations proved optimal for formation of each product.

<table>
<thead>
<tr>
<th>Scheme 4.9. Structure of Biaryl Monophosphine Ligands Controlled the Regioselectivity of Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.1a</strong></td>
</tr>
<tr>
<td>[Diagram of ligands and reaction conditions]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A) Ortho-Substituents Improved Yield of Branched Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>CyJohnPhos</td>
</tr>
<tr>
<td>branched: 2%</td>
</tr>
<tr>
<td>b/l = 2 : 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B) Substituents on P Altered Selectivity of Branched and Linear Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{t}-BuXPhos</td>
</tr>
<tr>
<td>linear: 81%</td>
</tr>
<tr>
<td>b/l = 1 : 9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C) Substituents on Left Ring Altered Yield and Selectivity of Linear Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me\textsubscript{4}\textit{t}-BuXPhos</td>
</tr>
<tr>
<td>linear: 68%</td>
</tr>
<tr>
<td>b/l = 1 : 3</td>
</tr>
</tbody>
</table>
In the present reaction, the ligand-controlled regioselectivity was only observed for the α,α-difluorinated substrate 4.1a (entry 1, Table 4.1), and the analogous mono- and non-fluorinated substrates (4.1b and 4.1c) did not provide branched products in good yield and regioselectivity (entries 2–3, Table 4.1). Therefore, the physicochemical perturbation resulting from fluorination of the substrate 4.1a facilitated formation of the branched product. Moreover, the difluorinated substrate 4.1a operates via a decarboxylation followed by allylation mechanism, while the mono- and non-fluorinated substrates (4.1b and 4.1c) might undergo a different mechanism, such as allylation followed by decarboxylation. Thus, the present catalyst systems that operate via decarboxylation followed by allylation mechanism may not be appropriate for the transformation of the mono- and non-fluorinated substrates. However, allylation reactions of monofluorinated cyclic-16 and non-fluorinated cyclic- and acyclic ketone enolates1b,8–10 have been realized using different catalysts developed by other research groups.
Table 4.1. Ligand-Controlled Regioselective Allylation Reactions of Fluorinated Substrates

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst system A</th>
<th>catalyst system B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="4.1a" /></td>
<td><img src="image" alt="4.2a" />, 89% (b/l = 1 : 18)</td>
<td><img src="image" alt="4.3a" />, 94% (b/l = 99 : 1)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="4.1b" /></td>
<td><img src="image" alt="4.2b" />, 24% (b/l &lt; 1 : 24)</td>
<td><img src="image" alt="4.3b" />, 36% (b/l = 21 : 1) (dr, b = 2 : 1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="4.1c" /></td>
<td><img src="image" alt="4.2c" />, 85% (b/l &lt; 1 : 50)</td>
<td><img src="image" alt="4.3c" />, 5% (b/l = 1 : 2)</td>
</tr>
</tbody>
</table>

* Catalyst System A: substrate (1.0 equiv), Pd(OAc)$_2$ (3.0 mol%), $t$-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 20 h; Catalyst System B: substrate (1.0 equiv), Pd(OAc)$_2$ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 20 h. For fluorinated products, yields and selectivities were determined by $^{19}$F NMR using PhCF$_3$ or PhF as an internal standard, respectively. For non-fluorinated products, yields and selectivities were determined by $^1$H NMR using CH$_2$Br$_2$ as an internal standard.
Based on classical reactivity patterns, the ability of $\alpha,\alpha$-difluoracetophenone to provide both branched and linear products is unexpected. Traditionally for Pd-catalyzed alkylation reactions, “hard” and “soft” nucleophiles have been identified by their $pK_a$ values, with hard nucleophiles ($pK_a > 25$) being less acidic than soft nucleophiles ($pK_a < 25$).\(^{20}\) However for most pronucleophiles, the presence of a resonance-stabilizing group lowers the $pK_a$ value and increases the polarizability of the molecular orbitals (e.g. ketone vs. $\beta$-ketoester or $\beta$-diketone).\(^{1b,21}\) In contrast for $\alpha,\alpha$-difluoroketones ($pK_a = 20.2$),\(^{22}\) the lower $pK_a$ results from an inductive effect that makes the anions harder (negative fluorine effect).\(^{23}\) Thus for the present alkylation reaction, the $\alpha,\alpha$-difluoroketone enolates should be harder than acetophenone ($pK_a = 24.7$),\(^{22}\) which typically provides linear products.\(^{1b,3c,8}\) Thus, based on classic hard/soft reactivity trends, the $\alpha,\alpha$-difluoroketones would not provide the uniquely observed branched product.

Utilizing the optimized conditions, a variety of substrates bearing electron-donating and -withdrawing functional groups on the cinnamyl component underwent regioselective coupling to provide both linear and branched products (Scheme 4.10). Notably, with catalyst system A [Pd(OAc)$_2$/t-BuBrettPhos/1,4-dioxane/ $60\,^\circ\text{C}$], substrates bearing electron-deficient allylic moieties 4.5a–c provided better selectivity than neutral 4.5d–e and electron-rich 4.5f–g substrates. In contrast, catalyst system B [Pd(OAc)$_2$/PhXPhos/1,4-dioxane/ $90\,^\circ\text{C}$] showed excellent selectivity for the branched products (generally $> 49 : 1$), regardless of the electronic properties of the cinnamyl moiety 4.6a–g. Both catalyst systems tolerated substitution at the C2 position of the allyl fragment 4.5h and 4.6h.
### Scheme 4.10. Decarboxylative Difluoroallylation of Substrates Bearing Distinct Allyl Moieties

<table>
<thead>
<tr>
<th>Catalyst System A</th>
<th>Catalyst System B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.5a</strong></td>
<td><strong>4.6a</strong></td>
</tr>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>92% (87%)</td>
<td>93% (83%)</td>
</tr>
<tr>
<td>b/l = 1 : 23</td>
<td>b/l = 99 : 1</td>
</tr>
<tr>
<td><strong>4.5b</strong></td>
<td><strong>4.6b</strong></td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>70% (43%)</td>
<td>92% (78%)</td>
</tr>
<tr>
<td>b/l = 1 : 30</td>
<td>b/l = 49 : 1</td>
</tr>
<tr>
<td><strong>4.5c</strong></td>
<td><strong>4.6c</strong></td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>89% (82%)</td>
<td>94% (80%)</td>
</tr>
<tr>
<td>b/l = 1 : 21</td>
<td>b/l = 99 : 1</td>
</tr>
<tr>
<td><strong>4.5d</strong></td>
<td><strong>4.6d</strong></td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td><img src="image8" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>84% (84%)</td>
<td>94% (76%)</td>
</tr>
<tr>
<td>b/l = 1 : 14</td>
<td>b/l = 49 : 1</td>
</tr>
<tr>
<td><strong>4.5e</strong></td>
<td><strong>4.6e</strong></td>
</tr>
<tr>
<td><img src="image9" alt="Chemical Structure" /></td>
<td><img src="image10" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>85% (86%)</td>
<td>96% (89%)</td>
</tr>
<tr>
<td>b/l = 1 : 10</td>
<td>b/l = 99 : 1</td>
</tr>
<tr>
<td><strong>4.5f</strong></td>
<td><strong>4.6f</strong></td>
</tr>
<tr>
<td><img src="image11" alt="Chemical Structure" /></td>
<td><img src="image12" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>77% (68%)</td>
<td>92% (80%)</td>
</tr>
<tr>
<td>b/l = 1 : 7</td>
<td>b/l = 99 : 1</td>
</tr>
<tr>
<td><strong>4.5g</strong></td>
<td><strong>4.6g</strong></td>
</tr>
<tr>
<td><img src="image13" alt="Chemical Structure" /></td>
<td><img src="image14" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>64% (55%)</td>
<td>81% (70%)</td>
</tr>
<tr>
<td>b/l = 1 : 6</td>
<td>b/l = 99 : 1</td>
</tr>
<tr>
<td><strong>4.5h</strong></td>
<td><strong>4.6h</strong></td>
</tr>
<tr>
<td><img src="image15" alt="Chemical Structure" /></td>
<td><img src="image16" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>73% (77%)</td>
<td>91% (82%)</td>
</tr>
<tr>
<td>b/l = 1 : 10</td>
<td>b/l = 28 : 1</td>
</tr>
</tbody>
</table>

**Notes:**
- **Catalyst System A:** 4.4a-h (1.0 equiv), Pd(OAc)$_2$ (3.0 mol%), t-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: 4.4a-h (1.0 equiv), Pd(OAc)$_2$ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. $^{19}$F NMR yields for the major isomers were determined using PhCF$_3$ as an internal standard (average of two runs). The values in parentheses represent the yields of the major products. The regioselectivities were determined by $^1$H NMR analysis of the crude reaction mixtures. $^b$ 70 °C. $^c$ Pd(OAc)$_2$ (5 mol%), t-BuBrettPhos (10 mol%).
However, substrates bearing β-hydrogens on the allyl fragment underwent β-H elimination (Scheme 4.11A) to generate dienes instead of coupling products. Non-cinnamyl substrates provided either no linear products or low yields of branched products. In these cases, α,α-difluoracetophenone was the major product under the present conditions (Scheme 4.11B).

<table>
<thead>
<tr>
<th>Scheme 4.11. Substrates that Did Not Provide Coupling Products or Gave Poor Results$^{ab}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A) Mechanism of β-H elimination</strong></td>
</tr>
<tr>
<td><img src="image.png" alt="Mechanism of β-H elimination" /></td>
</tr>
<tr>
<td><strong>B) β-Hydrogen-Containing and Non-Cinnamyl Substrates</strong></td>
</tr>
<tr>
<td><img src="image.png" alt="β-Hydrogen-Containing and Non-Cinnamyl Substrates" /></td>
</tr>
</tbody>
</table>

- either no linear products or low yields of branched products (< 23%)
- formation of dienes instead of coupling products
- PhCCF$_2$:H as the major product

---

$^a$ Catalyst System A: substrate (1.0 equiv), Pd(OAc)$_2$ (3.0 mol%), t-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: substrate (1.0 equiv), Pd(OAc)$_2$ (2.5 mol%), PhXPhos (6.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. The reactions were evaluated by $^{19}$F NMR with PhCF$_3$ as an internal standard and by GC-mass.

$^b$ The diene, buta-1,3-dien-1-ylbenzene, was determined by GC-mass.
Both catalyst systems also transformed substrates bearing distinct aryl and alkyl α,α-difluoroketone moieties (Scheme 4.12). Reactions of electron-rich and neutral aryl α,α-difluoroketone substrates afforded good selectivities and yields for the linear 4.8a–b and branched 4.9a–b products under the respective conditions. Even heteroaryl α,α-difluoroketone substrates 4.7c–d generated linear 4.8c–d and branched 4.9c–d products in good selectivities and yields. Under the standard reaction conditions, an aliphatic α,α-difluoroketone was less reactive; however, improved yields and high selectivities were obtained by increasing the catalyst loading [5 mol% Pd(OAc)₂, 10 mol% ligands] and reaction time.

Thus, both catalyst systems enabled access to a variety of unique α,α-difluoroketone products, which would be challenging to prepare otherwise.

### Scheme 4.12. Decarboxylative Difluoroallylation of Substrates Bearing Distinct Ketone Moieties

<table>
<thead>
<tr>
<th>Catalyst System A</th>
<th>Catalyst System B</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.8a, 87% (78%)²</td>
<td>4.9a, 93% (83%)²</td>
</tr>
<tr>
<td>b/l = 1 : 25</td>
<td>b/l = 49 : 1</td>
</tr>
<tr>
<td>4.8b, 87% (86%)</td>
<td>4.9b, 94% (83%)</td>
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<tr>
<td>b/l = 1 : 13</td>
<td>b/l = 99 : 1</td>
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<td>4.8c, 92% (86%)</td>
<td>4.9c, 94% (86%)²</td>
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<tr>
<td>b/l = 1 : 15</td>
<td>b/l = 49 : 1</td>
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<td>4.8d, 79% (63%)²</td>
<td>4.9d, 94% (71%)</td>
</tr>
<tr>
<td>b/l = 1 : 13</td>
<td>b/l = 99 : 1</td>
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<tr>
<td>4.8e, 62% (60)³</td>
<td>4.9e, 83% (71)</td>
</tr>
<tr>
<td>b/l = 1 : 20</td>
<td>b/l = 63 : 1</td>
</tr>
<tr>
<td>4.9f, 83% (71)²</td>
<td></td>
</tr>
<tr>
<td>b/l = 1 : 20</td>
<td></td>
</tr>
<tr>
<td>4.9g, 83% (71)²</td>
<td></td>
</tr>
<tr>
<td>b/l = 1 : 20</td>
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</tr>
</tbody>
</table>

² Catalyst System A: 4.7a–e (1.0 equiv), Pd(OAc)₂ (3.0 mol%), t-BuBrettPhos (6.0 mol%), 1,4-dioxane (0.50 M), 60 °C, 24 h; Catalyst System B: 4.7a–e (1.0 equiv), Pd(OAc)₂ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane (0.10 M), 90 °C, 24 h. ³ 19F NMR yields for the major isomers were determined by using PhCF₃ as an internal standard (average of two runs). The values in parentheses represent the yields of the major products. The regioselectivities were determined by ¹H NMR analysis of the crude reaction mixtures. ⁴ Pd(OAc)₂ (5.0 mol%), t-BuBrettPhos (10 mol%). ⁵ 70 °C, 36 h. ⁶ Pd(OAc)₂ (3.5 mol%), PhXPhos (7.0 mol%). ⁷ 16 h. ⁸ Pd(OAc)₂ (5.0 mol%), PhXPhos (10 mol%). ⁹ 90 °C, 36 h.
The complementary products may derive from a common $L_n$–Pd($\pi$-allyl)(enolate) intermediate 4.11 through distinct ligand-controlled regioselective C–C bond-forming events (Scheme 4.13A). To establish the intermediacy of a $\pi$-allyl complex, secondary ester 4.13 was subjected to both conditions A and B (Scheme 4.13B), and the results were compared to reactions of the corresponding linear substrate 4.4a in Scheme 4.11. System A transformed both linear and branched substrates 4.4a and 4.13 into linear product 4.5a with comparable selectivity (b/l = 1 : 23 vs. 1 : 21), while system B transformed both linear and branched substrates 4.4a and 4.13 into branched product 4.6a with high selectivity (b/l = 99 : 1). Combined, these data 1) implicate the intermediacy of $\pi$-allyl species 4.11 in both reaction pathways; 2) discount memory effects controlling the regioselectivity for either system; and 3) confirm that the ligands ultimately control the regiochemical fate of the reaction.
Subsequent reactions probed the extent of association and/or solvent separation of the α,α-difluoroketone enolate with the palladium π-allyl complex. If free enolate existed in solution, it would be protonated upon addition of an acidic additive. The conjugate base of the additive would then react with the π-allyl complex and regenerate Pd(0) to continue the catalytic cycle. When 4.1a was subjected to the standard reaction conditions A and B in the presence of 1.0 equivalent of pentane-2,4-dione (acetylacetone; acac; pKₐ = 13.3 in DMSO), distinct yields of fluorinated products 4.2a, 4.3a, alkylated product 4.2a', and protonated difluoroketone 4.3a' were detected (Table 4.2). Catalyst system A provided product 4.2a in 28% yield, and products 4.2a' and 4.3a' in ca. 66% yield (entry 2, Table 4.2). Alternatively, catalyst system B generated 4.3a in 67% yield, and 4.2a' and 4.3a' in lower yields (30% and 32%, respectively, entry 4, Table 4.2). Since formation of products 4.2a' and 4.3a' derive from dissociation of the Pd-bound difluoroenolate, the lower yields of 4.2a' and 4.3a' generated in the reactions of catalyst system B, which provides the branched product, indicate that the enolate is more tightly associated with the palladium π-allyl complex.

### Table 4.2. Distinct Pathways for Formation of Linear and Branched Products

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst system</th>
<th>additive</th>
<th>4.2a (%)</th>
<th>4.3a (%)</th>
<th>4.2a' (%)</th>
<th>4.3a' (%)</th>
<th>b/l</th>
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<td>A</td>
<td>none</td>
<td>89</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1 : 22</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>acac</td>
<td>28</td>
<td>1</td>
<td>66</td>
<td>66</td>
<td>1 : 28</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
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<td>1</td>
<td>94</td>
<td>0</td>
<td>0</td>
<td>94 : 1</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>acac</td>
<td>&lt;1</td>
<td>67</td>
<td>30</td>
<td>32</td>
<td>&gt;98 : 2</td>
</tr>
</tbody>
</table>

a Catalyst system A: 4.1a (1.0 equiv, 0.50 M solution in 1,4-dioxane), Pd(OAc)₂ (3.0 mol%), t-BuBrettPhos (8.0 mol%), 1,4-dioxane, 60 °C, 20 h. Catalyst system B: 4.1a (1.0 equiv, 0.10 M solution in 1,4-dioxane), Pd(OAc)₂ (2.5 mol%), PhXPhos (5.0 mol%), 1,4-dioxane, 90 °C, 20 h. b Yields were determined by 19F NMR spectroscopy using CF₃OCH₂F as an internal standard. c The yield of non-fluorinated product was determined by 1H NMR spectroscopy using CH₂Br₂ as an internal standard. d The selectivity for branched to linear products was the ratio of 4.3a to 4.2a.
Thus, we hypothesized that cinnamyl α,α-difluoro-β-keto esters underwent decarboxylative difluoromethylation to generate linear and branched products via different pathways under both catalyst systems. The linear product may come from outer sphere attack of the enolate on less hindered terminus of the π-allyl complex (path i, Scheme 4.13) while the branched product may result from the rearrangement of a seven-membered ring transition state composed of enolate-Pd-π-allyl complex (path iii, Scheme 4.13) as proposed by Stoltz, Goddard III, and Echavarren.24

An evaluation of the relationship between the electronic structures of the cinnamyl-derived substrates and the regioselectivities of the catalytic reactions suggests that the branched and linear products derive from distinct pathways. For outer-sphere processes, the electronic structure of the cinnamyl-derived substrates can perturb the regiochemical outcome of the reaction. Specifically, electron-rich substrates provide linear products in lower selectivity than electron-deficient substrates,7b,25 because S_N1-like attack at the stabilized secondary position of the π-allyl intermediates (path ii, Scheme 4.13) competes with S_N2-like attack at the unhindered primary position (path i, Scheme 4.13). For system A, a similar trend was observed, as confirmed by a linear free energy correlation (Figure 4.1). Thus, under system A, the reaction may proceed predominantly through an analogous outer-sphere mechanism (path i, Scheme 4.13).
Figure 4.1. Catalyst System A Improved Linear Selectivity for Electron-Deficient Substrates

\[ \text{X} = \text{H, 3-CF}_3, 4-\text{NO}_2, 3-\text{CO}_2\text{Et, 4-Me, 4-OMe} \]

\[ \text{Rd(OAc)}_2 \text{ (3.0 mol\%)} \quad \text{t-BuBriPhos} \text{ (6.0 mol\%)} \]

1,4-dioxane, 60 °C, 20-24 h

\[ \log \left( \frac{\text{Selectivity}_\text{y}}{\text{Selectivity}_\text{y}} \right) \text{ vs. } \sigma^+ \quad \rho = 0.45, r^2 = 0.998 \]

\[ \log \left( \frac{\text{Selectivity}_\text{y}}{\text{Selectivity}_\text{y}} \right) \text{ vs. } \sigma^- \]

\[ y = 0.448x - 0.1203 \quad R^2 = 0.9979 \]
In contrast, system B notably generates branched products, which are less commonly observed in Pd-catalyzed allylation reactions of hard ketone enolates. If $S_{N1}$-like attack of intermediate predominantly occurred at the secondary position (path ii, Scheme 4.13), the electronic properties of the cinnamyl-derived substrates 4.1a, 4.4a–c, 4.4e and 4.4g would likely allow path i to compete and influence the regioselectivity of the reactions. However for system B, substrates bearing electron-rich, -neutral, and -deficient cinnamyl moieties all underwent coupling to afford the branched products in high selectivities 4.3a, 4.6a–c, 4.6e and 4.6g (Figure 4.2). This lack of a correlation between the electronic properties of the cinnamyl-derived substrates and the regioselectivity may discount the outer-sphere path i.
An alternate explanation for the unique regioselectivity involves the sigmatropic rearrangement of an \( \eta^1 \)-allyl intermediate (path iii, Scheme 4.13).\(^{24} \) Although this mechanism has been computationally predicted, experimental evidence for palladacyclic transition state 4.12 has not been established. In support of this rearrangement mechanism, non-metal-catalyzed 3,3'-sigmatropic rearrangements of allyl \( \alpha,\alpha \)-difluoroenol ethers similarly proceed more rapidly than those of the non-fluorinated counterparts.\(^{13a,26} \) Thus, in the present case, the fluorine atoms might also provide unique physical properties that facilitate an analogous Pd-catalyzed rearrangement to provide the branched product.

4.5 Conclusion

The fluorine substituents of the substrate and the selection of appropriate ligands together facilitated a pair of orthogonal palladium-catalyzed regioselective decarboxylative allylation reactions to afford \( \alpha,\alpha \)-difluoroketone products. Computational studies should provide insight into the physicochemical basis on which fluorination enables formation of the branched product, and into the relationship between the ligand structures and the regioselectivity of the transformation. Ongoing work aims at exploiting this reaction pathway to generate other unique fluorinated substructures, including enantioenriched products. We envision that these strategies should be useful for accessing \( \alpha,\alpha \)-difluoroketone-based probes that would otherwise be challenging to prepare.
4.6 References for Chapter 4


Chapter 4 Appendix

Experimental Procedures and Spectral Analyses for Compounds in Chapter 4
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General Information

Unless otherwise noted, reactions were performed under an atmosphere of N₂ using oven-dried glassware. Palladium-catalyzed reactions were performed in 1 dram vials, which were sealed with PTFE-lined silicone septa, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing by quenching of fluorescence, or by staining with KMnO₄ or ninhydrin. Column chromatography was conducted using an automated system. ¹⁹F NMR yields and isolated yields reported in the manuscript represent an average of at least two independent runs of material deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment.

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. 1,4-Dioxane (anhydrous, 99.8%) and Pd(OAc)₂ (reagent grade, 98%) were purchased from Sigma Aldrich. All ligands for screening were purchased from Sigma Aldrich or Strem with the following exceptions: t-BuBrettPhos and PhXPhos were prepared according to previously reported syntheses.¹² Solvents including DMF, PhMe, CH₂Cl₂, THF, MeOH were used directly from a solvent purification system in which solvent was dried by passage through two columns of activated alumina under argon.

Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual CHCl₃ in the NMR solvent (CHCl₃: δ = 7.27 ppm or DMSO-d₆: δ = 2.50 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak (CDCl₃: δ = 77.23 ppm or DMSO-d₆: δ = 39.51 ppm). Fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz). ¹⁹F NMR chemical shifts (δ) are reported in ppm upfield from
trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in Hertz (Hz), integration. Gas chromatography (GC) data were obtained via analysis using an Agilent Technologies 7890A GC system with a FID detector and an Agilent Technologies 30 m x 0.320 mm i.d. HP–5 capillary column. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier™ mass spectrometer or by atmospheric-pressure chemical ionization (APCI–hexane/PhMe) on a Waters Q-Tof Premier™, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as ionization solvent. Infrared spectra were measured at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on Thomas Hoover Capillary Melting Point apparatus.

**Preparation of Known Compounds**

Potassium 2,2-difluoro-3-oxo-3-phenylpropanoate, potassium 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate, potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate, potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate, potassium 2,2-difluoro-3-oxo-3-(1-phenyl-1H-pyrazol-4-yl)propanoate, and potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate were prepared according to a previous report in our group.³

**Preparation of Compound 4.1a**

![Structure of 4.1a](image)

cinnamyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.1a)

An oven-dried one-neck round-bottom flask was charged with Potassium 2,2-difluoro-3-oxo-3-phenylpropanoate³ (3.00 g, 12.6 mmol), and the system was evacuated and backfilled with N₂(g) three times. Dry CH₂Cl₂ (0.040 L) and DMF (1.2 mL) were added via a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (1.2 mL, 14 mmol) was added dropwise, and then the reaction mixture
was stirred at 0 °C for 30 min, and rt for 1.5 h. Next, a solution of cinnamyl alcohol (2.54 g, 18.9 mmol) dissolved in dry CH2Cl2 (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et3N (2.6 mL, 19 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. H2O (10 mL) was added to quench the reaction, and CH2Cl2 was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic layers were dried over anhydrous Na2SO4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound 4.1a as a colorless oil (3.20 g, 80%). 1H NMR (CDCl3, 400 MHz) δ 8.09 (d, J = 7.6 Hz, 2 H), 7.67 (t, J = 7.6 Hz, 1 H), 7.51 (t, J = 7.6 Hz, 2 H), 7.38–7.29 (m, 5 H), 6.69 (d, J = 15.6 Hz, 1 H), 6.23 (dt, J = 16, 6.8 Hz, 1 H), 4.98 (d, J = 6.8 Hz, 2 H). 13C NMR (CDCl3, 125 MHz) δ 185.6 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 136.5, 135.8, 135.4, 131.2, 130.2 (t, J = 2.5 Hz), 129.2, 128.9, 128.7, 127.0, 120.9, 110.0 (t, J = 263.8 Hz), 68.2. 19F NMR (CDCl3, 376 MHz) δ –107.4 (s, 2 F). IR (film) 3061, 3028, 1776, 1715, 1699, 1597, 1450, 1312, 1159, 968, 922, 746, 712, 688 cm⁻¹. HRMS (ESI, m/z): calcd for C18H14F2O3Na [M+Na]+ 339.0809, found 339.0804.

Screening of Ligands

An oven-dried 1 dram vial was charged with substrate 4.1a (47.4 mg, 0.150 mmol), Pd(OAc)2 (1.7 mg, 0.0075 mmol), ligand (7.0 mg, 0.0150 mmol), and a magnetic stir bar. The vial was equipped with a three-way valve, evacuated and backfilled with N2(g) four times. Dry 1,4-dioxane (0.60 mL) was added via a syringe under N2(g). The vial was sealed with a screwed-cap under N2(g) flow, and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block, and stirred at 80 °C for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (3 mL). Dodecane (0.020 mL, 0.088 mmol) was added as a standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. A small aliquot was taken from the vial, passed through a plug of silica gel, and eluted with additional EtOAc (2 mL). The sample was analyzed using GC/FID, and the quantity of compounds 4.2a and 4.3a were determined using dodecane as an internal standard.
Characterization of Compounds 4.2a and 4.3a

(E)-2,2-difluoro-1,5-diphenylpent-4-en-1-one (4.2a)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.13 (dt, $J = 8.4$, 1.4 Hz, 2 H), 7.65 (tt, $J = 7.6$, 1.4 Hz, 1 H), 7.52 (t, $J = 8.0$ Hz, 2 H), 7.39–7.36 (m, 2 H), 7.32 (t, $J = 7.4$ Hz, 2 H), 7.27–7.23 (m, 1 H), 6.60 (d, $J = 15.6$ Hz, 1 H), 6.22 (dt, $J = 15.6$, 7.2 Hz, 1 H), 3.14 (tdd, $J = 17.2$, 7.2, 1.6 Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 189.4 (t, $J = 31.2$ Hz), 136.9, 136.4, 134.6, 132.2 (t, $J = 2.5$ Hz), 130.4 (t, $J = 3.1$ Hz), 128.9, 128.8, 128.0,
126.6, 119.0 (t, J = 5.6 Hz), 118.9 (t, J = 253.1 Hz), 38.0 (t, J = 23.1 Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –98.9 (t, J = 16.9 Hz, 2 F). IR (film) 3059, 3026, 1701, 1597, 1448, 1273, 1173, 1119, 1090, 1061, 966, 947, 914, 748, 716, 688, 667 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{17}$H$_{15}$F$_2$O [M+H]$^+$ 273.1091, found 273.1092. mp 45–46 °C.

2,2-difluoro-1,3-diphenylpent-4-en-1-one (4.3a)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.96 (dt, J = 8.8, 1.4 Hz, 2 H), 7.61 (tt, J = 7.6, 1.4 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 2 H), 7.33–7.28 (m, 5 H), 6.22 (ddd, J = 17.2, 10.4, 8.4 Hz, 1 H), 5.32 (d, J = 10.4 Hz, 1 H), 5.23 (dt, J = 16.8, 1.2 Hz, 1 H), 4.32 (td, J = 16.4, 8.4 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 190.0 (t, J = 29.4 Hz), 135.3, 134.2, 133.1, 132.6 (t, J = 4.4 Hz), 130.1 (t, J = 3.1 Hz), 129.8, 128.8, 128.0, 120.8, 118.8 (t, J = 257.5 Hz), 54.2 (t, J = 21.9 Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –103.5 (dd, A of ABX, $J_{AB} = 274.5$ Hz, $J_{AX} = 15.0$ Hz, 1 F), –103.1 (dd, B of ABX, $J_{AB} = 274.5$ Hz, $J_{BX} = 15.0$ Hz, 1 F). IR (film) 3065, 3032, 1701, 1597, 1448, 1267, 1178, 1049, 930, 746, 716, 698, 688 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{17}$H$_{14}$F$_2$ONa [M+Na]$^+$ 295.0910, found 295.0902.

Preparation of Compounds 4.1b and 4.1c in Table 4.1

cinnamyl 3-oxo-3-phenylpropanoate (4.1c)

Compound 4.1c was prepared according to a previous report.$^4$ A mixture of cinnamyl alcohol (1.34 g, 10.0 mmol), ethyl benzoylacetate (1.73 g, 10.0 mmol), DMAP (1.22 g, 10.0 mmol) was stirred with oven-dried 4 Å molecular sieves (50 g) in dry toluene (0.080 L) at 100–105 °C for 36 h. The reaction mixture was cooled to rt, and filtered to remove the molecular sieves. The solvents were removed under reduced
pressure, and EtOAc (60 mL) and water (60 mL) were added to the residue. The layers were separated, and the organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound 4.1c as a yellow oil (2.08 g, 74%, ketone : enol = 4:1). ^1H NMR (CDCl₃, 400 MHz) δ 12.53 (s, 1 H, enol), 7.98–7.96 (m, 2 H, keto), 7.82–7.79 (m, 2 H, enol), 7.61 (tt, J = 7.4, 1.6 Hz, 1 H, keto), 7.51–7.42 (m, 7 H, enol + keto), 7.39–7.25 (m, 8 H, enol + keto), 6.72 (d, J = 16.0 Hz, 1 H, enol), 6.64 (d, J = 16.0 Hz, 1 H, keto), 6.36 (dt, J = 16.0, 6.4 Hz, 1 H, enol), 6.26 (dt, J = 16.0, 6.4 Hz, 1 H, keto), 5.74 (s, 1 H, enol), 4.89 (dd, J = 6.4, 1.6 Hz, 2 H, enol), 4.83 (dd, J = 6.4, 1.6 Hz, 2 H, keto), 4.06 (s, 2 H, keto). HRMS (ESI, m/z): calcd for C₁₈H₁₆O₃Na [M+Na]^+ 303.0997, found 303.0996. Spectroscopic data matched that from the previous report.⁵

**cinnamyl 2-fluoro-3-oxo-3-phenylpropanoate (4.1b)**

Compound 4.1b was prepared according to a previous report.⁶ Compound 4.1c (1.03 g, 3.67 mmol) and CpTiCl₃ (39.5 mg, 0.180 mmol) were dissolved in CH₃CN (0.020 L) at rt, and selectfluor (1.40 g, 4.04 mmol) was added. The mixture was stirred at rt for 6 h, and filtered to remove solids. The filtrate was concentrated, and the crude product was purified by column chromatography using a gradient of EtOAc / hexanes (2% to 5%) for elution to furnish the compound 4.1b as a colorless oil (0.75 g, 68%). ^1H NMR (CDCl₃, 400 MHz) δ 8.06 (dt, J = 8.4, 1.2 Hz, 2 H), 7.64 (tt, J = 7.4, 1.4 Hz, 1 H), 7.51 (t, J = 8.0 Hz, 2 H), 7.35–7.26 (m, 5 H), 6.62 (dt, J = 16.0, 1.4 Hz, 1 H), 6.21 (dt, J = 16.0, 6.4 Hz, 1 H), 5.94 (d, J = 48.8 Hz, 1 H), 4.90 (dt, J = 6.4, 1.4 Hz, 2 H). ^13C NMR (CDCl₃, 125 MHz) δ 189.6 (d, J = 20.0 Hz), 164.9 (d, J = 23.8 Hz), 135.9, 135.8, 134.7, 133.5 (d, J = 2.5 Hz), 129.7 (d, J = 3.8 Hz), 129.0, 128.8, 128.5, 126.9, 121.5, 90.2 (d, J = 196.2 Hz), 67.1. ^19F NMR (CDCl₃, 376 MHz) δ −190.2 (d, J = 48.9 Hz, 1
Experimental Procedures and Characterization of Compounds for Table 4.1

General Procedure A: An oven-dried 1 dram vial was charged with substrate (4.1a, 4.1b or 4.1c), Pd(OAc)$_2$, ligand (t-BuBrettPhos or PhXPhos), and a magnetic stir bar. The vial was equipped with a three-way valve, evacuated and backfilled with N$_2$(g) four times. Dry 1,4-dioxane was added via a syringe under N$_2$(g). The vial was sealed with a screwed-cap under N$_2$(g) flow, and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block, and stirred at the indicated temperature for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc. An internal standard was added, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing before checking $^{19}$F or $^1$H yields.

$^{(E)}$-2,2-difluoro-1,5-diphenylpent-4-en-1-one (4.2a)

General procedure A was followed using 4.1a (84.1 mg, 0.300 mmol), Pd(OAc)$_2$ (2.0 mg, 0.0090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). $\alpha$,$\alpha$,$\alpha$-trifluorotoluene (15 µL) was added as an internal standard to obtain a $^{19}$F NMR yield of linear product 4.2a. Spectral data of 4.2a matched that described above.

2,2-difluoro-1,3-diphenylpent-4-en-1-one (4.3a)

General procedure A was followed using 4.1a (84.1 mg, 0.300 mmol), Pd(OAc)$_2$ (1.68 mg, 0.0075 mmol), PhXPhos (6.97 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). $\alpha$,$\alpha$,$\alpha$-trifluorotoluene (15 µL) was added as
an internal standard to obtain a $^{19}$F NMR yield of branched product 4.3a. Spectral data of 4.3a matched that described above.

(E)-2-fluoro-1,5-diphenylpent-4-en-1-one (4.2b)

General procedure A was followed using 4.1b (89.5 mg, 0.300 mmol), Pd(OAc)$_2$ (2.0 mg, 0.0090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Fluorobenzene (15 µL) was added as an internal standard to obtain $^{19}$F NMR yields. After determination of the $^{19}$F NMR yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. Removal of the solvents and chromatographic purification provided the linear product 4.2b (15.2 mg, 20%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.00 (d, $J = 8.0$ Hz, 2 H), 7.63 (tt, $J = 7.4$, 1.5 Hz, 1 H), 7.51 (t, $J = 8.0$ Hz, 2 H), 7.39–7.22 (m, 5 H), 6.53 (dt, $J = 16.0$, 1.6 Hz, 1 H), 6.27 (dt, $J = 16.0$, 7.2 Hz, 1 H), 5.69 (ddd, $J = 49.0$, 7.4, 4.8 Hz, 1 H), 3.02–2.82 (m, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 196.4 (d, $J = 20.0$ Hz), 137.0, 134.6, 134.3, 134.1, 129.2 (d, $J = 3.8$ Hz), 129.0, 128.8, 127.8, 126.5, 123.0 (d, $J = 3.8$ Hz), 93.2 (d, $J = 185.0$ Hz), 36.4 (d, $J = 21.2$ Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –187.8 (ddd, $J = 48.9$, 30.1, 22.5 Hz, 1 F). IR (film) 3026, 2922, 1701, 1597, 1578, 1448, 1228, 1072, 964, 744, 694 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{17}$H$_{15}$FONa [M+Na]$^+$ 277.1005, found 277.0995.

2-fluoro-1,3-diphenylpent-4-en-1-one (4.3b)

General procedure A was followed using 4.1b (89.5 mg, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Fluorobenzene (15 µL) was added as an internal standard to obtain $^{19}$F NMR yields. After determination of the $^{19}$F yield, the aliquot was
recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. Removal of the solvents and chromatographic purification provided the branched product 4.3b as two diastereoisomers (16 mg, 21%, A : B = 2.2 : 1). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.90–7.88 (m, 2 H, isomer A), 7.79 (dt, $J = 8.4$, 1.2 Hz, 2 H, isomer B), 7.62–7.22 (m, 16 H, isomers A and B), 6.19 (ddd, $J = 17.2$, 10.2, 8.2 Hz, 1 H, isomer A), 6.16 (ddd, $J = 17.2$, 10.4, 7.6 Hz, 1 H, isomer B), 5.83 (dd, $J = 48.4$, 4.0 Hz, 1 H, isomer A), 5.78 (dd, $J = 48.8$, 5.2, 1 H, isomer B), 5.24–5.18 (m, 1 H for isomer A and 2 H for isomer B), 5.07 (dt, $J = 17.2$, 1.2 Hz, 1 H, isomer A), 4.16–4.01 (m, 4 H, isomers A and B). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 196.5 (d, $J = 20.0$ Hz, isomer B), 196.0 (d, $J = 18.7$ Hz, isomer A), 139.4 (isomer A), 137.7 (isomer B), 136.1 (d, $J = 5.0$ Hz, isomer B), 135.3 (isomer B), 135.2 (isomer A), 134.3 (d, $J = 5.0$ Hz, isomer A), 133.9 (isomer A), 133.8 (isomer B), 129.1 (isomers A and B), 129.0 (isomers A and B), 128.9 (isomers A and B), 128.8 (isomers A and B), 127.6 (isomers A and B), 119.1 (isomer A), 118.1 (isomer B), 95.9 (d, $J = 190.0$ Hz, isomer B), 95.7 (d, $J = 191.2$ Hz, isomer B), 52.6 (d, $J = 20.0$ Hz, isomer A), 52.3 (d, $J = 20.0$ Hz, isomer B). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ −194.9 (dd, $J = 48.9$, 26.3 Hz, 1 F, isomer A), −191.9 (dd, $J = 48.9$, 26.3 Hz, 1 F, isomer B). IR (film) 3063, 2924, 1697, 1691, 1597, 1491, 1448, 1277, 1252, 1095, 926, 756, 698 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{15}$FONa [M+Na]$^+$ 277.1005, found 277.0999.

(E)-1,5-diphenylpent-4-en-1-one (4.2c)

General procedure A was followed using 4.1c (84.1 mg, 0.300 mmol), Pd(OAc)$_2$ (2.0 mg, 0.0090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Dibromomethane (15 µL) was added as an internal standard to obtain $^1$H NMR yields. Spectral data of the linear product 4.2c matched that from a previous report.$^7$
1,3-diphenylpent-4-en-1-one (4.3c)

General procedure A was followed using 4.1c (84.1 mg, 0.300 mmol), Pd(OAc)$_2$ (1.68 mg, 0.0075 mmol), PhXPhos (6.97 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Dibromomethane (10 µL) was added as an internal standard to obtain $^1$H NMR yields. Spectral data of the branched product 4.3c matched that from a previous report.$^8$

**Experimental Procedures and Characterization of Compounds in Scheme 4.10**

**General Procedure B:** An oven-dried round-bottom flask was charged with cinnamic acid derivative (12 mmol), and dry MeOH (25 mL) was added. The mixture was cooled to 0 °C, and thionyl chloride (24 mmol) was added dropwise. The reaction mixture was warmed to rt, and then stirred at reflux for 6 h. The reaction mixture was cooled to rt, and MeOH and thionyl chloride were removed under reduced pressure. EtOAc (25 mL) and H$_2$O (10 mL) were added to the residue, and the solution was neutralized with NaHCO$_3$(aq). The phases were separated, and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated to give the desired product without further purification.

**General Procedure C:** An oven-dried three-neck flask was charged with cinnamic ester (8.0 mmol). The reaction vessel was equipped with a liquid addition funnel, evacuated and backfilled with N$_2$(g) three times. Dry CH$_2$Cl$_2$ (0.020 L) was added at rt, and then the solution was cooled to –78 °C. DIBAL (1.0 M in hexane, 0.020 L, 0.020 mol) was added dropwise, and then the reaction solution was gradually warmed to rt. The reaction solution was cooled to 0 °C, and 1 N HCl was added dropwise to quench the reaction until no precipitate remained. The phases were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated to give the desired product without further purification.
General Procedure D: An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate\(^3\) (4.8 mmol), and the system was evacuated and backfilled with N\(_{2(g)}\) three times. Dry CH\(_2\)Cl\(_2\) (24 mL) and DMF (1.2 mL) were added \textit{via} a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (4.0 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. Next, a solution of cinnamyl alcohol derivative (4.0 mmol) dissolved in dry CH\(_2\)Cl\(_2\) (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et\(_3\)N (8.0 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 1.5 h. H\(_2\)O (10 mL) was added to quench the reaction, and the CH\(_2\)Cl\(_2\) was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. Purification by flash chromatography provided the desired product.

General Procedure E: Pd-Catalyzed Decarboxylation to Generate Linear Difluoroketone Product: An oven-dried 1 dram vial was charged with substrate \textit{4a–h} (0.300 mmol), Pd(OAc)\(_2\) (2.0 mg, 0.0090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and a magnetic stir bar. The vial was equipped with a three-way valve, and evacuated and backfilled with N\(_{2(g)}\) four times. Dry 1,4-dioxane (0.60 mL) was added \textit{via} a syringe under N\(_{2(g)}\). The vial was sealed with a screwed-cap under N\(_{2(g)}\), and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block at 60 °C, and stirred for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). \(\alpha,\alpha,\alpha\)-Trifluorotoluene (15 \(\mu\)L, 0.12 mmol) or 2,2,2-trifluoroethanol (0.010 mL, 0.14 mmol) was added as a standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial for \({}^{19}\text{F}\) NMR analysis. After determination of the \({}^{19}\text{F}\) yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. (In some cases, EtOAc was used for elution). Removal of the solvents and chromatographic purification provided the desired product \textit{5a–h}.

General Procedure F: Pd-Catalyzed Decarboxylation to Generate Branched Difluoroketone Product: An oven-dried 1 dram vial was charged with the substrate \textit{4a–h} (0.300 mmol), Pd(OAc)\(_2\) (1.7 mg, 0.0075 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and a magnetic stir bar. The vial was equipped with a three-way valve, and evacuated and backfilled with N\(_{2(g)}\) four times. Dry 1,4-dioxane (0.60 mL) was added \textit{via} a syringe under N\(_{2(g)}\). The vial was sealed with a screwed-cap under N\(_{2(g)}\), and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block at 60 °C, and stirred for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). \(\alpha,\alpha,\alpha\)-Trifluorotoluene (15 \(\mu\)L, 0.12 mmol) or 2,2,2-trifluoroethanol (0.010 mL, 0.14 mmol) was added as a standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial for \({}^{19}\text{F}\) NMR analysis. After determination of the \({}^{19}\text{F}\) yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. (In some cases, EtOAc was used for elution). Removal of the solvents and chromatographic purification provided the desired product \textit{5a–h}.
mmol), PhXPhos (7.0 mg, 0.0150 mmol), and a magnetic stir bar. The vial was equipped with a three-way valve, and evacuated and backfilled with N₂(g) four times. Dry 1,4-dioxane (3.0 mL) was added via a syringe under N₂(g). The vial was sealed with a screwed-cap under N₂(g), and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block at 90 °C, and stirred for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (0.50 mL). α,α,α-Trifluorotoluene (15 µL, 0.12 mmol) or 2,2,2-trifluoroethanol (0.010 mL, 0.14 mmol) was added as a standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial for 19F NMR analysis. After determination of the 19F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with ether. (In some cases, EtOAc was used for elution). Removal of the solvents and chromatographic purification provided the desired product 6a–h.

![Image](image1)

\((E)\)-methyl 3-(3-(trifluoromethyl)phenyl)acrylate (4.4a-2)

General procedure B was followed using 3-(trifluoromethyl)cinnamic acid (1.50 g, 6.94 mmol), thionyl chloride (1.0 mL, 14 mmol), and MeOH (15 mL). Workup afforded the title compound 4.4a-2 as a colorless solid (1.52 g, 95%). 1H NMR (CDCl₃, 400 MHz) δ 7.77–7.69 (m, 3 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.53 (t, J = 7.6 Hz, 1 H), 6.52 (d, J = 16.0 Hz, 1 H), 3.84 (s, 3 H). 19F NMR (CDCl₃, 376 MHz) δ –62.9 (s, 3 F). HRMS (ESI, m/z): calcd for C₁₁H₁₀F₃O₂ [M+H]⁺ 231.0633, found 231.0641. Spectroscopic data matched that from the previous report.⁹

![Image](image2)

\((E)\)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol (4.4a-1)
General procedure C was followed using \textbf{4.4a-2} (1.38 g, 6.00 mmol), DIBAL (1.0 M in hexane, 15 mL, 15 mmol), and CH$_2$Cl$_2$ (15 mL). Workup afforded the title compound \textbf{4.4a-1} as a light yellow oil (1.15 g, 95%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.63 (s, 1 H), 7.57–7.54 (m, 1 H), 7.51–7.49 (m, 1 H), 7.46–7.42 (m, 1 H), 6.67 (dt, $J = 16.0$, 1.6 Hz, 1 H), 6.45 (dt, $J = 16.0$, 5.4 Hz, 1 H), 4.37 (dd, $J = 5.4$, 1.6 Hz, 2 H), 1.63 (s, 3 H). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –62.8 (s, 3 F). HRMS (ESI, $m/z$): calcd for C$_{10}$H$_{10}$F$_3$O [M+H]$^+$ 203.0684, found 203.0674. Spectroscopic data matched that from the previous report.\(^9\)

(\textit{E})-3-(3-(trifluoromethyl)phenyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4a)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate\(^3\) (1.2 g, 4.8 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), \textbf{4.4a-1} (0.81 g, 4.0 mmol), Et$_3$N (1.1 mL, 8.0 mmol), DMF (1.2 mL), and CH$_2$Cl$_2$ (24 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound \textbf{4.4a} as a colorless oil (1.2 g, 78%). $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 8.10 (d, $J = 8.0$ Hz, 2 H), 7.69–7.66 (m, 1 H), 7.58–7.51 (m, 5 H), 7.48–7.45 (m, 1 H), 6.70 (d, $J = 16.0$ Hz, 1 H), 6.30 (dt, $J = 10.0$, 6.0, 1.5 Hz, 1 H), 5.00 (d, $J = 6.0$ Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.5 (t, $J = 27.5$ Hz), 161.8 (t, $J = 30.6$ Hz), 136.6, 135.4, 134.5, 131.3 (q, $J = 32.5$ Hz), 131.1, 130.2 (t, $J = 2.5$ Hz), 130.1, 129.4, 129.2, 124.2 (q, $J = 271.3$ Hz), 125.2 (q, $J = 3.8$ Hz), 123.6 (q, $J = 3.8$ Hz), 123.0, 110.1 (t, $J = 263.8$ Hz), 67.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.3 (s, 2 F), –62.8 (s, 3 F). IR (film) 3067, 2960, 1778, 1715, 1699, 1599, 1450, 1336, 1312, 1165, 1124, 1097, 966, 924, 793, 712, 696, 687 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{19}$H$_{13}$F$_5$O$_3$Na [M+Na]$^+$ 407.0683, found 407.0611.

(\textit{E})-2,2-difluoro-1-phenyl-5-(3-(trifluoromethyl)phenyl)pent-4-en-1-one (4.5a)
General procedure E was followed using 4.4a (115.3 mg, 0.300 mmol), Pd(OAc)$_2$ (2.0 mg, 0.090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.5a as a colorless oil (90.4 mg, 89%). \( ^1 \)H NMR (CDCl$_3$, 400 MHz) \( \delta \) 8.15 (dd, \( J = 8.2, 1.4, 2 \) H), 7.70–7.65 (m, 1 H), 7.62 (s, 1 H), 7.57–7.51 (m, 4 H), 7.47–7.43 (m, 1 H), 6.65 (d, \( J = 16.0 \) Hz, 1 H), 6.32 (dt, \( J = 16.0, 7.2 \) Hz, 1 H), 3.18 (tdd, \( J = 16.8, 7.2, 1.2 \) Hz, 2 H). \( ^{13} \)C NMR (CDCl$_3$, 125 MHz) \( \delta \) 189.2 (t, \( J = 31.3 \) Hz), 137.6, 135.0, 134.7, 132.0 (t, \( J = 2.5 \) Hz), 131.2 (q, \( J = 32.5 \) Hz), 130.4 (t, \( J = 3.1 \) Hz), 129.7, 129.0, 124.05 (q, \( J = 3.8 \) Hz), 124.3 (q, \( J = 271.3 \) Hz), 123.3 (q, \( J = 3.8 \) Hz), 121.3 (t, \( J = 5.0 \) Hz), 118.8 (t, \( J = 253.1 \) Hz), 37.9 (t, \( J = 23.5 \) Hz). \( ^{19} \)F NMR (CDCl$_3$, 376 MHz) \( \delta \) –98.7 (t, \( J = 16.9 \) Hz, 2 F), –62.8 (s, 3 F). IR (film) 3065, 1701, 1599, 1501, 1450, 1169, 1124, 1072, 966, 798, 716, 696 cm$^{-1}$. HRMS (APCI-hexane/PhMe, \( m/z \)): calcd for C$_{18}$H$_{14}$F$_5$O [M+H]$^+$ 341.0965, found 341.0951.

2,2-difluoro-1-phenyl-3-(3-(trifluoromethyl)phenyl)pent-4-en-1-one (4.6a)

General procedure F was followed using 4.4a (115 mg, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.6a as a colorless oil (86.5 mg, 85%). \( ^1 \)H NMR (CDCl$_3$, 400 MHz) \( \delta \) 7.99 (dd, \( J = 8.6, 1.0 \) Hz, 2 H), 7.66–7.61 (m, 1 H), 7.59–7.55 (m, 3 H), 7.51–7.44 (m, 3 H), 6.20 (ddd, \( J = 17.2, 10.4, 8.4 \) Hz, 1 H), 5.36 (dd, \( J = 10.2, 1.0 \) Hz, 1 H), 5.24 (d, \( J = 16.8 \) Hz, 1 H), 4.42 (ddd, \( J = 17.4, 14.6, 8.4 \) Hz, 1 H). \( ^{13} \)C NMR (CDCl$_3$, 125 MHz) \( \delta \) 189.4 (t, \( J = 29.4 \) Hz), 136.5, 134.5, 133.3, 132.8 (t, \( J = 2.5 \) Hz), 131.9 (t, \( J = 3.8 \) Hz), 131.1 (q, \( J = 31.9 \) Hz), 130.1 (t, \( J = 3.8 \) Hz), 129.3, 128.9, 126.7 (q, \( J = 3.8 \) Hz), 124.9 (q, \( J = 3.8 \) Hz), 124.2 (q, \( J = 270.0 \) Hz), 121.6, 118.5 (t, \( J = 257.5 \) Hz), 53.6 (t, \( J = 21.3 \) Hz). \( ^{19} \)F NMR (CDCl$_3$, 376 MHz) \( \delta \) –103.7 (dd, A of ABX, \( J_{AB} = 280.1 \) Hz, \( J_{AX} = 16.9 \) Hz, 1 F), –102.2 (dd, B of ABX, \( J_{AB} = 280.1 \) Hz, \( J_{AX} = 15.0 \) Hz, 1 F), –62.8 (s, 3 F). IR (film)
(E)-3-(4-nitrophenyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4b)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate\(^3\) (1.4 g, 5.5 mmol), oxalyl chloride (0.36 mL, 4.2 mmol), 4-nitrocinnamyl alcohol (0.75 g, 4.2 mmol), Et\(_3\)N (1.2 mL, 8.4 mmol), DMF (1.2 mL), and CH\(_2\)Cl\(_2\) (0.040 L). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound 4.4b as a pale yellow solid (1.2 g, 79%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.20 (d, \(J = 8.8\) Hz, 2 H), 8.11 (d, \(J = 7.6\) Hz, 2 H), 7.72–7.67 (m, 1 H), 7.56–7.50 (m, 4 H), 6.75 (dt, \(J = 16.0, 1.6\) Hz, 1 H), 6.41 (dt, \(J = 16.0, 6.4\) Hz, 1 H), 5.03 (dd, \(J = 6.4, 1.6\) Hz, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 185.6 (t, \(J = 27.5\) Hz), 161.8 (t, \(J = 30.6\) Hz), 147.7, 142.2, 135.5, 133.2, 131.0 (t, \(J = 264.4\) Hz), 129.3, 127.6, 125.8, 124.3, 110.2 (t, \(J = 264.4\) Hz), 67.1. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –107.0 (s, 2 F). IR (film) 3076, 1774, 1701, 1597, 1518, 1344, 1310, 1159, 1126, 1105, 922, 860, 822, 744, 714, 687 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{18}\)H\(_{12}\)F\(_2\)NO\(_5\) [M-H]\(^+\) 360.0684, found 360.0669. mp 65–66 °C.

(E)-2,2-difluoro-5-(4-nitrophenyl)-1-phenylpent-4-en-1-one (4.5b)

General procedure E was followed using 4.4b (108 mg, 0.300 mmol), Pd(OAc)\(_2\) (2.0 mg, 0.090 mmol), \(\tau\)-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). The reaction temperature was raised to 70 °C. Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.5b as a light yellow solid (41.9 mg, 44%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.18 (d, \(J = 8.8\) Hz,
2 H), 8.14 (dd, J = 8.6, 1.4 Hz, 2 H), 7.66 (tt, J = 7.6, 1.5 Hz, 1 H), 7.55–7.49 (m, 4 H), 6.68 (d, J = 16.0 Hz, 1 H), 6.43 (dt, J = 16.0, 7.4 Hz, 1 H), 3.20 (tdd, J = 16.8, 7.4, 1.4 Hz, 2 H). \( ^{13} \text{C} \text{ NMR (CDCl}_3, 125 \text{ MHz}) \delta \) 188.9 (t, J = 31.2 Hz), 147.3, 143.1, 134.8, 134.4, 131.8 (t, J = 3.1 Hz), 130.4 (t, J = 3.1 Hz), 129.0, 127.1, 124.4 (t, J = 5.0 Hz), 124.2, 118.7 (t, J = 253.1 Hz), 37.9 (t, J = 23.8 Hz). \( ^{19} \text{F} \text{ NMR (CDCl}_3, 376 \text{ MHz}) \delta \) –98.4 (t, J = 16.9 Hz, 2 F). IR (film) 3076, 1697, 1597, 1514, 1344, 1202, 1111, 1032, 972, 860, 716, 687, 667 cm\(^{-1}\). HRMS (APCI-hexane/PhMe, \text{m/z}): calcd for C\(_{17}\)H\(_{14}\)F\(_2\)NO\(_3\) [M+H]\(^+\) 318.0942, found 318.0935. mp 81–82 °C.

\[
2,2\text{-difluoro-3-(4-nitrophenyl)-1-phenylpent-4-en-1-one (4.6b)}
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General procedure F was followed using 4.4b (108 mg, 0.300 mmol), Pd(OAc)\(_2\) (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.6b as a yellow solid (74.4 mg, 78%). \( ^{1} \text{H} \text{ NMR (CDCl}_3, 400 \text{ MHz}) \delta \) 8.20 (d, J = 8.8 Hz, 2 H), 8.01 (dd, J = 8.2, 1.4 Hz, 2 H), 7.67–7.63 (m, 1 H), 7.56–7.48 (m, 4 H), 6.18 (ddd, J = 17.0, 10.4, 8.0 Hz, 1 H), 5.39 (d, J = 10.4 Hz, 1 H), 5.26 (d, J = 16.8 Hz, 1 H), 4.50 (td, J = 16.0, 8.0 Hz, 1 H). \( ^{13} \text{C} \text{ NMR (CDCl}_3, 125 \text{ MHz}) \delta \) 188.9 (t, J = 30.0 Hz), 147.7, 143.1, 134.7, 132.4 (t, J = 2.5 Hz), 131.4 (t, J = 4.4 Hz), 130.8, 130.2 (t, J = 3.8 Hz), 129.0, 123.9, 122.0, 118.3 (t, J = 258.1 Hz), 53.5 (t, J = 21.9 Hz). \( ^{19} \text{F} \text{ NMR (CDCl}_3, 376 \text{ MHz}) \delta \) –102.8 (dd, A of ABX, \( J_{AB} = 285.8 \text{ Hz, } J_{ax} = 15.0 \text{ Hz, } 1 \text{ F} \)), –101.7 (dd, B of ABX, \( J_{AB} = 285.8 \text{ Hz, } J_{bx} = 15.0 \text{ Hz, } 1 \text{ F} \)). IR (film) 3084, 1701, 1599, 1524, 1448, 1348, 1176, 1053, 922, 833, 717, 694, 667 cm\(^{-1}\). HRMS (APCI-hexane/PhMe, \text{m/z}): calcd for C\(_{17}\)H\(_{14}\)F\(_2\)NO\(_3\) [M+H]\(^+\) 318.0942, found 318.0927. mp 64–65 °C.
(E)-ethyl 3-(3-hydroxyprop-1-en-1-yl)benzoate (4.4c-1)

Compound 4.4c-1 was prepared according to a previous report. An oven-dried Schlenk tube was charged with Pd(OAc)$_2$ (0.14 g, 0.60 mmol), PPh$_3$ (0.32 g, 1.2 mmol), and AgOAc (2.0 g, 12 mmol). The vessel was evacuated and backfilled with N$_2$(g) three times. Dry DMF (18 mL) was added via a syringe, followed by addition of allyl alcohol (1.6 mL, 24 mmol) at rt. The reaction tube was sealed under N$_2$(g) flow, placed in a pre-heated oil bath at 70 °C, and stirred for 16 h. The tube was removed from the oil bath, and allowed to cool to rt. The reaction mixture was filtered through a pad of celite. The filtrate was added with H$_2$O (15 mL), and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (20% to 40%) for elution to afford the compound 4.4c-1 as a tan oil (0.93 g, 38%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.08 (t, $J = 2.0$ Hz, 1 H), 7.93 (dd, $J = 6.6$, 1.4 Hz, 1 H), 7.57 (dd, $J = 6.8$, 1.6 Hz, 1 H), 7.40 (t, $J = 7.6$ Hz, 1 H), 6.67 (dt, $J = 15.6$, 1.6 Hz, 1 H), 6.46 (dt, $J = 15.6$, 5.4 Hz, 1 H), 4.42–4.36 (m, 4 H), 1.56 (br, 1 H), 1.41 (t, $J = 7.2$ Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 166.7, 137.2, 131.1, 130.9, 130.2, 130.0, 128.9, 128.8, 127.7, 63.7, 61.3, 14.6. IR (film) 3458, 2982, 2868, 1716, 1443, 1367, 1288, 1261, 1198, 1105, 1022, 966, 746, 685 cm$^{-1}$. HRMS (APCI-hexane/PhMe, m/z): calcd for C$_{12}$H$_{15}$O$_3$ [M+H]$^+$ 207.1021, found 207.1020.

(E)-ethyl 3-(3-(2,2-difluoro-3-oxo-3-phenylpropanoyl)oxy)prop-1-en-1-yl)benzoate (4.4c)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^3$ (1.2 g, 4.8 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), 4.4c-1 (0.83 g, 4.0 mmol), Et$_3$N (1.1 mL, 8.0 mmol), DMF
(1.2 mL), and CH₂Cl₂ (24 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 4.4c as a light yellow oil (1.1 g, 71%). ¹H NMR (CDCl₃, 400 MHz) δ 8.10 (dd, J = 8.4, 1.6 Hz, 2 H), 8.03 (t, J = 1.6 Hz, 1 H), 7.97 (dt, J = 7.6, 1.6 Hz, 1 H), 7.69–7.65 (m, 1 H), 7.55–7.50 (m, 3 H), 7.41 (t, J = 7.6 Hz, 1 H), 6.72 (d, J = 16.0 Hz, 1 H), 6.31 (dt, J = 16.0, 6.4 Hz, 1 H), 5.00 (dd, J = 6.4, 1.2 Hz, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 1.42 (t, J = 7.2 Hz, 3 H). ¹³C NMR (CDCl₃, 125 MHz) δ 185.5 (t, J = 27.5 Hz), 166.5, 161.9 (t, J = 30.0 Hz), 136.1, 135.4, 135.2, 131.2, 131.1, 130.2 (t, J = 2.5 Hz), 129.6, 129.2, 128.9, 128.0, 122.2, 110.0 (t, J = 263.8 Hz), 67.8, 61.4, 14.5. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.3 (s, 2 F). IR (film) 2982, 1774, 1718, 1599, 1450, 1306, 1275, 1202, 1159, 1105, 748, 685 cm⁻¹. HRMS (ESI, m/z): calcd for C₂₁H₁₈F₂O₅Na [M+Na]+ 411.1020, found 411.1007.

(⁷)-ethyl 3-(4,4-difluoro-5-oxo-5-phenylpent-1-en-1-yl)benzoate (4.5c)

General procedure E was followed using 4.4c (116 mg, 0.300 mmol), Pd(OAc)₂ (2.0 mg, 0.090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.5c as a colorless oil (86.0 mg, 83%). ¹H NMR (CDCl₃, 400 MHz) δ 8.13 (dt, J = 8.4, 1.2 Hz, 2 H), 8.05 (t, J = 1.8 Hz, 1 H), 7.93 (dt, J = 7.6, 1.6 Hz, 1 H), 7.64 (tt, J = 7.4, 1.6 Hz, 1 H), 7.56–7.49 (m, 3 H), 7.38 (t, J = 8.0 Hz, 1 H), 6.63 (d, J = 16.0 Hz, 1 H), 6.30 (dt, J = 16.0, 7.2 Hz, 1 H), 4.39 (q, J = 7.2 Hz, 2 H), 3.16 (tdd, J = 17.2, 7.2, 1.5 Hz, 2 H), 1.41 (t, J = 7.2 Hz, 3 H). ¹³C NMR (CDCl₃, 125 MHz) δ 189.2 (t, J = 31.2 Hz), 166.6, 137.1, 135.4, 134.6, 132.0 (t, J = 2.5 Hz), 131.0, 130.7, 130.4 (t, J = 3.1 Hz), 128.9, 128.8, 127.6, 120.4 (t, J = 5.6 Hz), 118.8 (t, J = 253.1 Hz), 61.2, 37.9 (t, J = 23.1 Hz), 14.5. ¹⁹F NMR (CDCl₃, 376 MHz) δ –98.8 (t, J = 16.9 Hz, 2 F). IR (film) 2982, 1718, 1599, 1448, 1286, 1200, 1173, 1107, 1024, 968, 752, 716, 687, 667 cm⁻¹. HRMS (ESI, m/z): calcd for C₂₀H₁₈F₂O₃Na [M+Na]+ 367.1122, found 367.1104.
ethyl 3-(4,4-difluoro-5-oxo-5-phenylpent-1-en-3-yl)benzoate (4.6c)

General procedure F was followed using 4.4c (116 mg, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.6c as a colorless oil (86.0 mg, 83%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.03–7.97 (m, 4 H), 7.62 (tt, $J$ = 7.4, 1.2 Hz, 1 H), 7.56 (d, $J$ = 7.6 Hz, 1 H), 7.49–7.45 (m, 2 H), 7.41 (t, $J$ = 7.6 Hz, 1 H), 6.22 (ddd, $J$ = 16.8, 10.4, 8.4 Hz, 1 H), 5.33 (dd, $J$ = 10.4, 1.2 Hz, 1 H), 5.23 (dt, $J$ = 17.2, 1.2 Hz, 1 H), 4.47–4.36 (m, 3 H), 1.40 (t, $J$ = 7.2 Hz, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 189.6 (t, $J$ = 30.0 Hz), 166.4, 135.9, 134.4, 134.2, 132.8 (t, $J$ = 2.5 Hz), 132.2 (dd, $J$ = 5.0, 3.8 Hz), 131.0, 130.1 (t, $J$ = 3.1 Hz), 129.2, 128.9, 128.8, 121.2, 118.6 (t, $J$ = 257.5 Hz), 61.3, 53.8 (t, $J$ = 21.9 Hz), 14.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –103.8 (dd, A of ABX, $J_{AB}$ = 278.2 Hz, $J_{AX}$ = 18.8 Hz, 1 F), –102.3 (dd, B of ABX, $J_{AB}$ = 278.2 Hz, $J_{BX}$ = 11.3 Hz, 1 F). IR (film) 2984, 1718, 1597, 1448, 1367, 1282, 1180, 1107, 1051, 933, 750, 719, 694 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{20}$H$_{18}$F$_2$O$_3$Na [M+Na]$^+$ 367.1122, found 367.1104.

(E)-tert-butyl 4-(3-(3-hydroxyprop-1-en-1-yl)phenyl)piperazine-1-carboxylate (4.4d-1)

An oven-dried Schlenk tube was charged with Pd$_2$dba$_3$ (46 mg, 0.050 mmol), DavePhos (47 mg, 0.12 mmol), and 1-N-Boc-piperazine (1.1 g, 6.0 mmol). The vessel was evacuated and backfilled with N$_2$(g) three times. Dry THF (5.0 mL) was added via a syringe, followed by drop wise addition of LHMDS (1.1 M in THF/ethylbenzene, 0.010 L, 11 mmol). The reaction mixture was stirred at rt for 5 min, and then a solution of (E)-3-(3-bromophenyl)prop-2-en-1-ol (1.1 g, 5.0 mmol) dissolved in dry THF (2.0 mL) was
added. The reaction tube was sealed under N\textsubscript{2}(g) flow, placed in a pre-heated oil bath at 65 °C, and stirred for 7 h. The tube was removed from the oil bath, and allowed to cool to rt. The reaction mixture was diluted with EtOAc (20 mL), and washed with H\textsubscript{2}O (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (10% to 40%) for elution to afford the compound 4.4d-1 as a tan solid (1.0 g, 63%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.24 (t, \(J\) = 8.2 Hz, 1 H), 6.96–6.94 (m, 2 H), 6.85–6.83 (m, 1 H), 6.59 (dt, \(J\) = 16.0, 1.6 Hz, 1 H), 6.36 (dt, \(J\) = 16.0, 5.6 Hz, 1 H), 4.33 (d, \(J\) = 4.8 Hz, 2 H), 3.59 (t, \(J\) = 5.2 Hz, 4 H), 3.15 (t, \(J\) = 5.2 Hz, 4 H), 1.50 (s, 9 H). HRMS (ESI, m/z): calcd for C\textsubscript{18}H\textsubscript{26}N\textsubscript{2}O\textsubscript{3}Na \([M+Na]^{+}\) 341.1841, found 341.1827. Spectroscopic data matched that from the previous report.\textsuperscript{9} (E)-tert-butyl-4-(3-(3-(2,2-difluoro-3-oxo-3-phenylpropanoyl)oxy)prop-1-en-1-yl)phenyl)piperazine-1-carboxylate (4.4d)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate\textsuperscript{3} (1.5 g, 5.8 mmol), oxalyl chloride (0.38 mL, 4.5 mmol), 4.4d-1 (1.4 g, 4.5 mmol), Et\textsubscript{3}N (1.2 mL, 8.9 mmol), DMF (1.2 mL), and CH\textsubscript{2}Cl\textsubscript{2} (45 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound 4.4d as a tan solid (1.5 g, 67%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 8.09 (d, \(J\) = 7.6 Hz, 2 H), 7.69–7.65 (m, 1 H), 7.52 (t, \(J\) = 7.8 Hz, 2 H), 7.24 (t, \(J\) = 8.0 Hz, 1 H), 6.91–6.86 (m, 3 H), 6.65 (d, \(J\) = 16.0 Hz, 1 H), 6.21 (dt, \(J\) = 16.0, 6.8 Hz, 1 H), 4.97 (dd, \(J\) = 6.8, 1.2 Hz, 2 H), 3.59 (t, \(J\) = 5.2 Hz, 4 H), 3.14 (t, \(J\) = 5.2 Hz, 4 H), 1.50 (s, 9 H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) 185.6 (t, \(J\) = 27.5 Hz), 161.9 (t, \(J\) = 30.6 Hz), 154.9, 151.8, 136.8, 135.4, 131.2, 130.2 (t, \(J\) = 2.5 Hz), 129.6, 129.2, 120.9, 119.1, 117.1, 115.2, 110.1 (t, \(J\) = 263.8 Hz), 80.2, 68.2, 49.6, 43.7, 28.6. \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 376 MHz) \(\delta\) −107.3.
(E)-tert-butyl-4-(3-(4,4-difluoro-5-oxo-5-phenylpent-1-en-1-yl)phenyl)piperazine-1-carboxylate

(4.5d)

General procedure E was followed using 4.4d (0.150 g, 0.300 mmol), Pd(OAc)$_2$ (3.4 mg, 0.015 mmol), $t$-BuBrettPhos (14.5 mg, 0.0300 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.5d as a red oil (118 mg, 86%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.13 (dd, $J = 8.4$, 1.6 Hz, 2 H), 7.67–7.63 (m, 1 H), 7.51 (t, $J = 8.0$ Hz, 2 H), 7.22 (t, $J = 8.0$ Hz, 1 H), 6.93–6.91 (m, 2 H), 6.85–6.82 (m, 1 H), 6.56 (d, $J = 15.6$ Hz, 1 H), 6.18 (dt, $J = 15.6$, 7.2 Hz, 1 H), 3.59 (t, $J = 5.2$ Hz, 4 H), 3.18–3.06 (m, 6 H), 1.50 (s, 9 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 189.4 (t, $J = 31.2$ Hz), 154.9, 151.8, 137.8, 136.7, 134.6, 132.2 (t, $J = 2.5$ Hz), 130.4 (t, $J = 3.1$ Hz), 129.6, 128.9, 119.0 (t, $J = 5.6$ Hz), 118.9 (t, $J = 252.5$ Hz), 118.8, 116.5, 114.9, 80.1, 49.7, 43.8, 38.0 (t, $J = 23.8$ Hz), 28.6. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –98.8 (t, $J = 16.9$ Hz, 2 F). IR (film) 2976, 1697, 1597, 1421, 1366, 1242, 1171, 1122, 997, 968, 777, 716, 687 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{27}$H$_{30}$F$_2$N$_2$O$_5$Na [M+Na]$^+$ 523.2020, found 523.1995. mp 81–82 °C.

tert-butyl 4-(3-(4,4-difluoro-5-oxo-5-phenylpent-1-en-3-yl)phenyl)piperazine-1-carboxylate (4.6d)

General procedure F was followed using 4.4d (0.150 g, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.6d as a yellow oil (107 mg, 78%). $^1$H NMR
(CDCl₃, 400 MHz) δ 7.94 (d, J = 8.0 Hz, 2 H), 7.63–7.58 (m, 1 H), 7.45 (t, J = 8.0 Hz, 2 H), 7.23–7.19 (m, 1 H), 6.86–6.81 (m, 3 H), 6.20 (ddd, J = 17.2, 10.4, 8.4 Hz, 1 H), 5.30 (d, J = 10.0 Hz, 1 H), 5.24 (d, J = 17.2 Hz, 1 H), 4.26 (td, J = 16.4, 8.4 Hz, 1 H), 3.56 (t, J = 5.2 Hz, 4 H), 3.08 (t, J = 5.2 Hz, 4 H), 1.49 (s, 9 H). ¹³C NMR (CDCl₃, 125 MHz) δ 190.1 (t, J = 29.4 Hz), 154.9, 151.6, 136.2, 134.2, 133.2, 132.5 (t, J = 4.4 Hz), 130.0 (t, J = 3.1 Hz), 129.6, 128.8, 121.6, 120.7, 118.8 (t, J = 256.9 Hz), 118.2, 116.2, 80.1, 54.5 (t, J = 21.9 Hz), 49.5, 43.6, 28.6. ¹⁹F NMR (CDCl₃, 376 MHz) δ −103.8 (dd, A of ABX, J_{AB} = 270.7 Hz, J_{AX} = 15.0 Hz, 1 F), −102.6 (dd, B of ABX, J_{AB} = 270.7 Hz, J_{BX} = 15.0 Hz, 1 F). IR (film) 2976, 2860, 1697, 1601, 1450, 1421, 1366, 1236, 1171, 1124, 1051, 997, 932, 868, 775, 698 cm⁻¹. HRMS (ESI, m/z): calcd for C₂₆H₃₀F₂N₂O₃Na [M+Na]⁺ 479.2122, found 479.2130.

(‡E)-methyl 3-(p-tolyl)acrylate (4.4e-2)

General procedure B was followed using 4-methylcinnamic acid (1.95 g, 12.0 mmol), thionyl chloride (1.7 mL, 24 mmol), and MeOH (25 mL). Workup afforded the title compound 4.4e-2 as a colorless solid (1.99 g, 94%). ¹H NMR (CDCl₃, 400 MHz) δ 7.68 (d, J = 16.0 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 6.41 (d, J = 16.0 Hz, 1 H), 3.81 (s, 3 H), 2.38 (s, 3 H). Spectroscopic data of ¹H NMR matched that from the previous report.¹¹

(‡E)-3-(p-tolyl)prop-2-en-1-ol (4.4e-1)

General procedure C was followed using 4.4e-2 (1.41 g, 8.00 mmol), DIBAL (1.0 M in hexane, 0.020 L, 0.020 mmol), and CH₂Cl₂ (0.020 L). Workup afforded the title compound 4.4e-1 as a colorless solid (1.15 g, 97%). ¹H NMR (CDCl₃, 400 MHz) δ 7.30 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 6.60 (dt, J =
16.0, 1.4 Hz, 1 H), 6.33 (dt, \( J = 16.0, 5.8 \) Hz, 1 H), 4.32 (td, \( J = 5.8, 1.4 \) Hz, 2 H), 2.36 (s, 3 H), 1.59 (t, \( J = 5.8 \) Hz, 1 H). Spectroscopic data of \(^1\)H NMR matched that from the previous report.\(^{12}\)

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\begin{align*}
& \text{(E)-3-(p-tolyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4e)} \\
& \text{General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate}^3 (1.4 \text{ g}, 5.4 \text{ mmol}, \text{oxalyl chloride (0.38 mL, 4.5 mmol), } \text{4.4e-1 (0.67 g, 4.5 mmol), Et}_3\text{N (1.2 mL, 9.0 mmol), DMF (1.2 mL), and CH}_2\text{Cl}_2 (25 mL). Workup and chromatographic purification (2\% to 5\% EtOAc in hexanes) afforded the title compound 4.4e as a colorless oil (1.1 g, 74\%). \(^1\)H NMR (CDCl}_3, 400 MHz) \( \delta \) 8.09 (dd, \( J = 8.8, 1.2 \) Hz, 2 H), 7.69–7.64 (m, 1 H), 7.54–7.49 (m, 2 H), 7.26 (d, \( J = 8.8 \) Hz, 2 H), 7.14 (d, \( J = 8.4 \) Hz, 2 H), 6.66 (d, \( J = 16.0 \) Hz, 1 H), 6.18 (dt, \( J = 15.6, 6.8 \) Hz, 1 H), 4.96 (dd, \( J = 6.4, 1.2 \) Hz, 2 H), 2.36 (s, 3 H). \\
& \text{\(^{13}\)C NMR (CDCl}_3, 125 MHz) \( \delta \) 185.6 (t, \( J = 27.5 \) Hz), 161.9 (t, \( J = 30.6 \) Hz), 138.7, 136.6, 135.3, 133.0, 131.2 (t, \( J = 1.9 \) Hz), 130.2 (t, \( J = 2.5 \) Hz), 129.5, 129.2, 126.9, 119.8, 110.0 (t, \( J = 263.1 \) Hz), 68.4, 21.5. \\
& \text{\(^{19}\)F NMR (CDCl}_3, 376 MHz) \( \delta \) –107.4 (s, 2 F). IR (film) 3028, 2921, 1774, 1713, 1699, 1599, 1514, 1450, 1310, 1159, 1124, 1101, 970, 922, 795, 712, 685 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{19}\)H\(_{16}\)F\(_2\)O\(_3\)Na\(^{[M+Na]^+}\) 353.0965, found 353.0962.} \\
& \text{\begin{figure}} \\
& \text{\begin{center}} \\
& \text{\end{center}} \\
\end{align*}
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\begin{align*}
& \text{(E)-2,2-difluoro-1-phenyl-5-(p-tolyl)pent-4-en-1-one (4.5e)} \\
& \text{General procedure E was followed using 4.4e (99.1 mg, 0.300 mmol), Pd(OAc)}_2 (2.0 \text{ mg}, 0.090 \text{ mmol), } \text{t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0\% to 5\% EtOAc in hexanes) afforded the title compound 4.5e as an off-white solid (75.0 \text{ mg, 87\%}). \(^1\)H NMR (CDCl}_3, 400 MHz) \( \delta \) 8.14 (dt, \( J = 8.4, 1.2 \) Hz, 2 H), 7.65 (tt, \( J = 7.4, 1.5 \) Hz, 1 H),}
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7.54–7.50 (m, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 6.57 (d, J = 16.0 Hz, 1 H), 6.17 (dt, J = 16.0, 7.4 Hz, 1 H), 3.14 (tdd, J = 17.0, 7.4, 1.5 Hz, 2 H), 2.36 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 189.4 (t, J = 31.2 Hz), 137.8, 136.3, 134.5, 134.1, 130.4 (t, J = 3.1 Hz), 129.4, 128.9, 126.5, 118.9 (t, J = 252.5 Hz), 117.8 (t, J = 5.0 Hz), 38.1 (t, J = 23.8 Hz), 21.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –99.0 (t, J = 18.8 Hz, 2 F). IR (film) 3038, 2922, 1703, 1599, 1514, 1448, 1273, 1173, 1120, 968, 804, 716, 687, 667 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{18}$H$_{17}$F$_2$O [M+H]$^+$ 287.1247, found 287.1243. m.p. 50–52 °C.

2,2-difluoro-1-phenyl-3-(p-tolyl)pent-4-en-1-one (4.6e)

General procedure F was followed using 4.4e (99.1 mg, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.6e as a light yellow oil (77.0 mg, 90%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.97 (dt, J = 7.6, 1.2 Hz, 2 H), 7.61 (tt, J = 7.4, 1.4 Hz, 1 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.22 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 6.22 (ddd, J = 17.2, 10.4, 8.4 Hz, 1 H), 5.30 (dd, J = 10.4, 1.2 Hz, 1 H), 5.22 (dt, J = 17.2, 1.2 Hz, 1 H), 4.29 (td, J = 16.6, 8.4 Hz, 1 H), 2.33 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 190.1 (t, J = 29.4 Hz), 137.8, 134.2, 133.1, 132.8 (t, J = 3.8 Hz), 132.2 (t, J = 2.5 Hz), 130.1 (t, J = 3.8 Hz), 129.6, 129.5, 128.8, 120.5, 118.8 (t, J = 256.9 Hz), 53.8 (t, J = 21.2 Hz), 21.3. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –103.6 (dd, A of ABX, $J_{AB}$ = 274.5 Hz, $J_{AX}$ = 16.9 Hz, 1 F), –103.2 (dd, B of ABX, $J_{AB}$ = 274.5 Hz, $J_{BX}$ = 15.0 Hz, 1 F). IR (film) 3026, 2922, 1705, 1597, 1516, 1448, 1267, 1174, 1049, 924, 795, 714, 688, 667 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{18}$H$_{16}$F$_2$ONa [M+Na]$^+$ 309.1067, found 309.1064.

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(E)-methyl 3-(benzo[d][1,3]dioxol-5-yl)acrylate (4.4f-2)

General procedure B was followed using 3,4-(methylenedioxy)cinnamic acid (2.00 g, 10.4 mmol), thionyl chloride (1.5 mL, 21 mmol), and MeOH (15 mL). Workup afforded the title compound 4.4f-2 as a colorless solid (2.05 g, 96%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.61 (d, $J = 16.0$ Hz, 1 H), 7.04 (d, $J = 1.6$ Hz, 1 H), 7.01 (dd, $J = 8.0, 1.6$ Hz, 1 H), 6.82 (d, $J = 8.0$ Hz, 1 H), 6.28 (d, $J = 16.0$ Hz, 1 H), 6.02 (s, 2 H), 3.80 (s, 3 H). 1H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.61 (d, $J = 16.0$ Hz, 1 H), 7.04 (d, $J = 1.6$ Hz, 1 H), 7.01 (dd, $J = 8.0, 1.6$ Hz, 1 H), 6.82 (d, $J = 8.0$ Hz, 1 H), 6.28 (d, $J = 16.0$ Hz, 1 H), 6.02 (s, 2 H), 3.80 (s, 3 H). HRMS (ESI, m/z): calcd for C$_{11}$H$_{10}$O$_4$Na [M+Na]$^+$ 229.0477, found 229.0494. Spectroscopic data matched that from the previous report.$^{13}$

(E)-3-(benzo[d][1,3]dioxol-5-yl)prop-2-en-1-ol (4.4f-1)

General procedure C was followed using 4.4f-2 (1.50 g, 7.30 mmol), DIBAL (1.0 M in hexane, 15 mL, 15 mmol), and CH$_2$Cl$_2$ (15 mL). Workup afforded the title compound 4.4f-1 as a colorless solid (1.27 g, 98%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 6.94 (d, $J = 1.6$ Hz, 1 H), 6.83 (dd, $J = 8.0, 1.6$ Hz, 1 H), 6.77 (d, $J = 7.6$ Hz, 1 H), 6.53 (dt, $J = 16.0, 1.6$ Hz, 1 H), 6.21 (dt, $J = 16.0, 6.0$ Hz, 1 H), 5.97 (s, 2 H), 4.30 (d, $J = 6.0$ Hz, 2 H), 1.45 (br, 1 H). HRMS (ESI, m/z): calcd for C$_{10}$H$_{11}$O$_3$ [M+H]$^+$ 179.0708, found 179.0716. Spectroscopic data matched that from the previous report.$^{13}$

(E)-3-(benzo[d][1,3]dioxol-5-yl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4f)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^3$ (1.6 g, 6.0 mmol), oxalyl chloride (0.42 mL, 5.0 mmol), 4.4f-1 (0.89 g, 5.0 mmol), Et$_3$N (1.4 mL, 0.010 mol), DMF (1.2 mL), and CH$_2$Cl$_2$ (25 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound 4.4f as a colorless oil (1.3 g, 72%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$
8.08 (d, J = 8.0 Hz, 2 H), 7.67 (t, J = 7.4 Hz, 1 H), 7.52 (t, J = 7.6 Hz, 2 H), 6.89 (d, J = 1.6 Hz, 1 H), 6.82–6.75 (m, 2 H), 6.60 (d, J = 16.0 Hz, 1 H), 6.05 (dt, J = 16.0, 6.8 Hz, 1 H), 5.98 (s, 2 H), 4.94 (d, J = 6.8 Hz, 2 H). 13C NMR (CDCl3, 125 MHz) δ 185.5 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 148.3, 148.2, 136.4, 135.3, 131.2, 130.2, 130.1 (t, J = 2.5 Hz), 129.2, 122.1, 118.9, 110.0 (t, J = 263.8 Hz), 108.5, 106.1, 101.4, 68.3. 19F NMR (CDCl3, 376 MHz) δ –107.4 (s, 2 F). IR (film) 2895, 1774, 1711, 1699, 1504, 1491, 1448, 1308, 1252, 1159, 1040, 922, 712, 685 cm⁻¹. HRMS (ESI, m/z): calcd for C19H15F2O5 [M+H]⁺ 361.0888, found 361.0897.

**(E)-5-(benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-1-phenylpent-4-en-1-one (4.5f)**

General procedure E was followed using 4.4f (108 mg, 0.300 mmol), Pd(OAc)₂ (2.0 mg, 0.090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.5f as an off-white solid (66.0 mg, 70%). 1H NMR (CDCl3, 400 MHz) δ 8.12 (dt, J = 8.0, 1.2 Hz, 2 H), 7.67–7.62 (m, 1 H), 7.51 (t, J = 8.0 Hz, 2 H), 6.92 (d, J = 1.6 Hz, 1 H), 6.81–6.74 (m, 2 H), 6.49 (d, J = 16.0 Hz, 1 H), 6.03 (dt, J = 16.0, 7.2 Hz, 1 H), 5.95 (s, 2 H), 3.10 (tdd, J = 17.2, 7.2, 1.2 Hz, 2 H). 13C NMR (CDCl3, 125 MHz) δ 189.4 (t, J = 30.6 Hz), 148.2, 147.5, 135.9, 134.5, 132.2 (t, J = 1.9 Hz), 131.4, 130.4 (t, J = 3.1 Hz), 128.9, 121.3, 118.9 (t, J = 252.5 Hz), 117.1 (t, J = 5.0 Hz), 108.4, 105.9, 101.3, 38.0 (t, J = 23.1 Hz). 19F NMR (CDCl3, 376 MHz) δ –99.0 (t, J = 16.9 Hz, 2 F). IR (film) 3072, 2899, 1701, 1597, 1504, 1491, 1448, 1252, 1173, 1040, 966, 933, 804, 714, 687, 669 cm⁻¹. HRMS (ESI, m/z): calcd for C18H14F2O3Na [M+Na]⁺ 339.0809, found 339.0800. mp 77–78 °C.
3-(benzo[\(d\)][1,3]dioxol-5-yl)-2,2-difluoro-1-phenylpent-4-en-1-one (4.6f)

General procedure F was followed using 4.4f (108.1 mg, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.6f as a colorless oil (77.6 mg, 82%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.97 (dt, $J = 8.4$, 1.2 Hz, 2 H), 7.62 (tt, $J = 7.6$, 1.4 Hz, 1 H), 7.47 (t, $J = 8.0$ Hz, 2 H), 6.84 (s, 1 H), 6.74 (s, 2 H), 6.16 (ddd, $J = 16.8$, 10.4, 8.2 Hz, 1 H), 5.95 (s, 2 H), 5.30 (d, $J = 10.0$ Hz, 1 H), 5.22 (dt, $J = 16.8$, 1.2 Hz, 1 H), 4.24 (td, $J = 16.2$, 8.2 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 190.0 (t, $J = 29.4$ Hz), 148.0, 147.4, 134.3, 133.1, 132.6 (t, $J = 3.8$ Hz), 130.1 (t, $J = 3.1$ Hz), 128.8, 123.4, 120.6, 118.7 (t, $J = 257.5$ Hz), 110.0, 108.5, 101.3, 53.7 (t, $J = 21.9$ Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ −104.1 (dd, A of ABX, $J_{AB} = 274.5$ Hz, $J_{AX} = 15.0$ Hz, 1 F), −103.0 (dd, B of ABX, $J_{AB} = 274.5$ Hz, $J_{BX} = 15.0$ Hz, 1 F). IR (film) 3076, 2893, 1705, 1597, 1504, 1489, 1446, 1250, 1182, 1040, 932, 800, 719, 688, 669 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{14}$F$_2$O$_3$Na $[M+Na]^+$ 339.0809, found 339.0824.

(E)-methyl 3-(4-methoxyphenyl)acrylate (4.4g-2)

General procedure B was followed using 4-methoxycinnamic acid (5.0 g, 28 mmol), thionyl chloride (4.1 mL, 56 mmol), and MeOH (45 mL). Workup afforded the title compound 4.4g-2 as a colorless solid (5.3 g, 98%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.66 (d, $J = 16.0$ Hz, 1 H), 7.49 (d, $J = 8.8$ Hz, 2 H), 6.91 (d, $J = 8.4$ Hz, 2 H), 6.32 (d, $J = 16.0$ Hz, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H). Spectroscopic data of $^1$H NMR matched that from the previous report.$^{11}$

(E)-3-(4-methoxyphenyl)prop-2-en-1-ol (4.4g-1)

(E)-3-(4-methoxyphenyl)prop-2-en-1-ol (4.4g-1)
General procedure C was followed using 4.4g-2 (2.20 g, 11.4 mmol), DIBAL (1.0 M in hexane, 28.6 mL, 28.6 mmol), and CH₂Cl₂ (30.0 mL). Workup afforded the title compound 4.4g-1 as a colorless solid (1.84 g, 98%). ¹H NMR (CDCl₃, 400 MHz) δ 7.34 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.57 (dt, J = 16.0, 1.6 Hz, 1 H), 6.25 (dt, J = 16.0, 6.0 Hz, 1 H), 4.31 (d, J = 5.6 Hz, 2 H), 3.82 (s, 3 H), 1.42 (br, 1 H). HRMS (ESI, m/z): calcd for C₁₀H₁₃O₂ [M+H]+ 165.0916, found 165.0911. Spectroscopic data matched that from the previous report.¹⁴

(E)-3-(4-methoxyphenyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4g)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate³ (1.6 g, 6.0 mmol), oxalyl chloride (0.42 mL, 5.0 mmol), 4.4g-1 (0.82 g, 5.0 mmol), Et₃N (1.4 mL, 0.010 mol), DMF (1.2 mL), and CH₂Cl₂ (25 mL). Workup and chromatographic purification (10% to 20% EtOAc in hexanes) afforded the title compound 4.4g as a colorless solid (0.94 g, 54%). ¹H NMR (CDCl₃, 400 MHz) δ 8.08 (dt, J = 7.6, 1.2 Hz, 2 H), 7.66 (tt, J = 7.6, 1.4 Hz, 1 H), 7.51 (t, J = 7.8 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 6.64 (d, J = 16.0 Hz, 1 H), 6.09 (dt, J = 16.0, 6.8 Hz, 1 H), 4.95 (dd, J = 6.8, 1.2 Hz, 2 H), 3.82 (s, 3 H). ¹³C NMR (CDCl₃, 125 MHz) δ 185.6 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 160.1, 136.4, 135.3, 131.2 (t, J = 1.2 Hz), 130.2 (t, J = 2.5 Hz), 129.2, 128.5, 128.3, 118.5, 114.2, 110.0 (t, J = 263.8 Hz), 68.6, 55.5. ¹⁹F NMR (CDCl₃, 376 MHz) δ −107.4 (s, 2 F). IR (film) 2959, 2837, 1774, 1711, 1701, 1606, 1512, 1450, 1306, 1252, 1159, 922, 845, 711, 685 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₉H₁₆F₂O₄Na [M+Na]+ 369.0914, found 369.0898. mp 36–38 °C.

(E)-2,2-difluoro-5-(4-methoxyphenyl)-1-phenylpent-4-en-1-one (4.5g)
General procedure E was followed using 4.4g (104 mg, 0.300 mmol), Pd(OAc)$_2$ (2.0 mg, 0.090 mmol), t-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.5g as an off-white solid (52.0 mg, 57%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.13 (dt, $J = 8.4$, 1.2 Hz, 2 H), 7.66–7.62 (m, 1 H), 7.51 (t, $J = 8.0$ Hz, 2 H), 7.31 (d, $J = 8.8$ Hz, 2 H), 6.86 (d, $J = 8.4$ Hz, 2 H), 6.53 (d, $J = 16.0$ Hz, 1 H), 6.06 (dt, $J = 16.0$, 7.2 Hz, 1 H), 3.12 (tdd, $J = 17.2$, 7.2, 1.4 Hz, 2 H), 3.81 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 189.5 (t, $J = 30.6$ Hz), 159.5, 135.8, 134.5, 132.2 (t, $J = 2.5$ Hz), 130.4 (t, $J = 3.1$ Hz), 129.7, 128.9, 127.8, 118.9 (t, $J = 252.5$ Hz), 116.6 (t, $J = 5.0$ Hz), 114.1, 55.5, 38.1 (t, $J = 23.1$ Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –99.0 (t, $J = 16.9$ Hz, 2 F). IR (film) 2959, 1701, 1606, 1512, 1448, 1250, 1174, 1036, 968, 837, 806, 714, 687, 667 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{16}$F$_2$O$_2$Na [M+Na]$^+$ 325.1016, found 325.1005. mp 55–57 °C.

2,2-difluoro-3-(4-methoxyphenyl)-1-phenylpent-4-en-1-one (4.6g)

General procedure F was followed using 4.4g (104 mg, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.6g as a colorless oil (65.1 mg, 72%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.95 (dd, $J = 8.4$, 1.6 Hz, 2 H), 7.61 (tt, $J = 7.4$, 1.2 Hz, 1 H), 7.46 (t, $J = 8.0$ Hz, 2 H), 7.23 (d, $J = 8.4$ Hz, 2 H), 6.85 (d, $J = 8.8$ Hz, 2 H), 6.20 (ddd, $J = 17.2$, 10.2, 8.0 Hz, 1 H), 5.30 (d, $J = 10.4$ Hz, 1 H), 5.20 (dd, $J = 17.2$, 1.6 Hz, 1 H), 4.27 (td, $J = 16.4$, 8.0 Hz, 1 H), 3.79 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 190.2 (t, $J = 30.0$ Hz), 159.4, 134.2, 133.1, 132.8 (t, $J = 4.4$ Hz), 130.9, 130.1 (t, $J = 3.8$ Hz), 128.8, 127.2, 120.4, 118.8 (t, $J = 256.9$ Hz), 114.2, 55.4, 53.4 (t, $J = 21.9$ Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –104.1 (dd, A of ABX, $J_{AB} = 274.5$ Hz, $J_{AX} = 16.0$ Hz, 1 F), –103.0 (dd, B of ABX, $J_{AB} =$
274.5 Hz, $J_{XX} = 16.0$ Hz, 1 F). IR (film) 2957, 1703, 1612, 1599, 1514, 1448, 1252, 1180, 1036, 922, 804, 714, 688, 667 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{16}$F$_2$O$_2$Na $[M+Na]^+$ 325.1016, found 325.1001.

(E)-2-methyl-3-phenylallyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.4h)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^3$ (1.2 g, 4.8 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), trans-2-methyl-3-phenyl-2-propen-1-ol (0.59 g, 4.0 mmol), Et$_3$N (1.1 mL, 8.0 mmol), DMF (1.2 mL), and CH$_2$Cl$_2$ (24 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.4h as a colorless oil (0.94 g, 71%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.10 (d, $J = 8.4$ Hz, 2 H), 7.70–7.66 (m, 1 H), 7.53 (t, $J = 8.0$ Hz, 2 H), 7.35 (t, $J = 7.6$ Hz, 2 H), 7.28–7.23 (m, 3 H), 6.56 (s, 1 H), 4.89 (s, 2 H), 1.83 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.6 (t, $J = 26.9$ Hz), 161.9 (t, $J = 30.6$ Hz), 136.6, 135.4, 131.2 (t, $J = 1.9$ Hz), 131.0, 130.6, 130.2 (t, $J = 2.5$ Hz), 129.2, 129.1, 128.4, 127.3, 110.0 (t, $J = 263.1$ Hz), 73.4, 15.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ -107.3 (s, 2 F). IR (film) 3062, 2949, 1776, 1713, 1699, 1599, 1450, 1306, 1157, 1101, 922, 746, 698, 687 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{19}$H$_{16}$F$_2$O$_3$Na $[M+Na]^+$ 353.0965, found 353.0952.

(E)-2,2-difluoro-4-methyl-1,5-diphenylpent-4-en-1-one (4.5h)

General procedure E was followed using 4.4h (99.1 mg, 0.300 mmol), Pd(OAc)$_2$ (3.4 mg, 0.015 mmol), $t$-BuBrettPhos (15 mg, 0.030 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.5h as a colorless oil (67 mg, 78%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.14 (d, $J = 7.6$ Hz, 2 H), 7.66 (tt, $J = 7.6$, 1.5 Hz, 1 H), 7.52 (t, $J$ = 7.6 Hz, 2 H), 7.35 (t, $J = 7.6$ Hz, 2 H), 7.28–7.23 (m, 3 H), 6.56 (s, 1 H), 4.89 (s, 2 H), 1.83 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.6 (t, $J = 26.9$ Hz), 161.9 (t, $J = 30.6$ Hz), 136.6, 135.4, 131.2 (t, $J = 1.9$ Hz), 131.0, 130.6, 130.2 (t, $J = 2.5$ Hz), 129.2, 129.1, 128.4, 127.3, 110.0 (t, $J = 263.1$ Hz), 73.4, 15.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ -107.3 (s, 2 F). IR (film) 3062, 2949, 1776, 1713, 1699, 1599, 1450, 1306, 1157, 1101, 922, 746, 698, 687 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{19}$H$_{16}$F$_2$O$_3$Na $[M+Na]^+$ 353.0965, found 353.0952.
7.6 Hz, 2 H), 7.37–7.33 (m, 2 H), 7.26–7.22 (m, 3 H), 6.41 (s, 1 H), 3.10 (t, \( J = 17.8 \) Hz, 2 H), 2.01 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 189.9 (t, \( J = 30.0 \) Hz), 137.5, 154.1, 152.5 (t, \( J = 1.9 \) Hz), 132.3, 130.3 (t, \( J = 3.1 \) Hz), 129.2 (t, \( J = 3.1 \) Hz), 129.1, 128.9, 128.3, 126.8, 119.4 (t, \( J = 253.1 \) Hz), 44.8 (t, \( J = 22.5 \) Hz), 13.4. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –98.3 (t, \( J = 18.8 \) Hz, 2 F). IR (film) 3059, 2922, 1703, 1599, 1448, 1277, 1176, 1113, 1061, 1028, 918, 744, 716, 698, 687 cm\(^{-1}\). HRMS (ESI, \( m/\z \)): calcd for C\(_{18}\)H\(_{16}\)F\(_2\)ONa \([M+Na]^+\) 309.1067, found 309.1059.

![Image](image_url)

2,2-difluoro-4-methyl-1,3-diphenylpent-4-en-1-one (4.6h)

General procedure F was followed using 4.4h (99.1 mg, 0.300 mmol), Pd(OAc)\(_2\) (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.6h as a colorless oil (71 mg, 83%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 8.00 (d, \( J = 7.6 \) Hz, 2 H), 7.62 (t, \( J = 7.4 \) Hz, 1 H), 7.48 (t, \( J = 7.6 \) Hz, 2 H), 7.41–7.32 (m, 5 H), 5.08 (s, 1 H), 5.05 (s, 1 H), 4.31 (dd, \( J = 21.6, 14.4 \) Hz, 1 H), 1.74 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 190.3 (t, \( J = 30.0 \) Hz), 140.9 (d, \( J = 5.0 \) Hz), 134.5 (d, \( J = 2.5 \) Hz), 134.1, 133.2, 130.2, 130.0 (t, \( J = 3.1 \) Hz), 128.8, 128.6, 128.0, 119.1 (dd, \( J = 260.0, 253.8 \) Hz), 115.5 (d, \( J = 3.8 \) Hz), 55.7 (t, \( J = 20.6 \) Hz), 23.4. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –104.2 (dd, A of AMX, \( J_{AM} = 282.0 \) Hz, \( J_{AX} = 22.6 \) Hz, 1 F), –97.1 (dd, M of AMX, \( J_{AM} = 282.0 \) Hz, \( J_{MX} = 13.2 \) Hz, 1 F). IR (film) 3063, 2974, 1701, 1597, 1493, 1450, 1282, 1184, 1120, 1051, 922, 741, 717, 698, 665, 604 cm\(^{-1}\). HRMS (ESI, \( m/\z \)): calcd for C\(_{18}\)H\(_{16}\)F\(_2\)ONa \([M+Na]^+\) 309.1067, found 309.1069.

**Experimental Procedures and Characterization of Compounds in Scheme 4.12**
cinnamyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (4.7a)

General procedure D was followed using potassium 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate\(^3\) (1.5 g, 5.6 mmol), oxaly chloride (0.52 mL, 6.2 mmol), cinnamyl alcohol (1.1 g, 8.4 mmol), Et\(_3\)N (0.93 mL, 6.7 mmol), DMF (1.0 mL), and CH\(_2\)Cl\(_2\) (0.020 L). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound 4.7a as a colorless oil (1.6 g, 83%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.08 (d, \(J = 8.8\) Hz, 2 H), 7.37–7.28 (m, 5 H), 6.96 (d, \(J = 8.8\) Hz, 2 H), 6.68 (dt, \(J = 16.0,\) 1.2 Hz, 1 H), 6.23 (dt, \(J = 16.0,\) 6.4 Hz, 1 H), 4.97 (dd, \(J = 6.4,\) 1.2 Hz, 2 H), 3.87 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 183.8 (t, \(J = 26.9\) Hz), 165.3, 162.1 (t, \(J = 30.0\) Hz), 136.3, 135.8, 132.8 (t, \(J = 2.5\) Hz), 128.8, 128.6, 127.0, 124.0 (t, \(J = 1.9\) Hz), 121.0, 114.5, 110.3 (t, \(J = 263.1\) Hz), 68.0, 55.8. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –107.1 (s, 2 F). IR (film) 3028, 2960, 1774, 1701, 1690, 1601, 1574, 1512, 1427, 1312, 1269, 1157, 1099, 1026, 968, 924, 845, 746, 692, 579 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{19}\)H\(_{16}\)F\(_2\)O\(_4\)Na [M+Na]\(^+\) 369.0914, found 369.0896.

\[(E)-2,2\text{-difluoro-1-}(4\text{-methoxyphenyl})\text{-}5\text{-phenylpent-4-en-1-one (4.8a)}\]

General procedure E was followed using 4.7a (104 mg, 0.300 mmol), Pd(OAc)_2 (3.4 mg, 0.015 mmol), \(\tau\)-BuBrettPhos (14.5 mg, 0.0300 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.8a as an off-white solid (72.0 mg, 79%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.13 (dt, \(J = 8.8,\) 1.2 Hz, 2 H), 7.39–7.37 (m, 2 H), 7.32 (t, \(J = 7.4\) Hz, 2 H), 7.27–7.23 (m, 1 H), 6.98 (d, \(J = 9.2,\) 2 H), 6.59 (d, \(J = 16.0\) Hz, 1 H), 6.22 (dt, \(J = 16.0,\) 7.2 Hz, 1 H), 3.90 (s, 3 H), 3.12 (tdd, \(J = 17.2,\) 7.2, 1.6 Hz, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 187.8 (t,
$J = 30.6 \text{ Hz}$, $164.7, 136.9, 136.2, 133.0 (t, J = 3.1 \text{ Hz})$, $128.8, 127.9, 126.6, 125.0 (t, J = 2.5 \text{ Hz})$, $119.3 (t, J = 5.0 \text{ Hz})$, $119.1 (t, J = 252.5 \text{ Hz})$, $114.2, 55.8, 38.2 (t, J = 23.8 \text{ Hz})$. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ – 98.5 (t, $J = 16.9 \text{ Hz}$, 2 F). IR (film) 3026, 2935, 1690, 1601, 1574, 1512, 1425, 1265, 1167, 1119, 1028, 968, 845, 770, 746, 692, 619 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{16}$F$_2$O$_2$Na $[\text{M+Na}]^+$ 325.1016, found 325.0989. mp 41–42 °C.

2,2-difluoro-1-(4-methoxyphenyl)-3-phenylpent-4-en-1-one (4.9a)

General procedure F was followed using 4.7a (104 mg, 0.300 mmol), Pd(OAc)$_2$ (2.4 mg, 0.011 mmol), PhXPhos (9.8 mg, 0.021 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.9a as a light yellow oil (76.0 mg, 84%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.99 (dt, $J = 8.8, 1.0 \text{ Hz}$, 2 H), 7.33–7.28 (m, 5 H), 6.93 (d, $J = 8.8 \text{ Hz}$, 2 H), 6.23 (ddd, $J = 17.2, 10.4, 8.0 \text{ Hz}$, 1 H), 5.30 (d, $J = 10.4 \text{ Hz}$, 1 H), 5.22 (dt, $J = 17.2, 1.2 \text{ Hz}$, 1 H), 4.31 (td, $J = 16.4, 8.0 \text{ Hz}$, 1 H), 3.89 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 188.2 (t, $J = 29.4 \text{ Hz}$), 164.4, 135.6 (t, $J = 2.5 \text{ Hz}$), 132.8 (t, $J = 4.4 \text{ Hz}$), 132.7 (t, $J = 3.8 \text{ Hz}$), 129.8, 128.8, 128.0, 125.8 (t, $J = 1.9 \text{ Hz}$), 120.6, 119.0 (t, $J = 257.5 \text{ Hz}$), 114.1, 55.7, 54.3 (t, $J = 21.9 \text{ Hz}$). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –102.9 (d, A$_2$, $J = 15.0 \text{ Hz}$, 2 F). IR (film) 3030, 2935, 1691, 1601, 1574, 1510, 1456, 1423, 1315, 1265, 1178, 1117, 1028, 924, 845, 744, 700, 619 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{16}$F$_2$O$_2$Na $[\text{M+Na}]^+$ 325.1016, found 325.1004.

cinnamyl 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate (4.7b)
General procedure D was followed using potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate\(^3\) (1.20 g, 4.68 mmol), oxalyl chloride (0.40 mL, 4.7 mmol), cinnamyl alcohol (0.820 g, 6.08 mmol), Et\(_3\)N (0.98 mL, 7.0 mmol), DMF (0.75 mL), and CH\(_2\)Cl\(_2\) (16 mL). Workup and chromatographic purification (2\% to 5\% EtOAc in hexanes) afforded the title compound 4.7b as a colorless oil (1.14 g, 73\%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.14 (dd, \(J = 8.8, 5.2\) Hz, 2 H), 7.39–7.28 (m, 5 H), 7.22–7.16 (m, 2 H), 6.70 (dt, \(J = 16.0, 1.2\) Hz, 1 H), 6.24 (dt, \(J = 16.0, 6.8\) Hz, 1 H), 4.98 (dd, \(J = 6.8, 1.2\) Hz, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 184.1 (t, \(J = 27.5\) Hz), 167.1 (d, \(J = 257.5\) Hz), 161.8 (t, \(J = 30.6\) Hz), 136.7, 135.8, 133.2 (dt, \(J = 10.0, 3.8\) Hz), 128.9, 128.8, 127.6, 127.0, 120.8, 116.6 (d, \(J = 22.5\) Hz), 110.0 (t, \(J = 263.8\) Hz), 68.3. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –107.2 (s, 2 F), –100.3 (m, 1 F). IR (film) 3082, 3028, 1774, 1701, 1599, 1508, 1308, 1244, 1161, 1124, 1101, 968, 924, 852, 746, 692 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{18}\)H\(_{13}\)F\(_{3}\)O\(_3\)Na \([M+Na]^+\) 357.0714, found 357.0701.

\(\text{(E)-2,2-difluoro-1-(4-fluorophenyl)-5-phenylpent-4-en-1-one (4.8b)}\)

General procedure E was followed using 4.7b (0.100 g, 0.300 mmol), Pd(OAc)\(_2\) (2.0 mg, 0.090 mmol), \(t\)-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0\% to 5\% EtOAc in hexanes) afforded the title compound 4.8b as a light yellow oil (75.0 mg, 86\%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.18 (dd, \(J = 8.6, 5.4\) Hz, 2 H), 7.39–7.37 (m, 2 H), 7.34–7.30 (m, 2 H), 7.28–7.24 (m, 1 H), 7.18 (t, \(J = 8.6\) Hz, 2 H), 6.60 (d, \(J = 16.0\) Hz, 1 H), 6.21 (dt, \(J = 16.0, 7.4\) Hz, 1 H), 3.13 (tdd, \(J = 17.2, 7.4, 1.4\) Hz, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 187.8 (t, \(J = 31.2\) Hz), 166.6 (d, \(J = 256.2\) Hz), 136.8, 136.5, 133.3 (dt, \(J = 10.0, 3.8\) Hz), 129.8, 128.8, 128.5, 128.0, 126.6, 118.9 (t, \(J = 5.0\) Hz), 118.9 (t, \(J = 252.5\) Hz), 37.9 (t, \(J = 23.1\) Hz). \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –102.2 (s, 2 F), –98.6 (t, \(J = 16.9\) Hz, 2 F). IR (film) 3082, 1701, 1599, 1508, 1414, 1242, 1161, 966, 850, 766, 692 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{17}\)H\(_{13}\)F\(_{3}\)ONa \([M+Na]^+\) 313.0816, found 313.0830.
2,2-difluoro-1-(4-fluorophenyl)-3-phenylpent-4-en-1-one (4.9b)

General procedure F was followed using 4.7b (0.100 g, 0.300 mmol), Pd(OAc)\(_2\) (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.9b as an off-white solid (74.8 mg, 86%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.00 (dd, \(J = 8.6, 5.4\) Hz, 2 H), 7.33–7.28 (m, 5 H), 7.12 (t, \(J = 8.6\) Hz, 2 H), 6.22 (ddd, \(J = 16.8, 10.4, 8.4\) Hz, 1 H), 5.32 (d, \(J = 10.0\) Hz, 1 H), 5.24 (d, \(J = 16.8\) Hz, 1 H), 4.30 (td, \(J = 16.4, 8.4\) Hz, 1 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 188.5 (t, \(J = 29.4\) Hz), 166.4 (d, \(J = 256.2\) Hz), 135.2 (d, \(J = 3.8\) Hz), 133.0 (dt, \(J = 8.8, 3.8\) Hz), 132.5 (t, \(J = 4.4\) Hz), 129.8, 129.4 (d, \(J = 2.5\) Hz), 128.8, 128.1, 120.9, 118.8 (t, \(J = 256.2\) Hz), 116.1 (d, \(J = 21.2\) Hz), 54.1 (t, \(J = 21.9\) Hz). \(^19\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –103.4 (dd, A of ABX, \(J_{AB} = 276.4\) Hz, \(J_{AX} = 16.9\) Hz, 1 F), –102.6 (m, 1 F), –102.5 (dd, B of ABX, \(J_{AB} = 276.4\) Hz, \(J_{BX} = 16.9\) Hz, 1 F). IR (film) 3086, 1707, 1599, 1506, 1412, 1242, 1161, 1047, 926, 850, 744, 700 cm\(^{-1}\). HRMS (APCI-hexane/PhMe, \(m/z\)): calcd for C\(_{17}\)H\(_{14}\)F\(_3\)O [M+H]\(^+\) 291.0997, found 291.0994. mp 35–36 °C.

cinnamyl 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate (4.7c)

General procedure D was followed using potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate\(^3\) (1.5 g, 5.8 mmol), oxalyl chloride (0.49 mL, 5.8 mmol), cinnamyl alcohol (1.0 g, 7.5 mmol), Et\(_3\)N (1.2 mL, 8.7 mmol), DMF (1.0 mL), and CH\(_2\)Cl\(_2\) (21 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.7c as a colorless oil (1.4 g, 72%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.87–7.86 (m, 1 H), 7.39–7.29 (m, 5 H), 6.87 (dd, \(J = 4.0, 1.2\) Hz, 1 H), 6.70 (t, \(J = 7.2\) Hz, 1 H), 6.69 (d, \(J = 2.8\) Hz, 1 H), 6.58 (d, \(J = 6.8\) Hz, 1 H), 5.87 (dt, \(J = 10.0, 4.0\) Hz, 1 H), 5.78 (dd, \(J = 10.0, 4.0\) Hz, 1 H), 5.01 (ddd, \(J = 10.0, 6.8, 4.0\) Hz, 1 H), 4.37 (t, \(J = 10.0\) Hz, 1 H), 3.97 (d, \(J = 1.2\) Hz, 3 H), 3.87–3.82 (m, 1 H), 3.17 (t, \(J = 7.2\) Hz, 2 H), 2.58–2.52 (m, 2 H), 2.08–2.03 (m, 2 H), 1.98 (s, 3 H), 1.60 (s, 1 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 188.3 (t, \(J = 29.7\) Hz), 166.2 (d, \(J = 256.2\) Hz), 135.1 (t, \(J = 2.9\) Hz), 132.9 (dd, \(J = 8.8, 3.8\) Hz), 132.2 (t, \(J = 4.4\) Hz), 129.8, 129.4 (d, \(J = 2.5\) Hz), 128.8, 128.1, 120.9, 118.8 (t, \(J = 256.2\) Hz), 116.1 (d, \(J = 21.2\) Hz), 54.0 (t, \(J = 21.9\) Hz). \(^19\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –102.6 (dd, A of ABX, \(J_{AB} = 276.4\) Hz, \(J_{AX} = 16.9\) Hz, 1 F), –101.7 (m, 1 F), –101.6 (dd, B of ABX, \(J_{AB} = 276.5\) Hz, \(J_{BX} = 16.9\) Hz, 1 F). IR (film) 3087, 1705, 1599, 1506, 1412, 1242, 1161, 1047, 926, 850, 744, 700 cm\(^{-1}\). HRMS (APCI-hexane/PhMe, \(m/z\)): calcd for C\(_{20}\)H\(_{21}\)F\(_2\)O\(_3\) [M+H]\(^+\) 357.0756, found 357.0760. mp 95–96 °C.
6.69 (dt, $J = 16.0, 1.2$ Hz, 1 H), 6.25 (dt, $J = 16.0, 6.4$ Hz, 1 H), 4.97 (dd, $J = 6.4, 1.2$ Hz, 2 H), 2.57 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 177.9 (t, $J = 28.1$ Hz), 161.8 (t, $J = 30.6$ Hz), 154.6, 137.5 (t, $J = 5.0$ Hz), 136.4, 135.8, 135.2, 128.8, 128.7, 128.2, 127.0, 120.9, 109.7 (t, $J = 263.1$ Hz), 68.1, 16.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –108.0 (s, 2 F). IR (film) 3028, 1774, 1664, 1446, 1310, 1265, 1155, 1051, 968, 912, 812, 746, 692 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{17}$H$_{14}$F$_2$O$_3$SNa [M+Na]$^+$ 359.0529, found 359.0531.

(E)-2,2-difluoro-1-(5-methylthiophen-2-yl)-5-phenylpent-4-en-1-one (4.8c)

General procedure E was followed using 4.7c (101 mg, 0.300 mmol), Pd(OAc)$_2$ (2.0 mg, 0.090 mmol), $t$-BuBrettPhos (8.7 mg, 0.018 mmol), and 1,4-dioxane (0.60 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.8c as a light yellow solid (78.0 mg, 89%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.87–7.86 (m, 1 H), 7.38–7.36 (m, 2 H), 7.34–7.30 (m, 2 H), 7.26–7.22 (m, 1 H), 6.88 (dd, $J = 3.6, 1.2$ Hz, 1 H), 6.59 (d, $J = 16.0$ Hz, 1 H), 6.19 (dt, $J = 16.0, 7.4$ Hz, 1 H), 3.10 (tdd, $J = 17.0, 7.4, 1.4$ Hz, 2 H), 2.58 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 182.3 (t, $J = 31.2$ Hz), 153.3, 136.9 (t, $J = 5.0$ Hz), 136.8, 136.4, 136.3, 128.7, 128.0, 127.9, 126.6, 118.9 (t, $J = 5.0$ Hz), 118.6 (t, $J = 252.5$ Hz), 38.2 (t, $J = 23.8$ Hz), 16.3. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –100.0 (t, $J = 16.9$ Hz, 2 F). IR (film) 3026, 1670, 1448, 1223, 1184, 1171, 1057, 968, 812, 758, 739, 692 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{14}$F$_2$OSNa [M+Na]$^+$ 315.0631, found 315.0643. mp 49–50 °C.

2,2-difluoro-1-(5-methylthiophen-2-yl)-3-phenylpent-4-en-1-one (4.9c)

General procedure F was followed using 4.7c (101 mg, 0.300 mmol), Pd(OAc)$_2$ (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.015 mmol), and 1,4-dioxane (3.0 mL). The reaction time was 18 h. Workup and
chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.9c as a light yellow solid (76.0 mg, 87%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.73–7.72 (m, 1 H), 7.35–7.28 (m, 5 H), 5.81 (dd, $J = 4.0$, 1.2 Hz, 1 H), 6.22 (ddd, $J = 17.2$, 10.4, 8.4 Hz, 1 H), 5.31 (d, $J = 10.4$ Hz, 1 H), 5.24 (dt, $J = 17.2$, 1.2 Hz, 1 H), 4.26 (td, $J = 16.6$, 8.4 Hz, 1 H), 2.55 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 182.4 (t, $J = 30.0$ Hz), 153.2, 137.0, 136.6 (t, $J = 5.6$ Hz), 135.3 (t, $J = 1.9$ Hz), 132.4 (t, $J = 3.8$ Hz), 129.8, 128.7, 128.0, 127.8, 120.8, 118.7 (t, $J = 257.5$ Hz), 54.3 (t, $J = 21.9$ Hz), 16.2. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –104.8 (d, $J = 15.0$ Hz, 2 F). IR (film) 3030, 1662, 1448, 1275, 1171, 1061, 1040, 932, 812, 748, 719, 700 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{14}$F$_2$OSK $[M+K]^+$ 331.0371, found 331.0382. mp 55–56 °C.

cinnamyl 2,2-difluoro-3-oxo-3-(1-phenyl-1$H$-pyrazol-4-yl)propanoate (4.7d)

General procedure D was followed using potassium 2,2-difluoro-3-oxo-3-(1-phenyl-1$H$-pyrazol-4-yl)propanoate$^3$ (0.76 g, 2.5 mmol), oxalyl chloride (0.19 mL, 2.3 mmol), cinnamyl alcohol (0.28 g, 2.1 mmol), Et$_3$N (0.58 mL, 4.2 mmol), DMF (48 µL), and CH$_2$Cl$_2$ (12 mL). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) afforded the title compound 4.7d as a colorless solid (0.68 g, 85%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.61 (s, 1 H), 8.31 (s, 1 H), 7.72 (d, $J = 8.0$ Hz, 2 H), 7.50 (t, $J = 8.0$ Hz, 2 H), 7.43–7.37 (m, 3 H), 7.35–7.28 (m, 3 H), 6.72 (d, $J = 16.0$ Hz, 1 H), 6.27 (dt, $J = 16.0$, 6.4 Hz, 1 H), 4.98 (d, $J = 6.4$ Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 179.9 (t, $J = 28.8$ Hz), 161.7 (t, $J = 30.6$ Hz), 143.0 (t, $J = 2.5$ Hz), 139.0, 136.6, 135.7, 131.7 (t, $J = 3.8$ Hz), 129.9, 128.9, 128.8, 128.6, 127.0, 120.8, 120.2, 118.8, 109.6 (t, $J = 262.5$ Hz), 68.3. $^{19}$H NMR (CDCl$_3$, 376 MHz) $\delta$ –110.6 (s, 2 F). IR (film) 3138, 3059, 1774, 1688, 1541, 1504, 1308, 1242, 1171, 1126, 1036, 968, 951, 883, 758, 690 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{21}$H$_{16}$F$_2$N$_2$O$_3$Na $[M+Na]^+$ 405.1027, found 405.1025. mp 64–65 °C.
(E)-2,2-difluoro-5-phenyl-1-(1-phenyl-1H-pyrazol-4-yl)pent-4-en-1-one (4.8d)

General procedure E was followed using 4.7d (76.5 mg, 0.200 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), t-BuBrettPhos (9.7 mg, 0.020 mmol), and 1,4-dioxane (0.40 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.8d as a colorless solid (43 mg, 64%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.56 (s, 1 H), 8.29 (s, 1 H), 7.72–7.70 (m, 2 H), 7.51 (t, $J$ = 8.0 Hz, 2 H), 7.43–7.22 (m, 6 H), 6.61 (d, $J$ = 16.0 Hz, 1 H), 6.19 (dt, $J$ = 16.0, 7.4 Hz, 1 H), 3.10 (tdd, $J$ = 17.0, 7.4, 1.4 Hz, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 184.3 (t, $J$ = 31.9 Hz), 143.2 (t, $J$ = 2.5 Hz), 139.2, 136.7, 136.6, 131.6 (t, $J$ = 5.0 Hz), 129.9, 128.8, 128.4, 128.1, 126.6, 120.0, 119.6, 118.7 (t, $J$ = 5.0 Hz), 118.5 (t, $J$ = 251.2 Hz), 37.6 (t, $J$ = 23.8 Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –102.4 (t, $J$ = 16.9 Hz, 2 F). IR (film) 1686, 1541, 1502, 1186, 1038, 951, 908, 876, 833, 756, 688 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{20}$H$_{17}$F$_2$N$_2$O [M+H]$^+$ 339.1309, found 339.1320. mp 95–97 °C.

2,2-difluoro-3-phenyl-1-(1-phenyl-1H-pyrazol-4-yl)pent-4-en-1-one (4.9d)

General procedure F was followed using 4.7d (76.5 mg, 0.200 mmol), Pd(OAc)$_2$ (2.2 mg, 0.010 mmol), PhXPhos (9.3 mg, 0.020 mmol), and 1,4-dioxane (2.0 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.9d as a colorless solid (49 mg, 72%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.38 (s, 1 H), 8.16 (s, 1 H), 7.67 (dt, $J$ = 8.4, 1.9 Hz, 2 H), 7.50 (t, $J$ = 8.0 Hz, 2 H), 7.42–7.25 (m, 6 H), 6.25 (ddd, $J$ = 17.2, 10.4, 8.4 Hz, 1 H), 5.35 (d, $J$ = 10.4 Hz, 1 H), 5.29 (dt, $J$ = 16.8, 1.2 Hz, 1 H), 4.28 (td, $J$ = 16.4, 8.4 Hz, 1 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 184.8 (t, $J$ = 31.2 Hz), 143.0 (t, $J$ = 3.1 Hz), 139.1, 135.2 (d, $J$ = 5.0 Hz), 132.2 (dd, $J$ = 4.4, 3.1 Hz), 131.4 (t, $J$ = 5.6 Hz), 129.9, 129.8, 218
128.8, 128.3, 128.2, 121.0, 120.4, 120.1, 118.6 (t, $J = 255.6$ Hz), 53.8 (t, $J = 22.5$ Hz). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.6 (dd, A of ABX, $J_{AB} = 263.2$ Hz, $J_{AX} = 15.0$ Hz, 1 F), –106.2 (dd, B of ABX, $J_{AB} = 263.2$ Hz, $J_{BX} = 15.0$ Hz, 1 F). IR (film) 3065, 3032, 1684, 1599, 1541, 1504, 1250, 1174, 1036, 951, 887, 758, 725, 700, 688, 658 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{20}$H$_{17}$F$_2$N$_2$O $[M+H]^+$ 339.1309, found 339.1303. mp 81–82 °C.

**cinnamyl 3-cyclohexyl-2,2-difluoro-3-oxopropanoate (4.7e)**

General procedure D was followed using potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate$^3$ (1.5 g, 6.1 mmol), oxalyl chloride (0.52 mL, 6.1 mmol), cinnamyl alcohol (1.1 g, 8.0 mmol), Et$_3$N (1.0 mL, 7.4 mmol), DMF (1.0 mL), and CH$_2$Cl$_2$ (20 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 4.7e as a colorless oil (1.6 g, 81%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.42–7.40 (m, 2 H), 7.37–7.30 (m, 3 H), 6.73 (d, $J = 15.6$ Hz, 1 H), 6.27 (dt, $J = 15.6$, 6.8 Hz, 1 H), 4.95 (d, $J = 6.8$ Hz, 2 H), 2.95–2.89 (m, 1 H), 1.94–1.89 (m, 2 H), 1.83–1.78 (m, 2 H), 1.71–1.68 (m, 1 H), 1.47–1.17 (m, 5 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 200.3 (t, $J = 26.9$ Hz), 161.7 (t, $J = 30.6$ Hz), 136.6, 135.8, 128.9, 128.8, 127.0, 120.9, 108.8 (t, $J = 263.8$ Hz), 68.1, 45.5, 28.3, 25.6, 25.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –112.9 (s, 2 F). IR (film) 2935, 2858, 1776, 1736, 1450, 1310, 1202, 1144, 966, 746, 692 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{20}$F$_2$O$_3$Na $[M+Na]^+$ 345.1278, found 345.1284.

![4.7e](image)

**(E)-1-cyclohexyl-2,2-difluoro-5-phenylpent-4-en-1-one (4.8e)**

General procedure E was followed using 4.7e (96.7 mg, 0.300 mmol), Pd(OAc)$_2$ (3.4 mg, 0.015 mmol), t-BuBrettPhos (14.5 mg, 0.0300 mmol), and 1,4-dioxane (0.60 mL). The reaction was run at 70 °C, and the
reaction time was extended to 36 h. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.8e as a light yellow oil (51.0 mg, 61%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.38–7.23 (m, 5 H), 6.54 (d, $J = 16.0$ Hz, 1 H), 6.08 (dt, $J = 16.0$, 7.4 Hz, 1 H), 2.98–2.86 (m, 3 H), 1.88–1.77 (m, 4 H), 1.71–1.67 (m, 1 H), 1.42–1.19 (m, 5 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 204.3 (t, $J = 29.4$ Hz), 136.8, 136.5, 128.8, 128.0, 126.5, 118.8 (t, $J = 5.6$ Hz), 118.0 (t, $J = 253.1$ Hz), 45.1, 37.2 (t, $J = 23.8$ Hz), 28.3, 25.8, 25.6. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –105.6 (t, $J = 16.9$ Hz, 2 F). IR (film) 2934, 2856, 1732, 1494, 1452, 1207, 1167, 1059, 1032, 968, 742, 692 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{20}$F$_2$ONa [M+Na]$^+$ 301.1380, found 301.1388.

![4.8e](image)

1-cyclohexyl-2,2-difluoro-3-phenylpent-4-en-1-one (4.9e)

General procedure F was followed using 4.7e (96.7 mg, 0.300 mmol), Pd(OAc)$_2$ (3.4 mg, 0.015 mmol), PhXPhos (13.9 mg, 0.0300 mmol), and 1,4-dioxane (3.0 mL). The reaction time was extended to 36 h. Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 4.9e as a light yellow oil (61.0 mg, 73%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.36–7.28 (m, 5 H), 6.17 (ddd, $J = 17.2$, 10.0, 8.4 Hz, 1 H), 5.32 (d, $J = 10.0$ Hz, 1 H), 5.24 (d, $J = 17.2$ Hz, 1 H), 4.16–4.05 (m, 1 H), 2.63–2.56 (m, 1 H), 1.78–1.74 (m, 2 H), 1.68–1.62 (m, 2 H), 1.44–1.39 (m, 1 H), 1.28–1.08 (m, 5 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 205.0 (t, $J = 28.8$ Hz), 135.2 (d, $J = 5.0$ Hz), 132.4 (dd, $J = 6.2$, 2.5 Hz), 129.8, 128.8, 128.1, 120.8, 118.1 (t, $J = 258.1$ Hz), 53.1 (t, $J = 21.9$ Hz), 45.9, 28.1, 27.7, 25.7, 25.6, 25.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –112.0 (dd, A of AMX, $J_{AM} = 263.2$ Hz, $J_{AX} = 16.9$ Hz, 1 F), –107.6 (dd, M of AMX, $J_{AM} = 263.2$ Hz, $J_{MX} = 15.0$ Hz, 1 F). IR (film) 2934, 2856, 1732, 1494, 1452, 1207, 1167, 1059, 1032, 966, 930, 742, 700 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{20}$F$_2$ONa [M+Na]$^+$ 301.1380, found 301.1378.
Preparation of Compound 4.13 in Scheme 4.13B

1-(3-(trifluoromethyl)phenyl)allyl 2,2-difluoro-3-oxo-3-phenylpropanoate (4.13)

An oven-dried one-neck round-bottom flask was charged with potassium salt potassium 2,2-difluoro-3-oxo-3-phenylpropanoate (1.0 g, 4.2 mmol), and the system was evacuated and backfilled with N$_2$(g) three times. Dry CH$_2$Cl$_2$ (21 mL) and DMF (0.10 mL) were added via a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (0.31 mL, 3.7 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 2 h. Next, a solution of 1-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol (0.71 g, 3.5 mmol) dissolved in dry CH$_2$Cl$_2$ (2.0 mL) was added dropwise at 0 °C followed by dropwise addition of Et$_3$N (0.97 mL, 7.0 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 2 h. H$_2$O (10 mL) was added to quench the reaction, and the CH$_2$Cl$_2$ was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated. Purification by flash chromatography (0% to 15% EtOAc in hexanes) afforded the title compound 4.13 as a colorless oil (0.81 g, 60%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.04 (dd, $J = 8.0, 1.4$ Hz, 2 H), 7.69–7.65 (m, 1 H), 7.59 (dt, $J = 6.4, 1.8$ Hz, 1 H), 7.54–7.47 (m, 5 H), 6.45 (d, $J = 6.0$ Hz, 1 H), 5.98 (ddd, $J = 17.0, 10.8, 6.2$ Hz, 1 H), 5.42–5.40 (m, 1 H), 5.37 (d, $J = 1.2$ Hz, 1 H).

$^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.4 (t, $J = 27.5$ Hz), 161.0 (t, $J = 30.6$ Hz), 138.0, 135.4, 133.7, 131.3 (q, $J = 32.5$ Hz), 131.1, 130.7, 130.1 (t, $J = 3.1$ Hz), 129.5, 129.2, 125.8 (q, $J = 3.7$ Hz), 124.1 (q, $J = 3.7$ Hz), 124.0 (q, $J = 270.9$ Hz), 119.9, 109.9 (t, $J = 263.7$ Hz), 79.0.

$^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.5 (d, A of AB, $J = 289.5$ Hz, 1 F), –107.1 (d, B of AB, $J = 289.5$ Hz, 1 F), –62.7 (s, 3 F).

IR (film) 3072, 1778, 1714, 1699, 1599, 1452, 1333, 1256, 1167, 1128, 1074, 926, 804, 704, 687, 580 cm$^{-1}$.

HRMS (EI, m/z): calcd for C$_{19}$H$_{12}$F$_5$O$_3$ [M–H$^-$] 383.0707, found 383.0698.
Experimental Procedures for Catalytic Reactions in Scheme 4.13B

An oven-dried 1 dram vial was charged with substrate 4.13 (57.6 mg, 0.150 mmol), Pd(OAc)$_2$ (1.0 mg, 0.0045 mmol for catalyst system A or 0.8 mg, 0.0037 mmol for catalyst system B), ligand ($t$-BuBrettPhos 4.4 mg, 0.0090 mmol for catalyst system A or PhXPhos 3.5 mg, 0.0075 mmol for catalyst system B), and a magnetic stir bar. The vial was equipped with a three-way valve, evacuated and backfilled with N$_2$(g) four times. Dry 1,4-dioxane (0.3 mL for catalyst system A or 1.5 mL for catalyst system B) was added via a syringe under N$_2$(g). The vial was sealed with a screwed-cap under N$_2$(g) flow, and was stirred at rt for 5 min. Subsequently, the vial was placed on a pre-heated reaction block, and stirred at 60 °C for catalyst system A or 90 °C for catalyst system B for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2.0 mL for catalyst system A or 0.1 mL for catalyst system B). 2,2,2-trifluoroethanol (10 µL, 0.1372 mmol) was added as a standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial for $^{19}$F NMR analysis. $^{19}$F NMR yields and selectivities reported in the manuscript represent an average of two independent runs for catalyst system A or B, respectively.

Experimental Procedures for Catalytic Reactions in the Presence of Acidic Additives

Entry 2 in Scheme 15: An oven-dried 1 dram vial A was charged with Pd(OAc)$_2$ (2.0 mg, 0.0090 mmol), $t$-BuBrettPhos (8.7 mg, 0.018 mmol), and a magnetic stir bar. The vial A was equipped with a three-way valve, and evacuated and backfilled with N$_2$(g) three times. Dry 1,4-dioxane (0.2 mL) was added via a syringe under N$_2$(g). The vial was sealed with PTFE-lined silicone septa under N$_2$(g), and the mixture was stirred at 80 °C for 10 min (pre-activation), and then cooled to rt. Subsequently, another oven-dried vial B was charged with a magnetic stir bar, the substrate 4.1a (0.300 mmol) and acetyl acetone (30 µL, 0.300 mmol), and the dry 1,4-dioxane (0.3 mL) was added via a syringe under N$_2$(g), and stirred at rt thoroughly. The solution in the vial B was transferred to the vial A via a syringe under N$_2$(g), and another dry 1,4-dioxane (0.1 mL) was used to wash inner wall of the vial B and the solution was transferred to the vial A again. The vial A was stirred at rt for 5 min, and then placed on a pre-heated reaction block at 60 °C, and
stirred for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (2 mL). α,α,α-Trifluorotoluene (15 µL, 0.12 mmol) was added as an internal standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial A for 19F NMR analysis to determine the ratio of fluorinated products 4.2a, 4.3a, and 4.3a′. After determination of the 19F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. The solvents were removed under reduced pressure, and 1H NMR of the crude mixture was analyzed for determining the ratio of allylated products 4.2a′ based on the integration related to 4.2a.

Entry 4 in Scheme 15: An oven-dried 1 dram vial A was charged with Pd(OAc)2 (1.7 mg, 0.0075 mmol), PhXPhos (7.0 mg, 0.0150 mmol) and a magnetic stir bar. The vial A was equipped with a three-way valve, and evacuated and backfilled with N2(g) three times. Dry 1,4-dioxane (1.0 mL) was added via a syringe under N2(g). The vial was sealed with PTFE-lined silicone septa under N2(g), and the mixture was stirred at 80 °C for 10 min (pre-activation), and then cooled to rt. Subsequently, another oven-dried vial B was charged with a magnetic stir bar, the substrate 4.1a (0.300 mmol) and acetyl acetone (30 µL, 0.300 mmol), and the dry 1,4-dioxane (1.5 mL) was added via a syringe under N2(g), and stirred at rt thoroughly. The solution in the vial B was transferred to the vial A via a syringe under N2(g), and another dry 1,4-dioxane (0.5 mL) was used to wash inner wall of the vial B and the solution was transferred to the vial A again. The vial A was stirred at rt for 5 min, and then placed on a pre-heated reaction block at 90 °C, and stirred for 20 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (0.5 mL). α,α,α-Trifluorotoluene (15 µL, 0.12 mmol) was added as an internal standard, and the reaction mixture was stirred at rt for 30 min to ensure thorough mixing. An aliquot was taken from the vial A for 19F NMR analysis to determine the ratio of fluorinated products 4.2a, 4.3a, and 4.3a′. After determination of the 19F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of silica gel, and eluted with EtOAc. The solvents were removed under reduced pressure,
and $^1$H NMR of the crude mixture was analyzed for determining the ratio of allylated products 4.2a' based on the integration related to 4.3a.

**Analysis of Selectivity Data in Figures 1 and 2**

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Substituent (X)</th>
<th>Selectivity (lin/br)</th>
<th>Log (Selectivity$_X$/Selectivity$_H$)</th>
<th>$\sigma^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4a</td>
<td>$m$-CF$_3$</td>
<td>23</td>
<td>0.1065</td>
<td>0.52</td>
</tr>
<tr>
<td>4b</td>
<td>$p$-NO$_2$</td>
<td>30</td>
<td>0.2218</td>
<td>0.79</td>
</tr>
<tr>
<td>4c</td>
<td>$m$-CO$_2$Et</td>
<td>21</td>
<td>0.0669</td>
<td>0.37</td>
</tr>
<tr>
<td>4e</td>
<td>$p$-Me</td>
<td>10</td>
<td>0.2553</td>
<td>–0.31</td>
</tr>
<tr>
<td>4g</td>
<td>$p$-OMe</td>
<td>6</td>
<td>0.4771</td>
<td>–0.78</td>
</tr>
</tbody>
</table>

Values for $\sigma^+$ were obtained from the literature.$^{16}$
\[
\text{Pd(OAc)}_2 (2.5 \text{ mol\%}) \quad \text{PhXPhos (5.0 \text{ mol\%})} \\
1,4\text{-dioxane, 90 }^\circ\text{C, 20–24 h}
\]

\[
\begin{array}{c|c|c|c|c}
\text{Substrate} & \text{Substituent (X)} & \text{Selectivity (br/lin)} & \log \left( \frac{\text{Selectivity}_x}{\text{Selectivity}_H} \right) & \sigma^+ \\
\hline
1a & H & 99 & - & - \\
4a & m-CF_3 & 99 & 0.0000 & 0.52 \\
4b & p-NO_2 & 98 & -0.0004 & 0.79 \\
4c & m-CO_2Et & 99 & 0.0000 & 0.37 \\
4e & p-Me & 99 & 0.0000 & -0.31 \\
4g & p-OMe & 99 & 0.0000 & -0.78 \\
\end{array}
\]
References for Chapter 4 Experimental Section

15 1-(3-(Trifluoromethyl)phenyl)prop-2-en-1-ol was prepared according to the procedure described in the following patent: O. Thiel, C. Bernard, R. Larsen, M. J. Martinelli, M. T. Raza (Amgen Inc., USA), 2009002427, 2008.
Chapter 5. Palladium-Catalyzed para-C–H Difluoroalkylation of Arenes via Decarboxylation of Benzyl α,α-Difluoro-β-keto-esters

5.1 Introduction to Selective para-C–H Functionalization of Arenes

The functionalization of C–H bonds represents an important and powerful strategy for converting simple arenes and hydrocarbons to more complex molecules. This strategy mainly utilizes transition metals to functionalize inert C–H bonds, and react them with carbon- and heteroatom-based reagents to generate coupling products. The C–H functionalization strategy avoids the use of pre-functionalized precursors, thus provides an atom-economic and time-saving transformation for building structurally complicated natural products, especially for late-stage modifications of bioactive molecules. Moreover, the C–H functionalization method enables distinct bond disconnections in retrosynthetic analysis of natural products, which could create new and efficient synthetic strategies. However, the reliability and value of such a C–H functionalization reaction depend on chemoselective activation of one C–H bond over others. To address selectivity issues, many methods have been developed to activate a specific C–H bond. For aromatic systems, the utilization of auxiliary groups and well-designed transition-metal catalysts has enabled selective ortho- and even meta-C–H functionalization of arenes.

However, the strategies to selectively activate C–H bonds at the para-position of arenes remain limited. Current methods for para-C–H functionalization reactions mainly utilize electronic control of substrates. In this strategy, arenes couple with in situ generated electrophilic intermediates, including iodonium salts or metal carbenoids, to generate para-functionalized arenes (Scheme 5.1). In the case of iodonium salts as reactive intermediates, electron-rich arenes proceeded much more quickly than electron-deficient arenes, most of which did not participate in the reactions (Scheme 5.1A). This result supported the assertion that the reactions proceeded by an electrophilic aromatic substitution or metalation (SeAr or EAM) mechanism, thus only tolerating electron-rich aromatic substrates. For the reactions that proceed through electrophilic gold carbenoids, more electron-deficient fluorinated α-
diazoester precursors were required to facilitate reactions of the substrates bearing alkyl- and halogen-substituted arenes (Scheme 5.1B).

Moreover, the combination use of electron-rich arenes with palladium catalysts under oxidative conditions provided an alternative strategy for accessing para-biphenyl derivatives (Scheme 5.2). The Yu group proposed that this method contains two C–H activation steps (Scheme 5.2A). First, the directing group (DG) on one aromatic ring facilitated the formation of a cyclopalladated Pd(II) complex, which was oxidized to a Pd(IV) species by oxidants. Then, the ligand/directing group-stabilized Pd(IV) species could undergo an electrophilic palladation of electron-rich arenes, followed by reductive elimination, to generate para-functionalized products. In the reactions, the Yu group also utilized 3-acetylpyridine as a ligand that coordinates to Pd(IV) center to facilitate electrophilic palladation, and avoided the use of stoichiometric amount of oxidant NFSI. Similarly, the Zhou lab also proposed a Pd(II)/Pd(IV) catalytic cycle for the reactions of phenol derivatives with aryl iodides (Scheme 5.2B). Despite these reactions provided para-functionalized products in high selectivity, they required the use of stoichiometric amount of oxidants, and directing group-containing aromatic systems, both of which caused organic wastes and narrowed the substrate scope.

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The auxiliary group-based approach presents difficulty in \( \text{para-C–H} \) transformations, because of the challenge of designing a directing group with appropriate length to reach the distal C–H bond, activate it, and form a pre-organized metallacycle for reactions. Recently, a silyl biphenyl-based template enabled for selective \( \text{para-C–H} \) functionalization of toluene and phenol derivatives (Scheme 5.3).\(^\text{10}\) However, this method requires the pre-installation of the template to the substrates through an appropriate functional group for attachment, and the removal of the heavy template at a late stage, which narrows the substrate scope and adds extra synthetic steps, respectively.
To overcome these limitations, the strategies that use transition-metal catalysts to control para-selectivity enables the activation of C–H bonds at the para-position of heterocycles and electron-deficient arenes. For example, the Ong and Hiyama labs utilized a Ni/Al bimetallic catalyst system to activate the para-C–H bond of pyridines and quinolones (Scheme 5.4A). The combination of Ni/Al catalysts enabled the formation of a reactive species A, in which Ni σ-bonds to two NHC ligands and η²-bonds to the pyridine with the nitrogen atom coordinating to Al, and directed the metalation to occur at the more acidic and less sterically congested para-position of pyridine to form the Ni(II) complex B. Subsequently, coordination of alkenes to the complex B, followed by migratory insertion into Ni–H bond generated the intermediate D, which underwent reductive elimination to provide the coupling product and regenerate Ni(0) to close the catalytic cycle (Scheme 5.4B). Moreover, the use of structurally distinct ligands enabled the regioselective formation of linear and branched products, thus extending reaction pattern (Scheme 5.4C). Recently, the Nakao group combined a bulky Ni/Al cocatalyst with a bulky NHC ligand to develop a powerful catalytic system that can functionalize the para-C–H bond of electron-deficient arenes, such as benzamides and aromatic ketones (Scheme 5.4D). In the reaction mode, the interaction of aluminum Lewis acid with the carbonyl group electronically enhanced the reactivity of the para-C–H bond toward an electron-rich Ni center, and a steric repulsion between the bulky Al center and the bulky ligand pushed the Ni catalyst to the para-C–H bond. The cooperation of the electronic and steric effects significantly improved the yields and selectivity compared to previous reports.
Additionally, the Itami group developed an iridium catalyst bearing a bulky ligand to undergo para-selective borylation (Scheme 5.5). This para-selectivity derived from a steric repulsion between the substrate and bulky ligand of the catalyst, which prevented meta-H from approaching the metal center, and inhibited its activation. The strategy utilizing bulky catalyst to drive para-selectivity enabled to functionalize electron-deficient arenes, which are challenging substrates to functionalize by alternative methods.
5.2 Base-Promoted Selective para-Difluoroalkylation of Arenes

To complement these known strategies, we report a base-mediated para-C–H difluoroalkylation of arenes using palladium catalysis (Scheme 5.6). In this reaction, amine additives play an essential role in promoting a C–H functionalization pathway (Scheme 5.6A) and disfavoring a traditional decarboxylative benzylation reaction (Scheme 5.6B). This reaction represents the unique example in which a base can switch the selectivity from cross-coupling to C–H functionalization.
The formation of such a $\alpha$-aryl-$\alpha$, $\alpha$-difluoroketone was initially observed as a side product during the exploration of the substrate scope in the decarboxylative benzylation of $\alpha,\alpha$-difluoroketone enolates. We found that the reaction of ortho-thio-substituted benzyl substrates generated the desired $\alpha$-benzyl-$\alpha,\alpha$-difluoroketone product together with the unexpected $\alpha$-aryl-$\alpha,\alpha$-difluoroketone (Scheme 5.7). After the isolation and 2D NMR analysis of the $\alpha$-aryl-$\alpha,\alpha$-difluoroketone product, it was concluded that the $\alpha,\alpha$-difluoroketone moiety was incorporated at the para-position of arenes relative to the methyl group.

![Scheme 5.7. Formation of $\alpha$-Aryl-$\alpha,\alpha$-difluoroketones under Benzylation Condition](image)

Although $\alpha$-aryl-$\alpha,\alpha$-difluoroketones can be accessed by known methods, its formation via a decarboxylative C–H functionalization reaction has not been reported. Thus, we aimed to develop a selective C–H functionalization method for accessing $\alpha$-aryl-$\alpha,\alpha$-difluoroketones. To begin the study, a variety of ortho- and meta-substituted benzyl $\alpha,\alpha$-difluoro-$\beta$-keto-esters were identified as potential substrates, and they were prepared through four steps, including 1) Reformatsky addition of ethyl bromodifluoroacetate to aldehydes; 2) oxidation of alcohols to ketones; 3) basic hydrolysis of ethyl esters; and 4) esterification of $\beta$-keto-$\alpha,\alpha$-difluoroacetate with substituted benzyl alcohols (Scheme 5.8).
Initial screening focused on the identification of appropriate ligands that can promote para-C–H arylation reaction, and suppress cross-coupling benzylation reaction (Table 5.1). Generally, electron-deficient ligands (entry 1) caused low conversion, and inhibited the arylation reaction, while more electron-rich ligands benefited the arylation reaction, and provided the arylated product in about 30% yields (entries 2–5). However, ligands that were excessively electron-rich (entry 6), hindered, and bidentate suppressed the catalytic C–H arylation reaction.
Table 5.1. Electron-Rich Triphenylphosphine Ligands Favored Formation of Arylated Product

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>arylation (%)</th>
<th>benzylation (%)</th>
<th>PhCOCF$_2$H (%)</th>
<th>conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(4-CF$_3$C$_6$H$_4$)$_3$</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$</td>
<td>33</td>
<td>2</td>
<td>22</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>PPh$_2$(4-OMeC$_6$H$_4$)$_2$</td>
<td>35</td>
<td>2</td>
<td>27</td>
<td>93</td>
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<tr>
<td>4</td>
<td>PPh(4-OMeC$_6$H$_4$)$_3$</td>
<td>32</td>
<td>2</td>
<td>29</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>P(4-OMeC$_6$H$_4$)$_3$</td>
<td>30</td>
<td>1</td>
<td>32</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>P(4-NMe$_2$C$_6$H$_4$)$_3$</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>37</td>
</tr>
</tbody>
</table>

Other ligands screened that produced < 25% arylated product by $^{19}$F NMR analysis were shown below.

Yields were determined by $^{19}$F NMR using o,o,o-trifluorotoluene as an internal standard.

Since S-containing groups can also serve as a ligand and coordinate to palladium that could interfere with a catalyst system and deactivate the palladium catalyst, we used another substrate (5.1) bearing a non-coordinating group for screening. During the optimization, we found that electronic properties of ligands and palladium catalysts or precatalysts affected the selectivity of arylation to benzylation products; however, no obvious trend was observed. For example, the catalyst system of PdCp($^3$C$_3$H$_4$)/P(4-OMeC$_6$H$_4$)$_3$ favored the arylated product, while the catalyst system of Pd(dba)$_2$/P(4-OMeC$_6$H$_4$)$_3$ still preferred the benzylated product. For these conditions, the yield of arylated product 5.2a was less than 40%. To further improve the yield, solvent screening was performed. Interestingly, the distribution of products closely correlated with the solvent used (Table 5.2). Specifically, hydrocarbon and ether solvents provided benzylated product 5.2b (entries 1–4), while polar and coordinating solvents favored arylated
product 5.2a (entries 5–8). Although full conversion was achieved for these conditions, the yield of arylated product 5.2a did not increase further.

Amine additives could favor the para-selective C–H arylation reaction. Considering that a dearomatization-rearomatization process might operate in the catalytic arylation reaction of α,α-difluoroketone enolates, we explored the use of bases that could facilitate the rearomatization step and enhance the yields. Interestingly, the strength of bases affected the selectivity of arylation to benzylation (Table 5.3). Nitriles, inorganic bases, and weak bases, such as pyridine and anilines, exclusively provided the benzylated product 5.2b (entries 2–7). In contrast, more basic amines, including N,N-dimethylaminopyridine (DMAP), tripropylamine (n-Pr3N), triethylamine (Et3N), and the chelating base (TMEDA) gave the arylated product 5.2a (entries 8–11). Further exploration of aliphatic amines demonstrated correlation between rigidity/hindrance and selectivity. The conformationally constrained base quinuclidine provided low yield of arylated product 5.2a (entry 12), while the bulky diisopropylethyl amine (DIPEA) favored the benzylated product 5.2b (entry 13). Thus, Et3N with a compromise between basicity and steric hindrance generated the arylated product 5.2a in the highest yield (entries 10). Additionally, the stoichiometry of Et3N also influenced the yield of arylated product 5.2a. Increased
amount of Et₃N improved the selectivity towards the arylated product 5.2a (entries 10, and 14–16), but more than 1 equivalent of Et₃N did not increase the yield (entries 10 and 17). After further optimization, the final conditions [2.5 mol% of Pd(PPh₃)₄/1.0 equiv of Et₃N/1,4-dioxane/100 °C] provided the desired arylated product 5.2a in 75% isolated yield (entry 18), thus manifesting the importance of Et₃N on the para-selective C–H difluoroalkylation of arenes.

Table 5.3. Bases Remarkably Affected Selectivity between Benzylation and Arylation

<table>
<thead>
<tr>
<th>entry</th>
<th>base (mol%)</th>
<th>5.2a (%)</th>
<th>5.2b (%)</th>
<th>PhCOCF₂H (%)</th>
</tr>
</thead>
<tbody>
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<td>-</td>
<td>0</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>butyronitrile (300)</td>
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<td>88</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Na₂CO₃ (300)</td>
<td>0</td>
<td>91</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>PhONa (100)</td>
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<td>0</td>
<td>18</td>
</tr>
<tr>
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<td>PhCO₂K (100)</td>
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<td>71</td>
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<td>6</td>
<td>pyridine (100)</td>
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<td>85</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>N, N-dimethylaniline (100)</td>
<td>0</td>
<td>89</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>DMAP (100)</td>
<td>54</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>N(n-Pr)₃ (100)</td>
<td>58</td>
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</tr>
<tr>
<td>10</td>
<td>Et₃N (100)</td>
<td>70</td>
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<td>6</td>
</tr>
<tr>
<td>11</td>
<td>TMEDA (100)</td>
<td>69</td>
<td>5</td>
<td>8</td>
</tr>
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<td>1</td>
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<tr>
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<td>DIPEA (100)</td>
<td>12</td>
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<td>14</td>
<td>Et₃N (50)</td>
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<td>Et₃N (10)</td>
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<td>4</td>
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<tr>
<td>17</td>
<td>Et₃N (300)</td>
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<tr>
<td>18</td>
<td>Et₃N (100)</td>
<td>82 (75)</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

a Yields were determined by 19F NMR using α,α,α-trifluorotoluene as an internal standard.

b Full conversion was observed.

c The optimized conditions: 5.1 (0.5 mmol), Pd(PPh₃)₄ (5 mol%), Et₃N (1.0 equiv), 1,4-dioxane (0.05 M), 100 °C, 12 h. 19F NMR yields were determined using α,α,α-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs).
A variety of substrates bearing distinct electronic properties and substituent patterns on benzylic moieties underwent the decarboxylative arylation to incorporate a \(\alpha,\alpha\)-difluoroketone moiety at the para-position of arenes relative to the methyl group (Table 5.4). Generally, ortho-substituted electron-rich (5.3a–b) and -deficient (5.3c–d) substrates provided the arylated products (5.4a–d) in modest to high yields. Particularly, in the case of the substrate 5.3d, no benzylated product was observed by \(^{19}\)F NMR. The reaction of the substrate (5.3e) bearing a bulky phenyl group on the ortho-position of the aromatic ring gave the product (5.4e) in modest yield. In this reaction of the substrates 5.3e, we isolated 35% of the major side product, 9\(H\)-fluorene, which might come from an intramolecular cyclization reaction. Moreover, substrates bearing a coordinating group (5.3f–g) at the ortho-positions tolerated the present reaction and produced the arylated products (5.4f–g) in good yields and selectivity using higher catalyst loading and increasing reaction temperatures. Even a non-substituted simple benzyl substrate (5.3h) was transformed to the arylated product (5.4h) in modest yield and selectivity. This example demonstrated Et\(_3\)N rather than the substitution pattern of arenes played a key factor for the catalytic para-C–H arylation reaction. However, meta-substituted substrates provided lower yields of arylated products than their ortho-substituted counterparts (5.4i vs 5.4a, and 5.4j vs 5.4d). This trend might derive from the steric hindrance imparted by the meta-substituent to the para-position that disfavors the attack of \(\alpha,\alpha\)-difluoroketone enolates, thus reducing the yields and selectivity towards arylated products.
The decarboxylative arylation reaction also converted substrates bearing a variety of aryl, heteroaryl, and alkyl α,α-difluoroketones into the products (Table 5.5). The substrate bearing an electron-neutral aryl α,α-difluoroketone moiety (5.5a) provided the arylated product (5.6a) in high yields. Even, heteroaryl-containing α,α-difluoroketone substrate (5.5b) worked well under the standard reaction conditions. The tolerance to S- and N-containing heterocycles represented potential application of the current reaction toward accessing fluorinated analogues of biologically active molecules. Additionally, the reaction of an aliphatic α,α-difluoroketone substrate (5.5c) afforded good yield of the arylated product (5.6c) without further optimization.
The α-aryl-α,α-difluoroketone products likely derive from a pathway that differs from that proposed for the formation of α-benzyl-α,α-difluoroketone products (Figure 5.1). In decarboxylative benzylation reactions, the α,α-difluoroketone enolate reacts with the benzylic position of (η^3-exobenzyl)palladium(II) intermediate by a S_N2-like reductive elimination, and forms the key C(α)–C(sp^3) bond (A, path a).\(^{13}\) However, in the present decarboxylative C–H arylation reaction, the α,α-difluoroketone enolate might attack the para-position of the aromatic ring to form a dearomatized product (B, path b), which could undergo Et_3N-facilitated rearomatization to generate the α-aryl-α,α-difluoroketone products (B→D, path b).
Such regioselective benzyl ation and arylation reactions have been reported by the Tunge lab (Figure 5.2). In the reactions, the use of the bidentate (S)-DTBM SEGPHOS ligand provided benzylated products, while the utilization of the monodentate PPh₃ ligand generated arylated products. Thus, the selectivity between benzylation and arylation is controlled by the ligands. However, in our cases, Et₃N seems to play an important role in switching the selectivity from benzylation to arylation.
In support of the proposed arylation mechanism, the Kuwano lab illustrated benzylic carbonates bearing an internal nucleophile undergo the palladium-catalyzed cyclization reactions with the nucleophile attacking the *para*-position to form a dearomatized product that rearomatizes to the final product (Scheme 5.9A).\(^{15a}\) Moreover, the Yamamoto and Bao labs have reported intermolecular palladium-catalyzed dearomatization reactions, in which the nucleophiles, including allyltributylstannane and secondary amines, attack the aromatic *para*-position instead of the benzylic position to generate dearomatized and C–N coupling products (Scheme 5.9B and 5.9C).\(^{15b,c}\) Additionally, the Tunge lab demonstrated decarboxylative coupling reactions of benzyl enol carbonates that can provide dearomatized and arylated ketone products using different palladium catalysts (Scheme 5.9D).\(^{15d}\)
The proposed arylation mechanism involves a dearomatization-rearomatization process, in which a proton shifts from the C5 (para-position) to the C1 (benzylic position) position. To confirm the involvement of a 1,5-prototropic shift in our arylation reaction, we prepared a deuterium-labeled substrate with deuterium incorporated on the C5 position to observe if the deuterium could relocate to the C1 position (Scheme 5.10).

The synthesis of the deuterium-labeled substrate 5.7 started with the commercially available 2-isopropylaniline, which underwent bromination followed by one-pot two-step nitration and iodination to generate aryl iodide 5.7-4. Subsequent formylation of aryl iodide 5.7-4 and reduction of the aldehyde 5.7-3 formed benzyl alcohol 5.7-2, which coupled with deuterated sodium formate to produce deuterated alcohol 5.7-1. Finally, the esterification of deuterated alcohol 5.7-1 with α,α-difluoro-β-keto acetate provided the deuterium-labeled probe 5.7 (95% of deuterium content) in good yields (Scheme 5.11).
To test the proposed 1,5-deuteron shift, the deuterium-labeled substrate 5.7 was subjected to the standard catalytic conditions (Scheme 5.12). This reaction generated the product 5.7a with deuterium relocated to the C1 (benzylic position) in the yield (71%) comparable to the non-deuterium-labeled counterpart 5.4b (77%). The result was consistent with the proposed mechanism. The dearomatization-rearomatization process occurs during the reactions and Et$_3$N might serve as a proton shuttle to facilitate such a process.

[Scheme 5.12. [1,5]-Deuteron Shift of Deuterium-Labeled Probe Occurred in the Present Reaction]

![Scheme 5.12 Diagram](image_url)
Meanwhile, we still cannot exclude out the role of Et$_3$N as a nucleophile. For this, another mechanism is also considered for selective para-fluoroalkylation reaction of arenes (Scheme 5.13). In this mechanism, Et$_3$N might serve as a nucleophile to attack the benzylic position of ($\eta^3$-exobenzyl)palladium(II) intermediate and generate an activated benzylic electrophile $E$. Then, the benzylic electrophile $E$ reacts with the $\alpha,\alpha$-difluoroketone enolate to form a dearomatized product, which rearomatizes to provide the arylated product.

![Scheme 5.13. Another Possible Mechanism with Et$_3$N Serving as a Nucleophile](image)

More studies to explain the role of Et$_3$N are necessary. Currently, mechanistic studies aiming to understand the origin for the selective para-C–H difluoroalkylation of arenes are in progress. This part of work is performed by Dr. Francisco de Azambuja in the lab. The proposed studies include 1) kinetic isotope effect (KIE) to understand if the cleavage of para-C–H bond is the rate-determining step; 2) the use of stoichiometric amount of deuterated methanol as an additive to see if the reaction involves the insertion of Pd catalyst into the C–H bond; 3) cross-over experiments to probe if the $\alpha,\alpha$-difluoroketone enolate dissociates from the ($\pi$-benzyl)palladium(II) complex; 4) competitive experiments of deuterated and non-deuterated substrates to probe the slowest step: oxidative addition or reductive elimination, and the role of Et$_3$N in the reaction; and 5) NMR experiments to elucidate if new intermediates form under the catalytic conditions. These results will be reported in the future.
5.3 Conclusion

Remote \textit{para}-\textit{C–H} functionalization of arenes has been a challenging topic. Current methods for \textit{para}-selective activation of C–H bonds mainly rely on electronic control of substrates, and utilization of auxiliary groups, which causes limited substrate scope, and contradicts atom economy, respectively. In contrast, the ability to use simple additives to direct a catalytic reaction to a remote position provides a new and complementary opportunity for C–H functionalization reactions. We reported a palladium-catalyzed decarboxylative C–H difluoroalkylation reaction of arenes, in which Et$_3$N overrides the anticipated coupling pathway, and instead provides a C–H functionalization product with \textit{para}-selectivity. This base-enabled C–H transformation tolerates electron-rich and -deficient substrates, and should provide an alternative strategy for designing \textit{para}-selective functionalization reactions.


Chapter 5 Appendix

Experimental Procedures and Spectral Analyses for Compounds in Chapter 5
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**General Information**

Unless otherwise noted, reactions were performed under an atmosphere of N\textsubscript{2} using oven-dried glassware. Palladium-catalyzed reactions were performed in 1 dram vials and 20 mL pressure-resistant scintillation vials, which were sealed with PTFE-lined silicone septa, and all other reactions were performed in round-bottom flasks that were sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualizing by quenching of fluorescence, or by staining with KMnO\textsubscript{4}, anisaldehyde, phosphomolybdic acid or iodine. Column chromatography was conducted using an automated and manual system for purifying substrates and catalytic products, respectively. In most cases, arylated and benzylated products are very close to each other or on the same spot on TLC plate. To visualize their separation, the staining reagent phosphomolybdic acid can be used to distinguish arylated and benzylated products while they represent different color. \textsuperscript{19}F NMR yields and isolated yields reported in the manuscript represent an average of at least two independent runs of material deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment.

Unless otherwise noted, reagents were purchased from commercial sources, and used as received. 1,4-Dioxane (anhydrous), Pd(PPh\textsubscript{3})\textsubscript{4} (reagent grade, 99%), and Et\textsubscript{3}N (anhydrous) were purchased from Sigma Aldrich. Solvents including DMF, PhMe, CH\textsubscript{2}Cl\textsubscript{2}, THF, MeOH were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon.

Proton nuclear magnetic resonance (\textsuperscript{1}H NMR) spectra and carbon nuclear magnetic resonance (\textsuperscript{13}C NMR) spectra were recorded on Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively) or Bruker 500 AVANCE spectrometer (500 and 125 MHz, respectively). Chemical shifts (\(\delta\)) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to proton resonance of residual CHCl\textsubscript{3} in the NMR solvent (CHCl\textsubscript{3}: \(\delta = 7.27\) ppm or DMSO-d\textsubscript{6}: \(\delta = 2.50\) ppm).
Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonances of the solvent residual peak (CDCl₃: δ = 77.23 ppm or DMSO-d₆: δ = 39.51 ppm). Fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded on a Bruker 400 AVANCE spectrometer (376 MHz). ¹⁹F NMR chemical shifts (δ) are reported in ppm upfield from trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pent, m = multiplet), coupling constant in Hertz (Hz), integration. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier™ mass spectrometer or by atmospheric-pressure chemical ionization (APCI–hexane/PhMe) on a Waters Q-Tof Premier™, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as ionization solvent. Infrared spectra were measured at a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer. Uncorrected melting points were measured on Thomas Hoover Capillary Melting Point apparatus.

**Preparation of Known Compounds**

2-methylbenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate **5.1**, 2-methoxybenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate **5.3a**, benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate **5.3h**, 3-(trifluoromethyl)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate **5.3j**, Potassium 2,2-difluoro-3-oxo-3-phenylpropanoate, potassium 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate, potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate, potassium 2,2-difluoro-3-oxo-3-(3-(trifluoromethyl)phenyl)propanoate potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate, potassium 2,2-difluoro-3-oxo-3-(1-phenyl-1H-pyrazol-4-yl)propanoate, and potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate were prepared according to previous reports in our group.¹

**General Procedure for Screening Conditions**

An oven-dried 1 dram vial was charged with substrate **5.1** (0.100 mmol), Pd catalysts, ligands (for ligand screening), bases (for base screening), a magnetic stir bar, and anhydrous solvents inside the glove box. Subsequently, the vial was sealed with a PTFE-lined screw cap, and transferred out of the glove box. The
sealed vial was placed on a pre-heated reaction block at the indicated temperature with stirring for 24 h. The vial was cooled to rt, and the mixture was diluted with EtOAc (0.5 mL). α,α,α-Trifluorotoluene (10 μL, 0.0814 mmol) was added as an internal standard, and the reaction mixture was stirred at rt at least 20 min to ensure thorough mixing. An aliquot was taken from the vial for 19F NMR analysis.

**Initial Screening and Optimization of Reaction Conditions**

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>arylation (%)</th>
<th>benzylation (%)</th>
<th>PhCOCF₂H (%)</th>
<th>conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>P(4-CF₃C₆H₄)₃</td>
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<td>1</td>
<td>2</td>
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<td>2</td>
<td>PF₃</td>
<td>33</td>
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<tr>
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<td>PF₃(4-OMeC₆H₄)</td>
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<td>93</td>
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<td>PF₃(4-OMeC₆H₄)₂</td>
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<td>0</td>
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<td>37</td>
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</tbody>
</table>

Other ligands screened that produced < 25% arylated product by 19F NMR analysis were shown below.

![Chemical Structures](image)

Yields were determined by 19F NMR using α,α,α-Trifluorotoluene as an internal standard.
Table 2. Solvents Affected Selectivity between Benzylation and Arylation\textsuperscript{a,b}

<table>
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<tr>
<th>entry</th>
<th>solvent</th>
<th>5.2a (%)</th>
<th>5.2b (%)</th>
<th>PhCOCF\textsubscript{2}H (%)</th>
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<td>97</td>
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<td>1,4-dioxane</td>
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<td>quant.</td>
<td>0</td>
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<tr>
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<td>45</td>
<td>8</td>
<td>25</td>
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<tr>
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<td>47</td>
<td>8</td>
<td>27</td>
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<tr>
<td>8</td>
<td>DMSO</td>
<td>24</td>
<td>6</td>
<td>50</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yields were determined by \textsuperscript{19}F NMR using \textit{α,α,α}-trifluorotoluene as an internal standard.

\textsuperscript{b} Full conversion was observed except for entry 4 (conv. 97\%).
Table 3. Bases Remarkably Affected Selectivity between Benzylation and Arylation\textsuperscript{a,b}

\begin{tabular}{|c|c|c|c|c|}
\hline
entry & base (mol\%) & 5.2a (%) & 5.2b (%) & PhCOCF\textsubscript{2}H (%) \\
\hline
1 & - & 0 & 89 & 0 \\
2 & butyronitrite (300) & 0 & 88 & 3 \\
3 & Na\textsubscript{2}CO\textsubscript{3} (300) & 0 & 91 & 3 \\
4 & PhONa (100) & 0 & 0 & 18 \\
5 & PhCO\textsubscript{2}K (100) & 2 & 71 & 6 \\
6 & pyridine (100) & 4 & 85 & 0 \\
7 & N, N-dimethylaniline (100) & 0 & 89 & 2 \\
8 & DMAP (100) & 54 & 4 & 17 \\
9 & N(n-Pr\textsubscript{3}) (100) & 58 & 13 & 6 \\
10 & Et\textsubscript{3}N (100) & 70 & 5 & 6 \\
11 & TMEDA (100) & 69 & 5 & 8 \\
12 & quinuclidine (100) & 12 & 1 & 10 \\
13 & DIPEA (100) & 12 & 68 & 4 \\
14 & Et\textsubscript{3}N (50) & 65 & 7 & 5 \\
15 & Et\textsubscript{3}N (25) & 63 & 11 & 5 \\
16 & Et\textsubscript{3}N (10) & 49 & 26 & 4 \\
17 & Et\textsubscript{3}N (300) & 69 & 5 & 5 \\
18\textsuperscript{c} & Et\textsubscript{3}N (100) & 82 (75) & 7 & 6 \\
\hline
\end{tabular}

\textsuperscript{a} Yields were determined by \textsuperscript{19}F NMR using \textsuperscript{19}F,\textsuperscript{19}F,\textsuperscript{19}F-trifluorotoluene as an internal standard.
\textsuperscript{b} Full conversion was observed.
\textsuperscript{c} The optimized conditions: 5.1 (0.5 mmol), Pd(PPh\textsubscript{3})\textsubscript{4} (5 mol\%), Et\textsubscript{3}N (1.0 equiv), 1,4-dioxane (0.05 M), 100 °C, 12 h. \textsuperscript{19}F NMR yields were determined using \alpha,\alpha,\alpha-trifluorotoluene as an internal standard (average of two runs). The value in parentheses indicates the isolated yield (average of two runs).

Experimental Procedures for Pd-Catalyzed Arylation of \(\alpha,\alpha\)-Difluoroketone Enolates

General Procedure A: An oven-dried 20 mL scintillation vial was charged with substrate 5.1, 5.3a–j (0.500 mmol), Et\textsubscript{3}N (70 \(\mu\)L, 0.500 mmol), Pd(PPh\textsubscript{3})\textsubscript{4} (14.4 mg, 0.0125 mmol), and a magnetic stir bar. Dry 1,4-dioxane (0.010 L) was added \textit{via} a syringe. Subsequently, the vial was sealed, transferred out of the glove box and placed on a pre-heated reaction block at 100 °C, and stirred for 12 h. The vial was
cooled to rt, and the mixture was diluted with EtOAc (1 mL). α,α,α-Trifluorotoluene (30 µL, 0.2443 mmol) was added as an internal standard, and the reaction mixture was stirred at rt for 15 mins to ensure thorough mixing. An aliquot was taken from the vial for 19F NMR analysis. After determining the 19F yield, the aliquot was recombined with the reaction mixture. The total reaction mixture was passed through a plug of celite, and eluted with EtOAc. Removal of the solvents under reduced pressure and chromatographic purification provided the desired product 5.2a and 5.4a–j.

Experimental Procedures and Characterization of Compounds for Table 5.3

![2-(3,4-dimethylphenyl)-2,2-difluoro-1-phenylethanone (5.2a)](image)

2-(3,4-dimethylphenyl)-2,2-difluoro-1-phenylethanone (5.2a)

General procedure A was followed using 5.1 (152 mg, 0.500 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), Et₃N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound 5.2a as an off-white solid (100 mg, 77%). ¹H NMR (CDCl₃, 400 MHz) δ 8.04–8.01 (m, 2 H), 7.61–7.56 (m, 1 H), 7.47–7.42 (m, 2 H), 7.37 (s, 1 H), 7.37–7.35 (m, 1 H), 7.22 (d, J = 8.0 Hz, 1 H), 2.29 (s, 6 H). ¹³C NMR (CDCl₃, 125 MHz) δ 189.4 (t, J = 31.2 Hz), 140.1, 137.6, 134.3, 132.4, 130.7 (t, J = 25.2 Hz), 130.5 (t, J = 2.7 Hz), 130.3, 128.8, 126.8 (t, J = 5.8 Hz), 123.1 (t, J = 5.9 Hz), 117.2 (t, J = 252.6 Hz), 20.1, 19.9. ¹⁹F NMR (CDCl₃, 376 MHz) δ –97.6 (s, 2 F). IR (film) 3061, 2924, 1701, 1597, 1580, 1504, 1449, 1300, 1261, 1175, 1126, 918, 851, 826, 723, 685, 644, 517 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₆H₁₄F₂ONa [M+Na]⁺ 283.0910, found 283.0921. mp 47–48 °C.

Experimental Procedures and Characterization of Compounds for Table 5.4

General Procedure B: An oven-dried one-neck round-bottom flask was charged with aldehyde (14 mmol). Methanol (30 mL) was added as solvent, followed by the addition of NaBH₄ (21 mmol) as solid portion. The reaction mixture was stirred at 0 °C for 30 min. H₂O was added to quench the reaction, and methanol
was removed under reduced pressure. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL) three times and the combined organic phases were dried over anhydrous MgSO$_4$ or Na$_2$SO$_4$, filtered and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (0% to 30%) for elution to afford the desired benzyl alcohol.

**General Procedure C:** An oven-dried one-neck round-bottom flask was charged with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate (7.2 mmol), and the system was evacuated and backfilled with N$_2$(g) three times. Dry CH$_2$Cl$_2$ (35 mL) and DMF (0.19 mL) were added $via$ a syringe, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (6.9 mmol) was added dropwise, and then the reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. Next, a solution of benzyl alcohol derivative (6.0 mmol) dissolved in dry CH$_2$Cl$_2$ (3.0 mL) was added dropwise at 0 °C, followed by dropwise addition of Et$_3$N (12 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min, and rt for 2.5 h. H$_2$O (10 mL) was added to quench the reaction, and the CH$_2$Cl$_2$ was removed under reduced pressure. The aqueous layer was extracted with ether (3 x 25 mL), and the combined organic layers were dried over anhydrous MgSO$_4$ or Na$_2$SO$_4$, filtered, and concentrated. Purification by flash chromatography provided the desired product.

![chemical structure](image)

**2,2-difluoro-2-(3-methoxy-4-methylphenyl)-1-phenylethanone (5.4a)**

General procedure A was followed using 5.3a (160 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (14.4 mg, 0.0125 mmol), Et$_3$N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 110 °C. Workup and chromatographic purification (10% to 25% DCM in hexanes) provided the title compound 5.4a as an off-white solid (100 mg, 72%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.03 (dt, $J = 7.4$, 1.1 Hz, 2 H), 7.59 (ddt, $J = 7.9$, 6.9, 1.3 Hz, 1 H), 7.47–7.42 (m, 2 H), 7.21 (d, $J = 7.6$ Hz, 1 H), 7.11 (d, $J = 8.0$ Hz, 1 H), 7.03 (s, 1 H), 3.85 (s, 3 H), 2.24 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 189.3 (t, $J = 30.6$ Hz), 158.2, 134.3, 132.4, 131.9 (t, $J = 25$ Hz), 131.1, 130.5 (t, $J = 2.5$ Hz), 130.3, 128.8, 117.6 (t, $J = 6.2$ Hz), 117.1 (t, $J = 251.2$ Hz)
Hz), 106.9 (t, $J = 5.6$ Hz), 55.6, 16.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –97.6 (s, 2 F). IR (film) 2959, 2938, 1699, 1597, 1508, 1450, 1410, 1294, 1265, 1223, 1175, 1128, 1047, 918, 849, 822, 712, 687, 656 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{14}$F$_2$O$_2$ [M]$^+$ 276.0962, found 276.0952. mp 51–52 °C.

(2-isopropylphenyl)methanol (5.3b-1)

General procedure B was followed using 2-isopropylbenzaldehyde$^2$ (1.97 g, 13.3 mmol), NaBH$_4$ (0.760 g, 20.0 mmol), and MeOH (28 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 5.3b-1 as a colorless oil (1.68 g, 84%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.37–7.29 (m, 3 H), 7.20 (td, $J = 7.1$, 1.7 Hz, 1 H), 4.77 (d, $J = 5.6$ Hz, 2 H), 3.28 (hept, $J = 6.8$ Hz, 1 H), 1.51 (t, $J = 6.0$ Hz, 1 H), 1.27 (d, $J = 6.8$ Hz, 6 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 147.4, 137.5, 128.6, 128.5, 126.1, 125.7, 63.5, 28.8, 24.2. IR (film) 3342, 2962, 2928, 2870, 1489, 1450, 1385, 1184, 1034, 1005, 758 cm$^{-1}$.

2-isopropylbenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.3b)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^1$ (1.4 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.8 mmol), 5.3b-1 (0.75 g, 5.0 mmol), Et$_3$N (1.4 mL, 10 mmol), DMF (0.15 mL), and CH$_2$Cl$_2$ (30 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 5.3b as a colorless oil (1.35 g, 81%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.04 (dd, $J = 8.8$, 1.2 Hz, 2 H), 7.69–7.64 (m, 1 H), 7.49 (dd, $J = 8.4$, 7.4 Hz, 2 H), 7.38–7.28 (m, 3 H), 7.17 (ddd, $J = 7.5$, 6.7, 1.9 Hz, 1 H), 5.41 (s, 2 H), 3.09 (hept, $J = 6.8$ Hz, 1 H), 1.20 (d, $J = 6.8$ Hz, 12 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.4 (t, $J = 27.5$ Hz), 161.9 (t, $J = 30.6$ Hz), 148.6, 135.3, 131.1 (t, $J = 1.9$ Hz), 259
130.7, 130.4, 130.1 (t, J = 1.9 Hz), 130.0, 129.1, 126.1, 126.0, 110.0 (t, J = 263.7 Hz), 67.6, 29.2, 24.1.

$^{19}$F NMR (CDCl$_3$, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3067, 2966, 1774, 1715, 1699, 1599, 1493, 1450, 1385, 1308, 1257, 1157, 1101, 922, 802, 760, 712, 685 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{19}$H$_{18}$F$_2$O$_3$K [M+K]$^+$ 371.0861, found 371.0862.

**2,2-difluoro-2-(3-isopropyl-4-methylphenyl)-1-phenylethanone (5.4b)**

General procedure A was followed using 5.3b (166 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (14.4 mg, 0.0125 mmol), Et$_3$N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound 5.4b as a colorless oil (112 mg, 78%). $^1$H NMR (CDCl$_3$, 500 MHz) δ 8.03 (dt, J = 8.3, 1.2 Hz, 2 H), 7.60–7.57 (m, 1 H), 7.48 (d, J = 2.0 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.32 (dd, J = 8.0, 2.0 Hz, 1 H), 7.21 (d, J = 8.0 Hz, 1 H), 3.16 (hept, J = 6.9 Hz, 1 H), 2.37 (s, 3 H), 1.22 (d, J = 6.9 Hz, 6 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 189.5 (t, J = 31.2 Hz), 147.9, 138.6, 134.3, 132.5, 131.1 (t, J = 25.0 Hz), 130.8, 130.5 (t, J = 2.9 Hz), 128.8, 122.9 (t, J = 5.9 Hz), 122.2 (t, J = 5.8 Hz), 117.4 (t, J = 252.7 Hz), 29.6, 23.2, 19.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) δ –97.6 (s, 2 F). IR (film) 3063, 2965, 1703, 1597, 1499, 1449, 1252, 1221, 1182, 1132, 920, 885, 826, 714, 687 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{18}$H$_{18}$F$_2$ONa [M+Na]$^+$ 311.1223, found 311.1216.

**methyl 2-(((2,2-difluoro-3-oxo-3-phenylpropanoyl)oxy)methyl)benzoate (5.3c)**

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^1$ (1.9 g, 7.9 mmol), oxalyl chloride (0.64 mL, 7.6 mmol), methyl 2-(hydroxymethyl)benzoate$^3$ (1.1 g, 6.6 mmol), Et$_3$N (1.8 mL, 13 mmol), DMF (0.20 mL), and CH$_2$Cl$_2$ (40 mL). Workup and chromatographic purification (5%
to 10% EtOAc in hexanes) afforded the title compound 5.3c as a colorless oil (1.4 g, 61%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.09 (dt, $J = 7.4$, 1.0 Hz, 2 H), 8.02 (dd, $J = 7.6$, 1.2 Hz, 1 H), 7.70–7.66 (m, 1 H), 7.54–7.49 (m, 3 H), 7.44–7.39 (m, 2 H), 5.78 (s, 2 H), 3.88 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.5 (t, $J = 27.5$ Hz), 167.0, 161.7 (t, $J = 30.6$ Hz), 135.8, 135.3, 132.9, 131.3, 131.2, 130.2 (t, $J = 2.5$ Hz), 129.2, 128.6 (overlap), 128.5, 110.1 (t, $J = 263.1$ Hz), 67.6, 52.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.7 (s, 2 F). IR (film) 3071, 2955, 1778, 1714, 1697, 1599, 1582, 1493, 1450, 1435, 1383, 1306, 1269, 1128, 1082, 959, 924, 791, 741, 712, 687, 582 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{18}$H$_{14}$F$_2$O$_5$Na [M+Na]$^+$ 371.0707, found 371.0703.

![Image 5.4c](image)

**methyl 5-(1,1-difluoro-2-oxo-2-phenylethyl)-2-methylbenzoate (5.4c)**

General procedure A was followed using 5.3c (174 mg, 0.500 mmol), Pd(PPh$_3$)$_4$ (28.9 mg, 0.0250 mmol), Et$_3$N (70 $\mu$L, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 120 °C. Workup and chromatographic purification (15% to 50% DCM in hexanes) provided the title compound 5.4c as a colorless oil (100 mg, 66%; a 11:1 mixture of the arylated to benzylated isomers by $^{19}$F NMR analysis). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.18 (d, $J = 2.0$ Hz, 1 H), 8.06–8.03 (m, 2 H), 7.64–7.59 (m, 2 H), 7.49–7.45 (m, 2 H), 7.36 (d, $J = 8.0$ Hz, 1 H), 3.91 (s, 3 H), 2.65 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 188.9 (t, $J = 31.2$ Hz), 167.2, 143.7, 134.6, 132.6, 132.1, 131.0 (t, $J = 25.0$ Hz), 130.5 (t, $J = 3.1$ Hz), 130.3, 129.1 (t, $J = 5.6$ Hz), 128.9, 128.2 (t, $J = 5.6$ Hz), 116.8 (t, $J = 252.5$ Hz), 52.3, 21.9. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –97.9 (s, 2 F). IR (film) 3073, 2953, 1732, 1703, 1597, 1449, 1310, 1267, 1229, 1132, 1084, 970, 907, 835, 779, 721, 687, 644 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{17}$H$_{14}$F$_2$O$_3$Na [M+Na]$^+$ 327.0809, found 327.0821.
2-(trifluoromethyl)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.3d)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate\(^1\) (0.86 g, 3.6 mmol), oxalyl chloride (0.29 mL, 3.4 mmol), 2-trifluoromethylbenzyl alcohol (0.53 g, 3.0 mmol), Et\(_3\)N (0.83 mL, 6.0 mmol), DMF (93 \(\mu\)L), and CH\(_2\)Cl\(_2\) (18 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 5.3d as a colorless oil (0.70 g, 65%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.09–8.06 (m, 2 H), 7.71–7.66 (m, 2 H), 7.58–7.45 (m, 5 H), 5.54 (s, 2 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 185.4 (t, \(J = 27.5\) Hz), 161.7 (t, \(J = 30.6\) Hz), 135.4, 132.5, 132.1, 131.0 (t, \(J = 1.9\) Hz), 130.3, 130.1 (t, \(J = 2.5\) Hz), 129.2, 129.1, 128.6 (q, \(J = 30.9\) Hz), 126.4 (q, \(J = 5.4\) Hz), 124.1 (q, \(J = 272.1\) Hz), 110.1 (t, \(J = 263.7\) Hz), 65.4 (q, \(J = 2.9\) Hz). \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –107.7 (s, 2 F), –60.4 (s, 3 F). IR (film) 3075, 1780, 1701, 1599, 1450, 1315, 1167, 1121, 1061, 924, 770, 712, 685, 654, 581 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{17}\)H\(_{11}\)F\(_5\)O\(_3\)Na [M+Na\(^+\)] \(381.0526\), found 381.0536.

2,2-difluoro-2-(4-methyl-3-(trifluoromethyl)phenyl)-1-phenylethanone (5.4d)

General procedure A was followed using 5.3d (179 mg, 0.500 mmol), Pd(PPh\(_3\))\(_4\) (28.9 mg, 0.0250 mmol), Et\(_3\)N (70 \(\mu\)L, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 18 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound 5.4d as a colorless oil (131 mg, 83%). \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 8.08–8.06 (m, 2 H), 7.87 (d, \(J = 1.9\) Hz, 1 H), 7.66–7.62 (m, 2 H), 7.51–7.48 (m, 2 H), 7.41 (d, \(J = 8.0\) Hz, 1 H), 2.54 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 188.7 (t, \(J = 31.5\) Hz), 140.2 (m), 134.7, 132.7, 132.0, 131.3 (t, \(J = 25.8\) Hz), 130.5 (t, \(J = 2.8\) Hz), 129.8 (q, \(J = 30.7\) Hz), 129.2 (t, \(J = 5.8\) Hz), 129.0, 124.1 (q, \(J = 272.5\) Hz), 123.5 (h, \(J = 5.8\) Hz), 116.8 (t,


$J = 254.4 \text{ Hz}$, 19.5 (m). $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –97.8 (s, 2 F), –62.5 (s, 3 F). IR (film) 3075, 2940, 1705, 1597, 1504, 1450, 1327, 1236, 1211, 1175, 1130, 1059, 1026, 905, 833, 806, 716, 687, 673, 613 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{12}$F$_5$O [M+H]$^+$ 315.0808, found 315.0800.

[1,1'-biphenyl]-2-ylmethanol (5.3e-1)

Compound 5.3e-1 was prepared from a known procedure$^4$ using 2-phenylbenzoic acid (2.0 g, 10 mmol), LAH (0.76 g, 20 mmol), and THF (50 mL) under refluxing. Workup and chromatographic purification (10% to 15% EtOAc in hexanes) provided the title compound 5.3e-1 as an off-white solid (1.37 g, 74%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.57 (dd, $J = 7.2$, 2.0 Hz, 1 H), 7.46–7.35 (m, 7 H), 7.30 (dd, $J = 7.0$, 1.8 Hz, 1 H), 4.64 (d, $J = 6.0$ Hz, 2 H), 1.57 (t, $J = 5.8$ Hz, 1 H). Spectroscopic data matched that from the previous report.$^5$ mp 43–44 °C (lit. 44 °C).$^6$

[1,1'-biphenyl]-2-ylmethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.3e)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^1$ (1.3 g, 5.4 mmol), oxalyl chloride (0.44 mL, 5.2 mmol), 5.3e-1 (0.83 g, 4.5 mmol), Et$_3$N (1.2 mL, 9.0 mmol), DMF (0.14 mL), and CH$_2$Cl$_2$ (30 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 5.3e as a colorless oil (1.45 g, 88%).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.06 (dd, $J = 8.4$, 1.6 Hz, 2 H), 7.71–7.66 (m, 1 H), 7.51 (t, $J = 7.8$ Hz, 2 H), 7.46–7.26 (m, 9 H), 5.26 (s, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.4 (t, $J = 26.9$ Hz), 161.7 (t, $J = 30.6$ Hz), 143.0, 140.0, 135.3, 131.2 (overlap), 130.4, 130.2, 130.1 (t, $J = 2.5$ Hz), 129.3, 129.2 (overlap), 128.5, 127.9, 127.7, 110.0 (t, $J = 263.7$ Hz), 67.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.8 (s, 2 F). IR (film) 3063, 3028, 1771, 1715, 1699,
1599, 1481, 1450, 1099, 1011, 922, 802, 746, 704, 685, 582 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{22}\)H\(_{16}\)F\(_2\)O\(_3\)Na [M+Na]\(^+\) 389.0965, found 389.0979.

### 2,2-difluoro-2-(6-methyl-[1,1'-biphenyl]-3-yl)-1-phenylethanone (5.4e)

General procedure A was followed using 5.3e (183 mg, 0.500 mmol), Pd(PPh\(_3\))\(_4\) (28.9 mg, 0.0250 mmol), Et\(_3\)N (70 \(\mu\)L, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (5% to 25% DCM in hexanes) provided the title compound 5.4e as a colorless oil (86 mg, 53%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 8.09–8.07 (m, 2 H), 7.63–7.59 (m, 1 H), 7.54–7.37 (m, 8 H), 7.34–7.31 (m, 2 H), 2.33 (s, 3 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 189.2 (t, \(J\) = 31.2 Hz), 142.7, 140.9, 138.9 (t, \(J\) = 2.5 Hz), 134.4, 132.4, 131.1, 130.9 (t, \(J\) = 25 Hz), 130.5 (t, \(J\) = 2.5 Hz), 129.3, 128.8, 128.4, 127.5, 127.1 (t, \(J\) = 5.6 Hz), 124.6 (t, \(J\) = 6.2 Hz), 117.2 (t, \(J\) = 251.2 Hz), 20.7. \(^19\)F NMR (CDCl\(_3\), 376 MHz) \(\delta\) –97.6 (s, 2 F). IR (film) 3059, 3028, 1703, 1597, 1489, 1449, 1267, 1227, 1128, 1105, 899, 827, 770, 702, 687 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{21}\)H\(_{17}\)F\(_2\)O [M+H]\(^+\) 323.1247, found 323.1244.

### (2-(methylthio)phenyl)methanol (5.3f-1)

Compound 5.3f-1 was prepared from a known procedure\(^4\) using 2-(methylthio)benzoic acid (1.3 g, 8.0 mmol), LAH (0.61 g, 16 mmol), and THF (40 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) provided the title compound 5.3f-1 as a colorless oil (1.1 g, 89%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.39 (d, \(J\) = 7.6 Hz, 1 H), 7.33–7.27 (m, 2 H), 7.22–7.18 (m, 1 H), 4.77 (s, 2 H), 2.50 (s, 3 H), 2.50 (s, 3 H),
2.13 (br, 1 H). Spectroscopic data matched that from the previous report. HRMS (ESI, m/z): calcd for C₈H₉OS [M-H]+ 153.0374, found 153.0369.

2-(methylthio)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.3f)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate¹ (1.8 g, 7.8 mmol), oxalyl chloride (0.63 mL, 7.5 mmol), 5.3f-1 (1.0 g, 6.5 mmol), Et₃N (1.8 mL, 13 mmol), DMF (0.20 mL), and CH₂Cl₂ (38 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 5.3f as a colorless oil (1.74 g, 80%). ¹H NMR (CDCl₃, 400 MHz) δ 8.06 (dt, J = 7.6, 1.1 Hz, 2 H), 7.66 (tt, J = 7.6, 1.4 Hz, 1 H), 7.52–7.47 (m, 2 H), 7.35–7.28 (m, 3 H), 7.18–7.14 (m, 1 H), 5.46 (s, 2 H), 2.43 (s, 3 H). ¹³C NMR (CDCl₃, 125 MHz) δ 185.3 (t, J = 26.9 Hz), 161.8 (t, J = 30.6 Hz), 138.7, 135.2, 132.2, 131.2, 130.1 (t, J = 2.5 Hz), 129.8 (overlap), 129.1, 127.5, 125.7, 109.9 (t, J = 263.1 Hz), 67.4, 16.7. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3065, 2924, 1778, 1713, 1697, 1597, 1472, 1450, 1381, 1256, 1157, 1101, 1080, 922, 800, 750, 712, 685, 582 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₇H₁₄F₂O₃SNa [M+Na]+ 359.0529, found 359.0542.

2,2-difluoro-2-(4-methyl-3-(methylthio)phenyl)-1-phenylethanone (5.4f)

General procedure A was followed using 5.3f (168 mg, 0.500 mmol), Pd(PPh₃)₄ (28.9 mg, 0.0250 mmol), Et₃N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 120 °C for 24 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound 5.4f as an off-white solid (90 mg, 62%). ¹H NMR (CDCl₃, 500 MHz) δ 8.03 (d, J = 8.1 Hz, 2 H), 7.62–7.58 (m, 1 H), 7.47–7.44 (m, 2 H), 7.34 (d, J = 1.8 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 7.22 (d, J = 8.0 Hz, 1 H), 2.48
(s, 3 H), 2.35 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 189.2 (t, $J = 31.1$ Hz), 139.5, 138.7, 134.3, 132.3, 131.6 (t, $J = 25.0$ Hz), 130.5 (t, $J = 2.8$ Hz), 130.2, 128.9, 121.7 (t, $J = 6.0$ Hz), 121.0 (t, $J = 6.0$ Hz), 117.1 (t, $J = 253.3$ Hz), 20.1, 15.2. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –97.8 (s, 2 F). IR (film) 3063, 2922, 1703, 1597, 1449, 1393, 1267, 1242, 1130, 1036, 908, 824, 721, 685, 644 cm$^{-1}$. HRMS (ESI, $m/z$): calcd for C$_{16}$H$_{15}$F$_2$OS [M+H]$^+$ 293.0812, found 293.0801. mp 46–47 °C.

(2-(phenylthio)phenyl)methanol (5.3g-1)

Compound 5.3g-1 was prepared from a known procedure$^4$ using 2-(phenylthio)benzoic acid$^7$ (3.0 g, 13 mmol), LAH (1.0 g, 27 mmol), and THF (65 mL). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) provided the title compound 5.3g-1 as an off-white solid (2.5 g, 88%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.54–7.51 (m, 1 H), 7.40–7.34 (m, 2 H), 7.31–7.26 (m, 3 H), 7.24–7.19 (m, 3 H), 4.79 (d, $J = 6.4$ Hz, 2 H), 2.06 (t, $J = 6.4$ Hz, 1 H). Spectroscopic data matched that from the previous report.$^8$ HRMS (ESI, $m/z$): calcd for C$_{13}$H$_{12}$OS [M]+ 216.0609, found 216.0602. mp 43–44 °C (lit. 44 °C).

2-(phenylthio)benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.3g)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^1$ (0.95 g, 4.0 mmol), oxalyl chloride (0.32 mL, 3.8 mmol), 5.3g-1 (0.71 g, 3.3 mmol), Et$_3$N (0.92 mL, 6.6 mmol), DMF (0.10 mL), and CH$_2$Cl$_2$ (20 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 5.3g as a colorless oil (0.93 g, 71%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.06 (d, $J = 7.6$ Hz, 2 H), 7.69–7.64 (m, 1 H), 7.50 (t, $J = 8.0$ Hz, 2 H), 7.41–7.17 (m, 9 H), 5.51 (s, 2 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.3 (t, $J = 27.5$ Hz), 161.7 (t, $J = 30.6$ Hz), 135.7, 135.4, 135.3, 134.7, 134.0,
131.2, 130.2, 130.1, 129.9, 129.7, 129.5, 129.1, 128.4, 127.1, 110.0 (t, \( J = 263.7 \) Hz), 67.3. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –107.8 (s, 2 F). IR (film) 3063, 1776, 1713, 1697, 1597, 1581, 1477, 1450, 1441, 1377, 1308, 1256, 1157, 1099, 1024, 924, 800, 746, 712, 687, 582 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{22}\)H\(_{16}\)F\(_2\)O\(_3\)SNa [M+Na]\(^+\) 421.0686, found 421.0688.

![Structure 5.4g](image)

**2,2-difluoro-2-(4-methyl-3-(phenylthio)phenyl)-1-phenylethanone (5.4g)**

General procedure A was followed using 5.3g (199 mg, 0.500 mmol), Pd(PPh\(_3\))\(_4\) (28.9 mg, 0.0250 mmol), Et\(_3\)N (70 \( \mu \)L, 0.500 mmol), and 1,4-dioxane (5.0 mL). The reaction was run at 120 °C for 24 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound 5.4g as a colorless oil (103 mg, 58%; a 10:1 mixture of the arylated to benzylated isomers by \(^{19}\)F NMR analysis). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.98–7.95 (m, 2 H), 7.62–7.57 (m, 1 H), 7.45–7.39 (m, 4 H), 7.33–7.26 (m, 4 H), 7.24–7.21 (m, 2 H), 2.41 (s, 3 H). \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \( \delta \) 188.8 (t, \( J = 31.2 \) Hz), 142.3, 136.2, 134.5, 134.4, 132.1, 131.8 (t, \( J = 25.0 \) Hz), 131.1, 130.9, 130.4 (t, \( J = 2.5 \) Hz), 129.6, 128.8 (overlap), 127.4, 124.7 (t, \( J = 5.6 \) Hz), 116.8 (t, \( J = 252.5 \) Hz), 20.7. \(^{19}\)F NMR (CDCl\(_3\), 376 MHz) \( \delta \) –98.0 (s, 2 F). IR (film) 3061, 2922, 1713, 1699, 1597, 1582, 1476, 1449, 1387, 1242, 1130, 1024, 908, 824, 721, 687 cm\(^{-1}\). HRMS (ESI, \( m/z \)): calcd for C\(_{21}\)H\(_{17}\)F\(_2\)OS [M+H]\(^+\) 355.0968, found 355.0954.

![Structure 5.4h](image)

**2,2-difluoro-1-phenyl-2-(p-tolyl)ethanone (5.4h)**

General procedure A was followed using 5.3h (145 mg, 0.500 mmol), Pd(PPh\(_3\))\(_4\) (14.4 mg, 0.0125 mmol), Et\(_3\)N (70 \( \mu \)L, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (0% to 10% DCM in hexanes) provided the title compound 5.4h as a
colorless oil (72 mg, 58%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.04–8.02 (m, 2 H), 7.61–7.57 (m, 1 H), 7.51 (d, $J = 8.0$ Hz, 2 H), 7.47–7.42 (m, 2 H), 7.27 (d, $J = 8.0$ Hz, 2 H), 2.39 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 189.3 (t, $J = 30.9$ Hz), 141.4, 134.3, 132.4, 130.5 (t, $J = 2.9$ Hz), 129.7, 128.8, 125.7 (t, $J = 6.0$ Hz), 117.3 (t, $J = 252.6$ Hz), 21.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –97.7 (s, 2 F). IR (film) 3063, 2926, 1699, 1597, 1448, 1259, 1186, 1122, 1095, 1007, 897, 822, 781, 725, 687, 627, 586, 542 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{15}$H$_{13}$F$_2$O $[M+H]^+$ 247.0934, found 247.0927.

![Diagram](image)

3-methoxybenzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.3i)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate$^1$ (2.0 g, 8.4 mmol), oxalyl chloride (0.69 mL, 8.1 mmol), 3-methoxybenzyl alcohol (0.97 g, 7.0 mmol), Et$_3$N (1.9 mL, 14 mmol), DMF (0.22 mL), and CH$_2$Cl$_2$ (42 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 5.3i as a colorless oil (1.6 g, 71%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.06–8.03 (m, 2 H), 7.69–7.65 (m, 1 H), 7.52–7.47 (m, 2 H), 7.25 (t, $J = 7.8$ Hz, 1 H), 6.90–6.86 (m, 2 H), 6.85–6.84 (m, 1 H), 5.32 (s, 2 H), 3.79 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 185.4 (t, $J = 27.5$ Hz), 161.9 (t, $J = 30.6$ Hz), 159.9, 135.4, 135.3, 131.1 (t, $J = 1.9$ Hz), 130.1 (t, $J = 2.5$ Hz), 130.0, 129.2, 120.7, 114.8, 113.8, 110.0 (t, $J = 263.7$ Hz), 69.1, 55.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –107.9 (s, 2 F). IR (film) 2963, 2839, 1778, 1715, 1697, 1599, 1489, 1454, 1379, 1310, 1267, 1126, 916, 783, 685, 582 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{17}$H$_{14}$F$_2$O$_4$Na $[M+Na]^+$ 343.0758, found 343.0766.

![Diagram](image)

22,2-difluoro-2-(2-methoxy-4-methylphenyl)-1-phenylethanone (5.4i)

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General procedure A was followed using 5.3i (160 mg, 0.500 mmol), Pd(PPh3)4 (14.4 mg, 0.0125 mmol), Et3N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (2% to 4% EtOAc in hexanes) provided the title compound 5.4i as an off-white solid (73 mg, 53%). 1H NMR (CDCl3, 400 MHz) δ 7.97–7.94 (m, 2 H), 7.68 (d, J = 7.6 Hz, 1 H), 7.57–7.52 (m, 1 H), 7.42–7.38 (m, 2 H), 6.93 (d, J = 7.6 Hz, 1 H), 6.67 (s, 1 H), 3.58 (s, 3 H), 2.38 (s, 3 H). 13C NMR (CDCl3, 150 MHz) δ 188.6 (t, J = 30.0 Hz), 156.7 (t, J = 5.3 Hz), 143.3, 133.6, 133.1, 129.7 (t, J = 2.2 Hz), 128.5, 126.3 (t, J = 6.8 Hz), 121.9, 120.6 (t, J = 24.1 Hz), 115.4 (t, J = 250.3 Hz), 112.8, 55.6, 22.0. 19F NMR (CDCl3, 376 MHz) δ −97.9 (s, 2 F). IR (film) 2939, 1716, 1614, 1585, 1508, 1464, 1414, 1284, 1238, 1167, 1148, 1121, 1038, 1005, 928, 901, 862, 816, 717, 690, 646, 604 cm⁻¹. HRMS (ESI, m/z): calcd for C16H14F2O2Na [M+Na]+ 299.0860, found 299.0858. mp 53–54 °C.

2,2-difluoro-2-(4-methyl-2-(trifluoromethyl)phenyl)-1-phenylethanone (5.4j)

General procedure A was followed using 5.3j (179 mg, 0.500 mmol), Pd(PPh3)4 (14.4 mg, 0.0125 mmol), Et3N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (0% to 10% DCM in hexanes) provided the title compound 5.4j as a colorless oil (40 mg, 25%); a 11:1 mixture of the arylated to benzylated isomers by 19F NMR analysis. 1H NMR (CDCl3, 400 MHz) δ 8.17–8.14 (m, 2 H), 7.70–7.64 (m, 2 H), 7.63 (s, 1 H), 7.55–7.51 (m, 2 H), 7.49 (d, J = 7.2 Hz, 1 H), 2.49 (s, 3 H). 13C NMR (CDCl3, 150 MHz) δ 188.8 (t, J = 33.0 Hz), 141.7, 134.4, 132.5, 132.2 (t, J = 3.0 Hz), 130.4 (t, J = 2.5 Hz), 128.9, 128.5 (q, J = 5.4 Hz), 128.3 (t, J = 9.8 Hz), 123.7 (q, J = 272.0 Hz), 117.6 (t, J = 256.9 Hz), 21.4. (Two set of peaks buried between 128.6 and 128.2 ppm). 19F NMR (CDCl3, 376 MHz) δ −94.1 (q, J = 11.3 Hz, 2 F), −58.6 (t, J = 11.3 Hz, 3 F) for the arylated isomer; δ −99.0 (t, J = 17.6 Hz, 2 F), −63.2 (s, 3 F) for the benzylated isomer. IR (film) 3072,
Experimental Procedures and Characterization of Compounds for Table 5.5

2-(trifluoromethyl)benzyl 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate (5.5a)

General procedure C was followed using potassium 2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoate\(^1\) (1.1 g, 4.2 mmol), oxalyl chloride (0.34 mL, 4.0 mmol), 2-trifluoromethylbenzyl alcohol (0.62 g, 3.5 mmol), Et\(_3\)N (0.97 mL, 7.0 mmol), DMF (0.11 mL), and CH\(_2\)Cl\(_2\) (21 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) or (15% to 30% DCM in hexanes) afforded the title compound 5.5a as a colorless oil (0.76 g, 58%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta 8.12\) (ddt, \(J = 7.5, 5.3, 1.1\) Hz, 2 H), 7.69 (d, \(J = 8.0\) Hz, 1 H), 7.60–7.52 (m, 2 H), 7.48 (t, \(J = 7.6\) Hz, 1 H), 7.21–7.16 (m, 2 H), 5.54 (s, 2 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta 184.0\) (t, \(J = 27.5\) Hz), 167.1 (d, \(J = 258.7\) Hz), 161.5 (t, \(J = 30.6\) Hz), 133.2 (dt, \(J = 9.6, 3.1\) Hz), 132.5, 132.0, 130.5, 129.2, 128.7 (q, \(J = 30.8\) Hz), 127.5 (q, \(J = 2.5\) Hz), 126.5 (q, \(J = 5.4\) Hz), 124.1 (q, \(J = 272.1\) Hz), 116.6 (d, \(J = 22.5\) Hz), 110.1 (t, \(J = 263.7\) Hz), 65.5 (q, \(J = 2.5\) Hz). \(^19\)F NMR (CDCl\(_3\), 376 MHz) \(\delta -107.6\) (s, 2 F), -100.7 (m, 1 F), -60.4 (s, 3 F). IR (film) 3082, 1778, 1697, 1599, 1510, 1456, 1416, 1315, 1244, 1123, 1040, 926, 851, 768, 654, 613, 571 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for C\(_{17}\)H\(_{11}\)F\(_6\)O\(_3\) [M+H]\(^+\) 377.0612, found 377.0606.

2,2-difluoro-1-(4-fluorophenyl)-2-(4-methyl-3-(trifluoromethyl)phenyl)ethanone (5.6a)

General procedure A was followed using 5.5a (188 mg, 0.500 mmol), Pd(PPh\(_3\))\(_4\) (28.9 mg, 0.0250 mmol), Et\(_3\)N (70 \(\mu\)L, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 18 h. Workup
and chromatographic purification (5% to 10% DCM in hexanes) provided the title compound 5.6a as a colorless oil (132 mg, 79%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.14–8.10 (m, 2 H), 7.84 (s, 1 H), 7.63 (d, $J$ = 8.0 Hz, 1 H), 7.41 (d, $J$ = 8.0 Hz, 1 H), 7.20–7.14 (m, 2 H), 2.55 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 187.2 (t, $J$ = 31.9 Hz), 166.7 (d, $J$ = 256.2 Hz), 140.3 (m), 133.4 (dt, $J$ = 10.0, 3.1 Hz), 132.7, 131.0 (t, $J$ = 25.0 Hz), 129.8 (q, $J$ = 30.4 Hz), 129.2 (t, $J$ = 5.6 Hz), 128.4 (q, $J$ = 2.5 Hz), 124.1 (q, $J$ = 272.5 Hz), 123.5 (h, $J$ = 5.7 Hz), 116.8 (t, $J$ = 253.1 Hz), 116.4 (d, $J$ = 22.5 Hz), 19.5. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –102.1 (m, 1 F), –97.6 (s, 2 F), –62.5 (s, 3 F). IR (film) 3084, 2941, 1705, 1601, 1508, 1414, 1327, 1285, 1238, 1175, 1130, 1059, 908, 853, 791, 766, 669, 604 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{11}$F$_6$O [M+H]$^+$ 333.0714, found 333.0711.

2-(trifluoromethyl)benzyl 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate (5.5b)

General procedure C was followed using potassium potassium 2,2-difluoro-3-(5-methylthiophen-2-yl)-3-oxopropanoate$^1$ (1.5 g, 6.0 mmol), oxalyl chloride (0.49 mL, 5.8 mmol), 2-trifluoromethylbenzyl alcohol (0.88 g, 5.0 mmol), Et$_3$N (1.4 mL, 10 mmol), DMF (0.15 mL), and CH$_2$Cl$_2$ (30 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) afforded the title compound 5.5b as a yellow oil (1.3 g, 69%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.86–7.85 (m, 1 H), 7.69 (d, $J$ = 8.0 Hz, 1 H), 7.59–7.52 (m, 2 H), 7.47 (t, $J$ = 7.8 Hz, 1 H), 6.89 (dd, $J$ = 4.0, 1.2 Hz, 1 H), 5.54 (s, 2 H), 2.59 (s, 3 H). $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 177.8 (t, $J$ = 28.7 Hz), 161.5 (t, $J$ = 31.2 Hz), 154.8, 137.5 (t, $J$ = 5.0 Hz), 135.1, 132.5, 132.2, 130.1, 129.0, 128.5 (q, $J$ = 31.2 Hz), 128.2, 126.4 (q, $J$ = 5.8 Hz), 124.1 (q, $J$ = 271.6 Hz), 109.8 (t, $J$ = 263.7 Hz), 65.3 (q, $J$ = 2.7 Hz), 16.4. $^{19}$F NMR (CDCl$_3$, 376 MHz) $\delta$ –108.2 (s, 2 F), –60.5 (s, 3 F). IR (film) 3078, 2926, 1778, 1682, 1666, 1447, 1315, 1171, 1124, 1040, 935, 812, 770, 675, 654, 582 cm$^{-1}$. HRMS (ESI, m/z): calcd for C$_{16}$H$_{11}$F$_3$O$_3$SNa [M+Na]$^+$ 401.0247, found 401.0252.
2,2-difluoro-2-(4-methyl-3-(trifluoromethyl)phenyl)-1-(5-methylthiophen-2-yl)ethanone (5.6b)

General procedure A was followed using 5.5b (189 mg, 0.500 mmol), Pd(PPh3)4 (28.9 mg, 0.0250 mmol), Et3N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 18 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound 5.6b as an off-white solid (134 mg, 80%). 1H NMR (CDCl3, 400 MHz) δ 7.87 (s, 1 H), 7.84–7.83 (m, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 6.87 (dd, J = 4.0, 1.2 Hz, 1 H), 2.57 (s, 3 H), 2.52 (s, 3 H). 13C NMR (CDCl3, 125 MHz) δ 181.4 (t, J = 31.9 Hz), 153.8, 140.1 (m), 137.1 (t, J = 5.0 Hz), 135.8, 132.6, 131.3 (t, J = 25.6 Hz), 129.7 (q, J = 30.4 Hz), 129.2 (t, J = 6.2 Hz), 128.0, 124.1 (q, J = 272.1 Hz), 123.5 (h, J = 6.0 Hz), 116.3 (t, J = 252.5 Hz), 19.5 (m), 16.3. 19F NMR (CDCl3, 376 MHz) δ –99.4 (s, 2 F), –62.5 (s, 3 F). IR (film) 2928, 1672, 1624, 1445, 1327, 1285, 1238, 1211, 1175, 1126, 1059, 910, 860, 816, 773, 739, 683, 608 cm⁻¹. HRMS (ESI, m/z): calcd for C15H12F5OS [M+H]⁺ 335.0529, found 335.0520. mp 44–45 °C.

2-(trifluoromethyl)benzyl 3-cyclohexyl-2,2-difluoro-3-oxopropanoate (5.5c)

General procedure C was followed using potassium potassium 3-cyclohexyl-2,2-difluoro-3-oxopropanoate (1.8 g, 7.2 mmol), oxalyl chloride (0.58 mL, 6.9 mmol), 2-trifluoromethylbenzyl alcohol (1.1 g, 6.0 mmol), Et3N (1.7 mL, 12 mmol), DMF (0.19 mL), and CH2Cl2 (36 mL). Workup and chromatographic purification (2% to 5% EtOAc in hexanes) or (15% to 30% DCM in hexanes) afforded the title compound 5.5c as a colorless oil (0.83 g, 38%). 1H NMR (CDCl3, 400 MHz) δ 7.72 (d, J = 8.0 Hz, 1 H), 7.63–7.54 (m, 2 H), 7.50 (t, J = 7.6 Hz, 1 H), 2.93–2.86 (m, 1 H), 1.90–1.77 (m, 4 H), 1.72–1.67 (m,
1 H), 1.45–1.19 (m, 5 H), 5.51 (s, 2 H). 13C NMR (CDCl3, 125 MHz) δ 200.2 (t, J = 26.9 Hz), 161.5 (t, J = 30.6 Hz), 132.5, 132.1, 130.5, 129.2, 128.8 (q, J = 30.8 Hz), 126.5 (q, J = 5.4 Hz), 124.1 (q, J = 272.5 Hz), 108.8 (t, J = 264.4 Hz), 65.3 (q, J = 2.9 Hz), 45.5, 28.2, 25.6, 25.4. 19F NMR (CDCl3, 376 MHz) δ –113.2 (s, 2 F), –60.4 (s, 3 F). IR (film) 2938, 2860, 1782, 1738, 1611, 1587, 1452, 1315, 1175, 1123, 1061, 1040, 959, 770, 654 cm−1. HRMS (ESI, m/z): calcd for C17H17F5O3Na [M+Na]+ 387.0996, found 387.1014.

1-cyclohexyl-2,2-difluoro-2-(4-methyl-3-(trifluoromethyl)phenyl)ethanone (5.6c)

General procedure A was followed using 5.5c (182 mg, 0.500 mmol), Pd(PPh3)4 (28.9 mg, 0.0250 mmol), Et3N (70 μL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 24 h. Workup and chromatographic purification (0% to 1% DCM in hexanes) provided the title compound 5.6c as a colorless oil (118 mg, 74%). 1H NMR (CDCl3, 400 MHz) δ 7.78 (s, 1 H), 7.59 (dd, J = 7.6, 1.6 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 2.95–2.88 (m, 1 H), 2.54 (s, 3 H), 1.81–1.75 (m, 4 H), 1.71–1.67 (m, 1 H), 1.43–1.19 (m, 5 H). 13C NMR (CDCl3, 125 MHz) δ 202.8 (t, J = 30.6 Hz), 140.1, 132.6, 130.6 (t, J = 26.2 Hz), 129.7 (q, J = 30.4 Hz), 129.2 (t, J = 6.2 Hz), 124.1 (q, J = 272.5 Hz), 123.4 (h, J = 5.9 Hz), 115.7 (t, J = 253.7 Hz), 45.3, 28.8, 25.7, 25.5, 19.5 (m). 19F NMR (CDCl3, 376 MHz) δ –105.6 (s, 2 F), –62.5 (s, 3 F). IR (film) 2938, 2860, 1738, 1624, 1452, 1327, 1287, 1240, 1175, 1128, 1059, 947, 908, 841, 829, 752, 681 cm−1. HRMS (ESI, m/z): calcd for C16H18F5O [M+H]+ 321.1278, found 321.1267.
Preparation of Deuterium-Labeled Probe 5.7

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| **4-bromo-2-isopropylaniline (5.7-5)** | **Compound 5.7-5** was prepared from a previously reported procedure using 2-isopropylaniline (8.5 mL, 60 mmol), NBS (12 g, 66 mmol), NH₄OAc (0.46 g, 6.0 mmol), and CH₃CN (0.24 L). Workup and chromatographic purification (5% to 10% EtOAc in hexanes) provided the title compound 5.7-5 as a brown oil (12 g, 93%). ¹H NMR (CDCl₃, 400 MHz) δ 7.22 (d, J = 2.4 Hz, 1 H), 7.11 (dd, J = 8.4, 2.4 Hz, 1 H), 6.56 (d, J = 8.4 Hz, 1 H), 3.65 (br, 2 H), 2.85 (hept, J = 6.8 Hz, 1 H), 1.25 (d, J = 6.8 Hz, 6 H). Spectroscopic data matched that from the previous report. HRMS (ESI, m/z): calcd for C₉H₁₅BrN [M+H]+ 214.0231, found 214.0239.  
| 5.7-4    | Preparation |  
| **4-bromo-1-iodo-2-isopropylbenzene (5.7-4)** | **Compound 5.7-4** was prepared from a known procedure using compound 5.7-5 (6.0 g, 28 mmol), H₂SO₄ (47 mL), CH₃CN (31 mL), NaNO₂ (3.5 g, 50 mmol), KI (16 g, 98 mmol), and water (0.12 L; 45 mL for dilution of H₂SO₄, 30 mL for solution of NaNO₂, and 45 mL for solution of KI). Workup followed by decolorization using Na₂S₂O₃ (sat’d), and chromatographic purification (hexanes) provided the title compound 5.7-4 as an orange oil (8.9 g, 98%). ¹H NMR (CDCl₃, 400 MHz) δ 7.67 (d, J = 8.4 Hz, 1 H), 7.35 (d, J = 2.4 Hz, 1 H), 7.02 (dd, J = 8.0, 2.4 Hz, 1 H), 3.14 (hept, J = 6.8 Hz, 1 H), 1.23 (d, J = 6.8 Hz, 6 H). |
Spectroscopic data matched that from the previous report.\(^9\) HRMS (ESI, \(m/z\)): calcd for \(\text{C}_9\text{H}_{10}\text{BrI} [\text{M}^+]\) 323.9011, found 323.9007.

**4-bromo-2-isopropylbenzaldehyde (5.7-3)**

Compound 5.7-3 was prepared from a previously reported procedure using a slight modification.\(^{11}\) Under an atmosphere of nitrogen, a solution of isopropylmagnesium chloride (2.0 M in THF, 57.5 mL, 115 mmol) was added dropwise to a solution of compound 5.7-4 (7.50 g, 23.0 mmol) in THF (80 mL) through an addition funnel at \(-15^\circ\text{C}\). After stirring at \(-15^\circ\text{C}\) for 30 min, DMF (11.0 mL, 138 mmol) was added dropwise by an addition funnel, and then the mixture was stirred at \(-15^\circ\text{C}\) for another 2 h. Subsequently, the reaction mixture was gradually warmed to rt, and was continually stirred at rt for another 2 hr. Next, the resulting reaction mixture was added with 1N HCl (aq) at 0 °C until the solid formed in the reaction mixture dissolved. The two phases were transferred to a separation funnel, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (0% to 5%) for elution, and the product was dried by a rotatory evaporator (not high vacuum) to provide the compound 5.7-3 as a yellow oil (5.1 g, 98%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 10.32 (s, 1 H), 7.69 (d, \(J = 8.4\) Hz, 1 H), 7.59 (d, \(J = 1.6\) Hz, 1 H), 7.50 (dd, \(J = 8.2, 1.8\) Hz, 1 H), 3.95 (hept, \(J = 6.8\) Hz, 1 H), 1.31 (d, \(J = 6.8\) Hz, 6 H). \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 191.4, 153.4, 133.0, 131.9, 129.8 (overlap of three carbons), 27.9, 23.9. IR (film) 2967, 2870, 2731, 1703, 1694, 1584, 1557, 1464, 1389, 1288, 1213, 1150, 1097, 1059, 901, 835, 818, 758 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for \(\text{C}_{10}\text{H}_{12}\text{BrO} [\text{M}+\text{H}]^+\) 227.0072, found 227.0062.

**4-bromo-2-isopropylphenyl)methanol (5.7-2)**

General procedure B was followed using compound 5.7-3 (970 mg, 4.27 mmol), NaBH\(_4\) (242 mg, 6.40 mmol), and MeOH (0.0120 L). Workup and chromatographic purification (10% to 15% EtOAc in hexanes) afforded the title compound 5.7-2 as an off-white solid (910 mg, 93%). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.43 (d, \(J = 2.0\) Hz, 1 H), 7.32 (dd, \(J = 8.4, 2.0\) Hz, 1 H), 7.23 (d, \(J = 8.4\) Hz, 1 H), 4.71 (d, \(J = 6.8\) Hz, 1 H), 1.31 (d, \(J = 6.8\) Hz, 6 H). IR (film) 3278, 3074, 2961, 2893, 2740, 1586, 1456, 1244, 1083, 915, 842, 758 cm\(^{-1}\). HRMS (ESI, \(m/z\)): calcd for \(\text{C}_{10}\text{H}_{13}\text{BrO} [\text{M}+\text{H}]^+\) 232.9011, found 232.9007.

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5.2 Hz, 2 H), 3.21 (hept, J = 6.8 Hz, 1 H), 1.56 (br, 1 H), 1.25 (d, J = 7.2 Hz, 6 H). 13C NMR (CDCl3, 125 MHz) δ 149.6, 136.4, 130.1, 129.1, 129.0, 122.5, 62.8, 28.9, 24.0. IR (film) 3395, 2963, 2870, 1589, 1566, 1485, 1462, 1398, 1223, 1101, 1040, 1003, 897, 880, 841, 814 cm⁻¹. HRMS (ESI, m/z): calcd for C10H13BrO [M]+ 228.0150, found 228.0151. mp 64–65 °C.

(4-deuterium-2-isopropylphenyl)methanol (5.7-1)

Compound 5.7-1 was prepared from a previously reported procedure using a slight modification. An oven-dried microwave tube was charged with compound 5.7-2 (458 mg, 2.00 mmol), DCOONa (414 mg, 6.00 mmol), Pd2dba3 (36.6 mg, 0.0400 mmol), P(t-Bu)3 (24.3 mg, 0.120 mmol), and dry DMSO (2.0 mL). Subsequently, the tube was sealed, and moved out of the glove box. The sealed tube was put into a preheated oil-bath at 80 °C, and stirred for 8 h. The tube was then removed out of the oil-bath, and cooled to rt. The reaction mixture was quenched with 2.0 mL of NH4Cl (sat’d), and diluted with 6.0 mL of water. The mixture was transferred to a separation funnel, and the aqueous layer was extracted with DCM (4 x 12 mL). The combined organic phases were dried over anhydrous Na2SO4, filtered, and concentrated. The crude product was purified by column chromatography using a gradient of EtOAc / hexanes (10% to 5%) for elution to provide the compound 5.7-1 as a colorless oil (250 mg, 83%). 1H NMR (CDCl3, 400 MHz) δ 7.35 (d, J = 7.6 Hz, 1 H), 7.35 (s, 1 H), 7.20 (dd, J = 7.6, 1.6 Hz, 1 H), 4.77 (d, J = 4.8 Hz, 2 H), 3.28 (hept, J = 6.8 Hz, 1 H), 1.52 (t, J = 5.2 Hz, 1 H), 1.27 (d, J = 6.8 Hz, 6 H). 2H NMR (CDCl3, 125 MHz) δ 7.33 (s, 1 D). 13C NMR (CDCl3, 125 MHz) δ 147.4, 137.4, 128.6, 128.3 (t, J = 24.4 Hz), 125.9, 125.6, 63.5, 28.8, 24.2. IR (film) 3331, 2963, 2928, 2870, 1599, 1483, 1462, 1410, 1182, 1026, 1007, 907, 851, 669, 523 cm⁻¹.

2-isopropyl-4-deuterium-benzyl 2,2-difluoro-3-oxo-3-phenylpropanoate (5.7)

General procedure C was followed using potassium 2,2-difluoro-3-oxo-3-phenylpropanoate1 (834 mg, 3.50 mmol), oxalyl chloride (0.28 mL, 3.36 mmol), compound 5.7-1 (442 mg, 2.92 mmol), Et3N (0.81 mL, 5.84 mmol), DMF (91 μL), and CH2Cl2 (18 mL). Workup and chromatographic purification (0% to 5% EtOAc in hexanes) afforded the title compound 5.7 as a colorless oil (848 mg, 87%). 1H NMR (CDCl3,
Procedures of Deuterium-Labeling Experiments in Scheme 5.12

General procedure A was followed using 5.7 (167 mg, 0.500 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), Et₃N (70 µL, 0.500 mmol), and 1,4-dioxane (0.010 L). The reaction was run at 100 °C for 12 h. Workup and chromatographic purification (5% to 15% DCM in hexanes) provided the title compound 5.8a as a colorless oil (104 mg, 72%). ¹H NMR (CDCl₃, 400 MHz) δ 8.04–8.02 (m, 2 H), 7.60–7.56 (m, 1 H), 7.48 (d, J = 1.2 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.33–7.30 (m, 1 H), 7.21 (d, J = 8.0 Hz, 1 H), 3.15 (hept, J = 6.8 Hz, 1 H), 2.35 (br, 2 H), 1.22 (d, J = 6.8 Hz, 6 H). ²H NMR (CDCl₃, 61.4 MHz) δ 2.35 (t, J = 2.2 Hz, 1 D). ¹³C NMR (CDCl₃, 125 MHz) δ 189.5 (t, J = 31.2 Hz), 147.9, 138.5, 134.2, 132.5, 131.1 (t, J = 25.0 Hz), 130.8, 130.5 (t, J = 2.5 Hz), 128.8, 122.9 (t, J = 5.6 Hz), 122.2 (t, J = 5.6 Hz), 117.4 (t, J = 251.2 Hz), 29.5, 23.2, 19.2 (m). ¹⁹F NMR (CDCl₃, 376 MHz) δ –97.6 (s, 2 F). IR (film) 2965, 2932, 1703, 1597, 1499, 1449, 1244, 1217, 1132, 924, 887, 824, 714, 679 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₉H₁₇DF₂O₃Na [M+Na]⁺ 356.1184, found 356.1190.

400 MHz) δ 8.04 (dd, J = 8.2, 1.4 Hz, 2 H), 7.69–7.64 (m, 1 H), 7.49 (t, J = 8.0 Hz, 2 H), 7.33 (s, 1 H), 7.29 (d, J = 7.6 Hz, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 5.41 (s, 2 H), 3.09 (hept, J = 6.8 Hz, 1 H), 1.20 (d, J = 6.8 Hz, 6 H). ²H NMR (CHCl₃, 61.4 MHz) δ 7.36 (s, 1 D). ¹³C NMR (CDCl₃, 125 MHz) δ 185.4 (t, J = 27.5 Hz), 161.9 (t, J = 30.6 Hz), 148.6, 135.3, 131.1, 130.7, 130.4, 130.1 (t, J = 2.5 Hz), 129.7 (t, J = 24.4 Hz), 129.1, 126.0, 125.9, 110.0 (t, J = 263.1 Hz), 67.6, 29.2, 24.1. ¹⁹F NMR (CDCl₃, 376 MHz) δ –107.8 (s, 2 F). IR (film) 3067, 2967, 1774, 1715, 1697, 1599, 1450, 1385, 1310, 1157, 1101, 1026, 922, 841, 799, 712, 675, 584 cm⁻¹. HRMS (ESI, m/z): calcd for C₁₀H₁₇DF₂O₃Na [M+Na]⁺ 356.1184, found 356.1190.
## 2D NMR Analyses of Compounds 5.4b, 5.4d, and 5.4f

![Chemical Structure](image)

**Molecular Formula:** C_{10}H_{12}F_{2}O

**Molecular Weight:** 268.337

### 2D NMR Analyses of Compounds 5.4b, 5.4d, and 5.4f

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References for Chapter 5 Experimental Section


3 Methyl 2-(hydroxymethyl)benzoate was prepared from a previously reported procedure using phthalide (1.34 g, 10 mmol), 1 N NaOH(aq) solution (10 mL, 10 mmol), iodomethane (1.9 mL, 30 mmol), and DMF (10 mL): Senboku, H.; Yoneda, K.; Hara, S. “Electrochemical Direct Carboxylation of Benzyl Alcohols Having an Electron-Withdrawning Group on the Phenyl Ring: One-Step Formation of Phenylacetic Acids from Benzyl Alcohols under Mild Conditions” Tetrahedron Lett. 2015, 56, 6772–6776. Spectroscopic data of this compound matched that from the previous report: Rajan, R.; Badgujar, S.; Kaur, K.; Malpani, Y.; Kanjilal, P. R. “Practical and Chemoselective Reduction of Acyl Chloride to Alcohol by Borohydride in Aqueous Dichloromethane” Synth. Commun. 2010, 40, 2897–2907.


7 2-(Phenylthio)benzoic acid was prepared from a previously reported procedure using 2-iodobenzoic acid (5.0 g, 20 mmol), thiophenol (2.1 mL, 20 mmol), KOH (5.6 g, 100 mmol), copper (0.13 g, 2.0 mmol), and water (80 mL): Majmudar, J. D.; Hodges-Loaiza, H. B.; Hahne, K.; Donelson, J. L.; Song, J.; Shrestha, L.; Harrison, M. L.; Hrycyna, C. A.; Gibbs, R. A. “Amide-Modified Prenylcysteine Based lCmt Inhibitors: Structure-Activity Relationships, Kinetic Analysis and Cellular Characterization” Bioorg. Med. Chem. 2012, 20, 283–295. Spectroscopic data of this compound matched that from the previous report: Liu, S.; Pestano, J. P. C.; Wolf, C. “Regioselective Copper-catalyzed C—N and C—S Bond Formation Using Amines, Thiols and Halobenzoic Acids” Synthesis 2007, 3519–3527.


