Strategies for the Fluorine-Retentive Functionalization of Gem-

Difluoroalkenes

By

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**Strategies for the Fluorine-Retentive Functionalization of Gem-Difluoroalkenes**

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Abstract

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Fluorination is an important strategy for perturbing the biophysical properties of compounds in medicinal chemistry. Specifically, fluorination modulates both the pharmacodynamic and pharmacokinetic properties of bioactive molecules in generally beneficial ways. However, fluorination similarly manipulates the reactivity of compounds in synthetic chemistry, leaving many traditional synthetic methods unable to perform as expected in organofluorine chemistry. Chapter 1 provides background on the effects of fluorine on medicinal and synthetic chemistry, and specifically discusses the effects of fluorine upon alkenes.

Gem-difluoroalkenes are an appealing substructure for nucleophilic addition reactions, as they readily react with nucleophiles. However, upon nucleophilic addition defluorination reactions occur, providing fluoroalkene products. Reactions of difluoroalkenes which retain both fluorine atoms would provide access to underexplored difluorinated substructures. To this end, Chapter 2 describes the development of organocatalyzed addition of thiols to gem-difluoroalkenes to provide \( \beta,\beta \)-difluorophenethyl thioethers.

Alcohol nucleophiles possess similar reactivity to thiols, including with gem-difluoroalkenes. Moreover, in medicinal chemistry ethers are a more common
substructure than thioethers. Thus, Chapter 3 describes the addition of phenolic nucleophiles across gem-difluoroalkenes in a hydrophenolation reaction to provide β,β-difluorophenethyl arylethers.

Gem-difluoroalkenes also possess unusual reactivity with transition metal catalysts. Typically, transition metals perform oxidative addition to C–halogen bonds to initiate cross coupling chemistry. However, the high C–F bond strength generally precludes oxidative addition, enabling alternate mechanistic pathways. Chapter 4 discusses the development of a Co-catalyzed deoxygenation reaction of gem-difluoroalkenes with phenol nucleophiles and O₂ to provide β-phenoxy-β,β-difluorobenzyl alcohols. This reaction proceeds by an unusual radical reaction pathway in which superoxide oxidizes phenol to phenoxy radical, which adds to gem-difluoroalkenes to provide a benzyl radical that quenches with peroxide anion.

Finally, Chapter 5 discusses the ongoing work on metal-catalyzed dioxygenation reactions of gem-difluoroalkenes. This work covers the further development of β-phenoxy-β,β-difluorobenzyl alcohols under Pt catalysis, specifically to expand the reaction scope to heteroaryl alcohols, aliphatic alcohols, and aliphatic gem-difluoroalkenes. Further, Cu-catalysis enables the production of β-phenoxy-β,β-difluorobenzyl ketones.
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List of Abbreviations/Acronyms

A/E: Addition / Elimination

acac: Acetylacetonate

AcOH: Acetic acid

Aq.: Aqueous

Atm.: atmosphere

BHT: Butylated Hydroxytoluene

BMPO: 5-tert-butoxycarbonyl-5-methyl-1-pyrroline-N-oxide

Bn: Benzyl

Boc: tert-butyloxycarbonyl

Boc$_2$O: di-tert-butyl decarbonate

"BuLi: n-butyl lithium

CHCl$_3$: Chloroform

cod: cis,cis-1,5-cyclooctadiene

CYP: Cytochrome

DABCO: 1,4-Diazabicyclo[2.2.2]octane
dba: dibenzylideneacetone

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCB: 1,2-Dichlorobenzene

DCE: 1,2-dichloroethane

DCM: Dichloromethane

DMAP: Dimethylaminopyridine

DMA: N,N-Dimethylacetamide

DME: Dimethoxyethane

DMF: Dimethylformamide

DMP: Dess-Martin Periodinane

DMPO: 5,5-dimethyl-1-pyrroline-N-oxide

DMSO: Dimethylsulfoxide

E⁺: Electrophile

EPR: Electron Paramagnetic Resonance

Equiv.: Molar Equivalents

ESI: Electrospray ionization
Et$_3$N: Triethylamine

EtOAc: Ethyl Acetate

Et$_2$O: diethyl ether

EtOH: Ethanol

EWG: Electron-withdrawing group

GC-FID: Gas chromatography-flame ionization detector

Gem: Geminal

HCl: Hydrochloric acid

HRMS: High resolution mass spectrometry

Hz: Hertz

IBX: 2-iodoxybenzoic acid

IPA: Isopropyl alcohol

IR: Infrared Spectrum

K$_2$CO$_3$: Potassium carbonate

KHMDS: Potassium Hexamethyldisilazide

KMnO$_4$: Potassium permanganate
K₃PO₄: Potassium phosphate, tribasic

LAH: Lithium aluminum hydride

MeCN: Acetonitrile

MeOH: Methanol

MgSO₄: Magnesium Sulfate

MHz: Megahertz

mmu: milli mass unit

m.p.: Melting point

MsOH: Methanesulfonate

mT: Millitesla

NaBH₄: Sodium borohydride

Na₂CO₃: Sodium Carbonate

NaOH: Sodium Hydroxide

Na₂SO₄: Sodium sulfate

Na₂S₂O₅: Sodium metabisulfite

Na₂S₂O₈: Sodium persulfate
NaH: Sodium Hydride

NH₄Cl: Ammonium Chloride

NMO: 4-methylmorpholine N-oxide

NMP: N-Methylpyrrolidone

NMR: Nuclear Magnetic Resonance

Nu: Nucleophile

Oct.: Octane

Ox. Addn.: Oxidative Addition

PCy₃: Tricyclohexylphosphine

PD: Pharmacodynamics

Pdt: Product

P₂Et: Tetramethyl(tris(dimethylamino)phosphoranylidene)phosphorictriamid-Et-imin

PGP: P-Glycoprotein

PhMe: Toluene

PhNO₂: Nitrobenzene

PK: Pharmacokinetics
PLP: Pyridoxal Phosphate

PMB: Para-methoxybenzyl

POCl₃: Phosphorus(V) oxychloride

PPh₃: Triphenylphosphine

ppm: Parts per million

PTFE: Polytetrafluoroethylene

PTSA-H₂O: Para-toluene sulfonic acid monohydrate

2-Pym: 2-Pyrimidine

Red. Elim.: Reductive Elimination

R.T.: Room Temperature

SDS: sodium dodecyl sulfate

SOCl₂: Thionyl Chloride

TAPCI: Toluene Atmospheric Pressure Chemical Ionization

TBAF: Tetrabutylammonium Fluoride

TBD: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

TBHP: Tert-butyl hydroperoxide
TEMPO: 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical

Tf$_2$O: Trifluoromethylsulfonic anhydride

TFA: Trifluoroacetic acid

TFT: $\alpha,\alpha,\alpha$-Trifluorotoluene

THF: Tetrahydrofuran

TLC: Thin layer chromatography

TMG: 1,1,3,3-Tetramethylguanidine

TMS: trimethylsilyl

Tosyl (Ts): Para-toluenesulfonamide

Triflate (Tf): Trifluoromethylsulfonate

TsCl: para-toluenesulfonyl chloride
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Chapter 1 – Fluorine-Induced Perturbations of Reactivity

1.1. The Physical Chemistry of Fluorine

Fluorination affects a molecule’s physicochemical properties, which in turn can perturb a bioactive molecule’s pharmacodynamic (PD), pharmacokinetic (PK), distribution, and/or metabolic profiles.\(^1\) For example, the addition of fluorinated functional groups to a therapeutic candidate can greatly enhance the lipophilicity (logP; octanol/water partitioning coefficient) of a molecule,\(^{1e,1f}\) which in turn can enhance bioavailability, tissue distribution, and cell permeability.\(^1i\) This non-trivial relationship between the properties imparted by a fluorinated substituent and the subsequent biophysical perturbations also relates to synthetic transformations in which fluorinated substructures demonstrate distinct reactivity and/or selectivity relative to analogous non-fluorinated substrates. The chemical and biological perturbations attributed to fluorine drive the development of new methods in organofluorine chemistry.

These fluorine-induced perturbations arise due to the unique biophysical properties of fluorine. Electronically, fluorine is the most electronegative element, significantly more so than the other halogens or similarly sized atoms (Figure 1-1a),\(^1a\) allowing fluorine to easily adopt or stabilize a negative charge (Figure 1-1a). However, despite fluorine’s electronegativity and ionization potential, it is not highly polarizable. Fluorine is less polarizable than hydrogen, and significantly less polarizable than the other halogens or oxygen (Figure 1-1a).\(^1a\)
Figure 1-1: Electronic Characteristics of Fluorine

a) Electronic Characteristics of Fluorine and Related Atoms

<table>
<thead>
<tr>
<th>X</th>
<th>Electronegativity</th>
<th>Polarizability (Å³)</th>
<th>Ionization Potential (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2.2</td>
<td>0.667</td>
<td>314</td>
</tr>
<tr>
<td>F</td>
<td>4.0</td>
<td>0.557</td>
<td>402</td>
</tr>
<tr>
<td>Cl</td>
<td>3.2</td>
<td>2.18</td>
<td>299</td>
</tr>
<tr>
<td>Br</td>
<td>3.0</td>
<td>3.04</td>
<td>272</td>
</tr>
<tr>
<td>I</td>
<td>2.7</td>
<td>4.7</td>
<td>241</td>
</tr>
<tr>
<td>C</td>
<td>2.5</td>
<td>0.82</td>
<td>240</td>
</tr>
<tr>
<td>N</td>
<td>3.0</td>
<td>1.10</td>
<td>335</td>
</tr>
<tr>
<td>O</td>
<td>3.5</td>
<td>1.76</td>
<td>314</td>
</tr>
</tbody>
</table>

b) Effects of Fluorination on Reactive Intermediates

\[ \text{F} \text{R} \text{R} \sigma \text{-Induction Destabilizes Electron-Deficient Carbocation} \]
\[ \text{F} \text{R} \text{R} \sigma \text{-Induction Stabilizes Electron-Rich Carbanion} \]
\[ \text{CF}_3 \text{R} \sigma \text{-Induction Destabilizes Electron-Deficient Carbocation} \]
\[ \text{CF}_3 \text{R} \sigma \text{-Induction Stabilizes Electron-Rich Carbanion} \]
\[ \text{Hyperconjugation Stabilizes Electron-Rich Carbanion} \]

The electronic characteristics of fluorine affect the stability and reactivity of various organic intermediates. Fluorination decreases carbocation stability by σ-induction, reducing the electron density of an already electron deficient center (Figure 1-1b). Thus, fluorine reduces the susceptibility of a compound to electrophilic attack. Conversely, fluorination stabilizes carbanions through the same σ-inductive effect, while trifluoromethyl substituents stabilize carbanions through both a σ-inductive effect and hyperconjugation of the carbanion and the C–F σ* orbital (Figure 1-1b).
The electronic properties of fluorine influence the strength of X–F bonds. Fluorine forms exceptionally strong bonds with electropositive atoms, as the bond dissociation energy of alkyl C–F bond is 110 kcal/mol, stronger than a C–H bond (104 kcal/mol) and a C–O bond (90 kcal/mol).² Similarly, fluorine bonds tightly with silicon (129 kcal/mol) and boron (125–183 kcal/mol).² Conversely, fluorine forms exceedingly weak bonds with electronegative heteroatoms, such as oxygen (53 kcal/mol).² The weak bonds between F and electronegative atoms enable electrophilic fluorination with N–F fluorinating reagents, such as Selectfluor (64.0 kcal/mol),³ NFSI (63.4 kcal/mol),³ and the N–F pyridine fluorinating reagents (49.4–77.8 kcal/mol, Figure 1-2).³ Additionally, the low polarizability of fluorine (Figure 1-1) alters the strength of intermolecular interactions with fluorine, making dipole-dipole interactions, van der Waals interactions, and H-bonds generally weaker than with other heteroatoms.⁴

**Figure 1-2: N–F Fluorinating Reagents**

- Selectfluor
- N-Fluorobenzenesulfonimide (NFSI)
- N-Fluoropyridinium Reagents

1.2. *The Impact of Fluorine on Medicinal Chemistry*

Fluorination of bioactive compounds affects a molecule’s pharmacodynamic (PD), pharmacokinetic (PK), distribution, and metabolic profiles both *in vitro* and *in vivo*.¹ᵃ–ʰ Thus, many fluorinated bioisosteres exist to replace a wide variety of functional groups, providing a diverse toolkit of fluorinated functionalities to predictably modulate biophysical
properties.\textsuperscript{5} These effects of fluorine on biological properties are explained by the physicochemical effects of fluorine on organic compounds.

**Effects on PD:**

Fluorine is often invoked as an isosteric replacement for hydrogen, allowing an H to F substitution without affecting molecular size. Thus, in theory H to F substitutions can be employed without affecting potency. However, comparing the van der Waals radii, fluorine (1.47 Å) is actually closer in size to oxygen (1.52 Å) or nitrogen (1.55 Å) than to hydrogen (1.20 Å).\textsuperscript{1a} The Taft steric parameters $E^o_s$ shows the same results, as do the axial rotational barriers of a 2'-Me 2-X system, in which fluorine falls between hydrogen and a methyl group in size (**Figure 1-3**). Similarly, C–F bonds are longer than C–H bonds, closer to a C–O or a C–C bond.\textsuperscript{1a} Further, the trifluoromethyl group has been misidentified as an isosteric replacement for the methyl group. Comparing axial rotational barriers, the trifluoromethyl group is significantly larger than a methyl group, instead serving as an isostere for an isopropyl group (**Figure 1-3**). Further, comparing Taft steric parameters, the trifluoromethyl group is much closer in size to a 'Bu group than a methyl group (**Figure 1-3**).
Beyond molecular size, fluorine affects the binding of compounds with their biological targets. One direct effect of fluorine on binding interactions are multipolar interactions. Multipolar interactions occur when a properly oriented C–F bond creates a strong dipole-dipole interaction with the carbonyl C of a backbone amide or an arginine guanidine. While these interactions are not exceptionally strong, accounting for less binding energy than a hydrogen bond, they still can exert a fold change on potency (Figure 1-4). Multipolar interactions are commonly observed in crystal structures, although not all close contacts of fluorine with a carbonyl imply a multipolar interaction. Fluorine must come within 3.6 Å, and no closer than 2.8 Å, of the carbonyl carbon, or in rare cases the $C_\alpha$ proton, and lie within a narrow band of O=C---F--C angles. The constructive O=C---F--
C angles expand as the contact distance increases, although at further distances the strength of the interaction weakens.

**Figure 1-4:** Identifying Multipolar Interactions

According to a matched molecular pair analysis conducted by Pfizer, multipolar interactions of fluorine with carbonyl carbons occur when separated by 2.8–3.6 Å. Closer than 2.8 Å steric repulsion dominates, while beyond 3.3 Å (the van der Waals contact distance), the strength of the interaction falls rapidly. Further, the C–F bond must be oriented within 70–110˚ of the carbonyl carbon (Figure 1-4). This nearly perpendicular interaction between the C–F bond and the carbonyl carbon arises as the fluorine lone pair electrons must point at the π–orbital of the carbonyl. At smaller separations, this angle narrows. Computational predictions of when a fluorine multipolar interaction might occur are improving, enabling the purposeful incorporation of multipolar interactions.
Multipolar interactions help explain the increased potency of a 4-fluorinated aryl ring in a series of thrombin inhibitors (Figure 1-5a).\textsuperscript{6b} Multipolar interactions also help explain the increased potency of Lipitor relative to non-fluorinated analogs,\textsuperscript{6a} and more recently were observed in an HIV-1 gp120 inhibitor (PDB: 4DKO, Figure 1-5b)\textsuperscript{8} and a Procaspe-6 inhibitor (PDB: 4NBL; Figure 1-5c).\textsuperscript{9}
**Figure 1-5:** Beneficial Multipolar Interactions in Medicinal Chemistry

**a) Multipolar Interactions Improve Thrombin Inhibitor Activity**

<table>
<thead>
<tr>
<th>R</th>
<th>$K_i$ [µM]</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>0.31</td>
<td>15</td>
</tr>
<tr>
<td>2-F</td>
<td>0.50</td>
<td>10</td>
</tr>
<tr>
<td>3-F</td>
<td>0.36</td>
<td>26</td>
</tr>
<tr>
<td>4-F</td>
<td><strong>0.057</strong></td>
<td><strong>67</strong></td>
</tr>
<tr>
<td>2,6-F$_2$</td>
<td>0.61</td>
<td>9</td>
</tr>
<tr>
<td>3,5-F$_2$</td>
<td>0.59</td>
<td>25</td>
</tr>
<tr>
<td>1,2,3,4,5-F$_5$</td>
<td>0.27</td>
<td>44</td>
</tr>
</tbody>
</table>

**b) Multipolar Interactions in an HIV-1 gp120 inhibitor**

$R = H$ $K_d = 3.7$ µM  
$R = F$ $K_d = 0.76$ µM

**c) Multipolar Interactions in a Procaspe-6 Inhibitor**

$R = H$ $K_d = 2.9$ µM  
$R = F$ $K_d = 0.47$ µM
Fluorine also alters PD properties through conformational control of organic molecules. Specifically, fluorine can lock bioactive compounds into the active conformation without paying an entropic penalty for reorganization. This ability is particularly useful in saturated systems or systems with a high fraction of sp\(^3\) carbons, which are highly flexible in the absence of fluorine. Bioactive compounds gain many benefits through a high fraction of sp\(^3\) carbons, such as improved solubility and higher binding affinity through chirality.\(^{10}\) Typically, such improvements come with an entropic penalty to binding free energy, as sp\(^3\) carbons possess rotational freedom and require pre-organization before binding. Strategic incorporation of fluorine at a key site can preclude structural rearrangement, avoiding preorganization and the attendant entropic penalty.

Fluorine exerts conformational control via several means. First, the high electronegativity of fluorine destabilizes improperly aligned dipoles through electrostatic repulsion (Figure 1-6),\(^{11}\) which occurs when the dipoles of fluorine and another electronegative substituent align in the same direction. In contrast, alignment of the dipoles in an anti-conformation stabilizes the structure by minimizing electrostatic repulsion. In the case of an \(\alpha\)-fluoro amide, anti-alignment of dipoles increases stability by 8 kcal/mol over the eclipsed, electrostatically repelling conformation (Figure 1-6). This effect extends to 1,3-substituted systems, and is particularly strong in cyclic ammonium species.\(^{11}\)
In addition to dipole alignment, fluorine can also control conformation by other means. In non-fluorinated alkanes, the large substituents prefer an anti-alignment to one another. This alignment keeps the larger substituents as far apart as possible to minimize unfavorable steric overlaps. Alternately, the anti-alignment of heteroatom-based substituents might stabilize through hyperconjugation and anomeric effects, in which the occupied orbital of one substituent donates electron density into the $\sigma^*$ orbital of the other substituent. The anomeric effect requires an anti-orientation for proper orbital overlap.\textsuperscript{11a}

In contrast, fluorine prefers gauche orientations with non-hydrogen substituents, especially heteroatoms. This gauche preference arises as the low-lying $\sigma^*$ C–F orbital is stabilized by hyperconjugation with C–H $\sigma$-bonds. This gauche preference is typically <2 kcal/mol, although with cationic or electropositive groups the gauche effect is reinforced by electrostatic attraction between the free electrons of fluorine and the electropositive...
substituent. As such, when positioned vicinal to an ammonium group the gauche preference increases to $-5.8 \text{ kcal/mol}$ (Figure 1-7a). Further, the gauche effect is additive, thus the more substituents fluorine can orient gauche to the stronger the effect.\textsuperscript{11} The gauche preference of fluorine helps stabilize the active conformation of nucleoside HIV viral replication inhibitors (Figure 1-7b).\textsuperscript{12} In these compounds, the sugar conformation affects binding to HIV-1 reverse transcriptase. Thus, stabilizing the appropriate sugar conformer improves potency. Several effects from fluorination increase structural rigidity and conformational preference, observed in crystal structures\textsuperscript{12a, 12b} or by analysis of 1- and 2-D NMR spectra.\textsuperscript{11a, 12c, 13} In a monofluorinated system, the gauche preference of fluorine drives conformational rigidity. In the inactive conformer, an $\alpha$-2' fluorine orients gauche to the ring oxygen and anti to the nucleobase, which aligns the nucleobase nitrogen and the tetrahydrofuran oxygen to stabilize the conformation through the anomeric effect (Figure 1-7b.i).\textsuperscript{13} In the active conformer, the $\alpha$-2' fluorine orients gauche to the nucleobase, but anti to the ring oxygen, which does not properly align the nucleobase nitrogen and tetrahydrofuran oxygen to stabilize through the anomeric effect.\textsuperscript{13} However, a $\beta$-2' fluorine has a stable conformer that forms gauche interactions with both the nucleobase and the ring oxygen in the active conformer, generating a single rigid structure (Figure 1-7b.ii). In the active conformer, a $\beta$-2', $\alpha$-3' difluorinated nucleoside possesses two stabilizing gauche interactions through the $\beta$-2' fluorine, a stabilizing anti-alignment of the fluorine dipoles of the $\beta$-2' and $\alpha$-3' fluorine, and an additional stabilizing gauche orientation between the $\alpha$-3' fluorine and the ring oxygen, further rigidifying the active conformer (Figure 1-7b.iii).
Figure 1-7: The Gauche Preference of Fluorine Controls Alkane Rotamers

a) Gauche Preference of Fluorine Substituents\textsuperscript{11}

<table>
<thead>
<tr>
<th>X</th>
<th>–F</th>
<th>–OH</th>
<th>–OAc</th>
<th>–CO\textsubscript{2}Me</th>
<th>–NH\textsubscript{2}</th>
<th>–NH\textsubscript{3}\textsuperscript{+}</th>
<th>–NAc</th>
<th>–Pyr</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔG (kcal/mol)</td>
<td>–0.5 –0.9</td>
<td>–0.3</td>
<td>–0.95</td>
<td>–1.6</td>
<td>–1.0</td>
<td>–5.8</td>
<td>–1.8</td>
<td>–3.7</td>
</tr>
</tbody>
</table>

b) Fluorination Controls Nucleoside Conformation\textsuperscript{12, 13}

b.i)

b.ii)

b.iii)
Fluorinated aryl ethers exhibit another form of conformational control. Non-fluorinated aryl methyl ethers align the methyl group in the plane of the aryl ring, and the oxygen lone pair of electrons resonate with the \( \pi \)-system.\(^{14}\) Fluorination decreases the participation of the oxygen lone pair electrons in resonance, by withdrawing electron density from the oxygen atom and into hyperconjugation with the C–F \( \sigma^* \).\(^{15}\) Therefore, for partially fluorinated aryl methyl ethers, a variety of torsion angles are observed, indicating mixed steric and resonance effects.\(^{15}\) Once the methyl group becomes fully fluorinated, the lone pair electrons of the ether oxygen no longer resonate with the \( \pi \)-system, instead interacting with the C–F \( \sigma^* \), thus steric hindrance of the 2 and 6 groups dominates. Thus, trifluoromethyl ethers sit orthogonal to the aromatic ring, increasing their effective size (Figure 1-8).\(^{15}\)

**Figure 1-8: Physical and Biological Effects of Fluorinated Aryl Ethers**\(^{15}\)

<table>
<thead>
<tr>
<th>Conformational Control</th>
<th>Modulate Lipophilicity (LogD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coplanar ( \theta(\text{Ar–Me}) = 0 \text{ or } 180^\circ )</td>
<td>( \theta(\text{Ar–CF}_2\text{H}) = \text{No Trend} )</td>
</tr>
<tr>
<td>Variable</td>
<td>( \theta(\text{Ar–CF}_3) = 90^\circ )</td>
</tr>
</tbody>
</table>

One specific fluorinated substructure, the difluoromethyl group, acts as an H-bond donor. Specifically, the \( \sigma \)-withdrawing effects of fluorine weakens the C–H bond, making the C–H bond act like a heteroatom–H bond. Thus, difluoromethyl groups are lipophilic H-bond donors, improving permeability and PGP efflux activity.\(^{16}\) In analogous systems,
the difluoromethyl group formed H-bonds with nearly the same strength as H-bond to a hydroxyl group (−3.1 vs −3.5 kcal/mol), and a recently developed HCV NS3 protease inhibitor exploits a difluoromethyl group to strengthen binding to the protease (Figure 1-9).
Figure 1-9: CF₂H Donates Lipophilic H-Bonds

a) CF₂H H-Bond Strength

HCV NS3 Protease Inhibition GT-1b Replicon

<table>
<thead>
<tr>
<th>AA</th>
<th>IC₅₀ (nM)</th>
<th>EC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>13</td>
<td>64</td>
</tr>
<tr>
<td>HF₂C</td>
<td>1</td>
<td>7.6</td>
</tr>
<tr>
<td>CF₂H</td>
<td>12</td>
<td>58.9</td>
</tr>
<tr>
<td>CF₃</td>
<td>17</td>
<td>125</td>
</tr>
</tbody>
</table>

The conformational effects of fluorine enable the investigation of the active conformers of bioactive compounds. For example, peptide amide bonds interchange between cis and trans conformations; thus, the active conformation is often unknown. One method to
interrogate the active conformation is to institute conformationally locked amide mimics, such as fluoroalkenes, in both the cis and trans isomer, and then investigate the biological activity.\textsuperscript{19} In a PEPT1 peptide transporter study, such a strategy revealed that only the cis isomer was recognized by PEPT1, implying that only one amide isomer, the trans amide isomer, is recognized by PEPT1.\textsuperscript{19a} In another example, intramolecular H-bonding of fluorine has been exploited to enforce $\gamma$-turns structures in investigational therapeutics.\textsuperscript{20} In a non-peptide Calcitonin Gene-Related Peptide (CGRP) antagonist, dipole alignment and H-bonding of fluorinated aryl rings with an amide enforced two different rotamers, demonstrating the likely active conformer (Figure 1-10).\textsuperscript{18}
Fluorination also alters pK<sub>a</sub> and hydrogen bonding, as fluorine affects the polarization and ionization of functional groups, disrupting solvation networks and partitioning characteristics.<sup>1a</sup> In the case of carboxylic acids and alcohols, fluorination increases the acidity and H-bond donating ability and decreases the H-bond accepting ability (Figure 1-11). Similarly, fluorination increases the acidity of amines, decreasing the H-bond accepting ability without a major effect upon H-bond donating ability. For carbonyls, fluorination decreases H-bond accepting ability (Figure 1-11). Since the σ-inductive effect
drives these perturbations, the more fluorine added, the greater the acidity increase, making the $pK_a$ changes due to fluorination predictable, as seen for amines (Figure 1-12b).\(^{21}\)

**Figure 1-11**: Effect of Fluorination on $pK_a$\(^{1a}\)

<table>
<thead>
<tr>
<th>R(^\cdot)OH</th>
<th>R(^\cdot)OH</th>
<th>$\alpha_2^H$</th>
<th>$\beta_2^H$</th>
<th>R(^\cdot)R</th>
<th>R(^\cdot)R</th>
<th>$\beta_2^H$</th>
<th>R(^\cdot)NH(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$-\text{CH}_3$</td>
<td>4.76</td>
<td>$-\text{CH}_3\text{CH}_3$</td>
<td>15.9</td>
<td>0.33</td>
<td>0.44</td>
<td>$-\text{CH}_3$</td>
<td>0.48</td>
</tr>
<tr>
<td>$-\text{CH}_2\text{F}$</td>
<td>2.6</td>
<td>$-\text{CH}_2\text{CF}_3$</td>
<td>12.4</td>
<td>0.57</td>
<td>0.18</td>
<td>$-\text{CF}_3$</td>
<td>0.24</td>
</tr>
<tr>
<td>$-\text{CF}_2\text{H}$</td>
<td>1.3</td>
<td>$-\text{C(CH}_3)_3$</td>
<td>19.0</td>
<td>0.32</td>
<td>0.49</td>
<td>$-\text{C}_6\text{H}_5$</td>
<td>4.3</td>
</tr>
<tr>
<td>$-\text{CF}_3$</td>
<td>0.5</td>
<td>$-\text{C(CF}_3)_3$</td>
<td>5.4</td>
<td>0.86</td>
<td>–</td>
<td>$-\text{C}_6\text{F}_5$</td>
<td>0.36</td>
</tr>
<tr>
<td>$-\text{C}_6\text{H}_5$</td>
<td>4.21</td>
<td>$-\text{C}_6\text{H}_5$</td>
<td>10.0</td>
<td>0.60</td>
<td>0.22</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>$-\text{C}_6\text{F}_5$</td>
<td>1.75</td>
<td>$-\text{C}_6\text{F}_5$</td>
<td>5.5</td>
<td>0.76</td>
<td>0.02</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

$\alpha_2^H$ = H-Bond Donating Ability; $\beta_2^H$ = H-Bond Accepting Ability

The perturbations in acidity due to fluorine can control the tissue selectivity of bioactive compounds by selectively modulating the binding interactions with molecular targets through tissue pH. For example, the opioid fentanyl is constitutively active throughout the body. $\mu$-Opioid receptor activation requires an ion-pairing interaction with the basic nitrogen in Fentanyl. Since the $pK_a$ of Fentanyl is approximately 8, once within the body fentanyl is active. However, fluorination near the basic nitrogen reduces the $pK_a$ to <7, preventing Fentanyl from activating $\mu$-opioid receptors in non-acidic tissues. Damaged tissue is acidic, thus the fluorinated Fentanyl derivative activates the $\mu$-opioid receptor only at the site of injury. Thus, in mouse models the fluorinated Fentanyl derivative shows similar analgesic activity to Fentanyl, without the same neurological effects, theoretically functioning as a non-addictive analgesic (Figure 1-12c).\(^{22}\)
**Figure 1-12: pKₐ Modulation of Amines via Fluorination**

<table>
<thead>
<tr>
<th>Amine</th>
<th>ΔpKₐ Predicted</th>
<th>ΔpKₐ Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NMe</td>
<td>–1.4</td>
<td>–1.7</td>
</tr>
<tr>
<td>MeN</td>
<td>–2.0</td>
<td>–1.8</td>
</tr>
<tr>
<td>MeN</td>
<td>–2.8</td>
<td>–2.6</td>
</tr>
<tr>
<td>MeN</td>
<td>–4.0</td>
<td>–3.7</td>
</tr>
</tbody>
</table>

**a) Fluorination Affect on pKₐ Decreases as Distance Increases**

**b) Predictable Affect of Fluorination Affect on amine pKₐ**

**c) Fluorination Controls Fentanyl pKₐ and Tissue Selective Activity**

**Effects on PK:**

Fluorine modulates the PK properties of bioactive compounds, especially in the late stages of lead development, when modifying PK properties with minor effects on binding become necessary. As detailed above, fluorine is a small element that, despite being extremely electronegative, is not highly polarizable. Thus, when fluorine is incorporated
in a compound, intermolecular interactions with fluorine are weak. Specifically, fluorine does not form strong H-bonding interactions with water molecules and affects the intermolecular interactions of vicinal functional groups with water by σ-induction. As such, fluorination generally results in increases in logP and permeability, with a few unique fluorinated substituents reducing logP.

The effect of fluorine on logP can be predicted and controlled by fluorination patterning. First, the vicinity of a heteroatom to the fluorine substitution greatly affects the resulting modulation of logP (Figure 1-13). In the absence of a heteroatom, fluorination reduces logP, as in the case of ethane. When close to a heteroatom, fluorination increases logP, such as for ethanol or propanol. As the fluorination moves further from the heteroatom, the logP increase decreases, as in hexanol. Additionally, the amount of fluorine in a molecule affects to what extent fluorine changes logP. Generally, the more fluorine in a molecule, the greater the effect.

**Figure 1-13: Fluorine-Driven logP Modulation**

<table>
<thead>
<tr>
<th>Parent Compound</th>
<th>LogP</th>
<th>Fluorinated Compound</th>
<th>LogP</th>
<th>ΔLogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃–CH₃</td>
<td>1.81</td>
<td>CH₃–CHF₂</td>
<td>0.75</td>
<td>–1.06</td>
</tr>
<tr>
<td>CH₃CH₂OH</td>
<td>0.32</td>
<td>CF₃CH₂OH</td>
<td>0.36</td>
<td>+0.04</td>
</tr>
<tr>
<td>CH₃(CH₂)₂OH</td>
<td>0.34</td>
<td>CF₃(CH₂)₂OH</td>
<td>0.39</td>
<td>+0.05</td>
</tr>
<tr>
<td>CH₃(CH₂)₅OH</td>
<td>1.64</td>
<td>CF₃(CH₂)₅OH</td>
<td>1.36</td>
<td>–0.28</td>
</tr>
</tbody>
</table>

Polarity vector analysis enables prediction of the effects of fluorination on logP. For instance, in the case of a cyclohexane ring, trans fluorination makes the polarity vectors cancel (Figure 1-14a). Thus, fluorine acts as a lipophilic hydrogen and increases logP without altering the overall polarity of the compound. However, with all cis fluorination, the
polarity vectors add together, increasing the overall polarity and reducing logP. For an all-cis tetrafluorinated cyclohexane, the logP decreases by 2.41 log units relative to the non-fluorinated cyclohexane (Figure 1-14b). Recently, the Müller group recently systematically explored the effect of many fluorination patterns on polarity, logP, solubility, and metabolism. In their studies, by patterning the fluorine substitutions to enable additive polarity vectors, vicinal fluorination reliably reduced logP and increased solubility beyond either the non-fluorinated or germinal difluorinated analog. In cases where the fluorine polarity vectors cancelled, specifically germinal difluorination, logP increased and solubility decreased relative to the non-fluorinated compound (Figure 1-14c).
**Figure 1-14:** Fluorination Patterning Increases the Effect of Fluorination on Biological Properties

### a) Fluorination Patterning of Cyclohexane Rings Controls Polarity

| Dipole Moment (Debye) | 0.80 | 3.39 | 1.93 | 3.57 | 0.00 | 4.72 |

### b) Fluorination Patterning of Cyclohexane Rings Lowers LogP

| LogP | 3.76 | 4.99 | 3.30 | 2.79 | 2.64 | 2.58 |

### c) Fluorination Patterning Perturbs PK Properties

<table>
<thead>
<tr>
<th>Alkyl Fluoride</th>
<th>LogP</th>
<th>Solubility (µmol/L)</th>
<th>Clearance (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—Me</td>
<td>3.3</td>
<td>200</td>
<td>513</td>
</tr>
<tr>
<td>R—CF₃</td>
<td>3.1</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>R—Me</td>
<td>2.8</td>
<td>820</td>
<td>508</td>
</tr>
<tr>
<td>R—F</td>
<td>2.5</td>
<td>&gt;1700</td>
<td>212</td>
</tr>
<tr>
<td>R—Me</td>
<td>3.1</td>
<td>182</td>
<td>644</td>
</tr>
<tr>
<td>R—F</td>
<td>3.0</td>
<td>115</td>
<td>321</td>
</tr>
<tr>
<td>R—Me</td>
<td>2.8</td>
<td>277</td>
<td>245</td>
</tr>
</tbody>
</table>

Polarity Analysis:

- α: \( \mu_{calc} = 2.26 \) D
- anti: \( \mu_{calc} = 0.00 \) D
- gauche: \( \mu_{calc} = 2.67 \) D
In aromatic systems, the effect of fluorination is more simple, as no additive or cancelling polarity vectors form. Instead, fluorination adjusts the electron density of the \( \pi \)-system, resulting in a small increase in \( \log P \) for each fluorine substituent.\(^1\) Such an effect is maintained for perfluoroalkyl groups. Partially fluorinated aryl substituents, such as difluoromethylene groups, reduce \( \log P \) through the previously discussed polarity vector addition (Figure 1-15).\(^{14, 23} \) The effect is especially pronounced for fluorinated alkyl chains with vicinal rather than germinal fluorination.\(^{15, 24} \)

**Figure 1-15: Effect of Aromatic Fluorination on Lipophilicity**

<table>
<thead>
<tr>
<th>( R )</th>
<th>( \pi ) (Hansch-Leo)(^1)</th>
<th>( R )</th>
<th>( \Delta \log P )(^{15, 24} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>-H</td>
<td>0</td>
<td>-CH(_2)CH(_2)CH(_3)</td>
<td>0</td>
</tr>
<tr>
<td>-F</td>
<td>0.14</td>
<td>-CH(_2)CH(_2)CH(_2)F</td>
<td>-0.7</td>
</tr>
<tr>
<td>-CH(_3)</td>
<td>0.56</td>
<td>-CH(_2)CH(_2)CF(_2)H</td>
<td>-0.6</td>
</tr>
<tr>
<td>-CF(_3)</td>
<td>0.88</td>
<td>-CH(_2)CH(_2)CF(_3)</td>
<td>-0.4</td>
</tr>
<tr>
<td>-CH(_2)CH(_3)</td>
<td>1.02</td>
<td>-OCH(_3)</td>
<td>0</td>
</tr>
<tr>
<td>-CH(_2)CF(_3)</td>
<td>1.89</td>
<td>-OCH(_2)F</td>
<td>0.1</td>
</tr>
<tr>
<td>-OCH(_3)</td>
<td>-0.02</td>
<td>-OCF(_2)H</td>
<td>0.3</td>
</tr>
<tr>
<td>-OCF(_3)</td>
<td>1.04</td>
<td>-OCF(_3)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Mostly, fluorine is used to block metabolism, or shift the site of metabolism. Multiple effects, including the strength of C–F bonds relative to C–H bonds, and the electronic character of fluorine, drive these shifts in metabolism. First, at aliphatic metabolic sites, fluorination precludes metabolism altogether, due to the interactions of fluorine and the main metabolic enzymes, CYP\(_{450}\)s. At aliphatic sites, CYP\(_{450}\)s use electron rich iron-bound hydroxyl radicals to homolytically cleave C–H bonds (Figure 1-16a). In non-
fluorinated systems, the hydrogen of the C–H bond is not electron-rich, enabling the iron-oxo species to approach and interact with the hydrogen. Thus, the transition state of homolytic cleavage is relatively low in energy. Since the resulting O–H bond is stable, the reaction intermediate is also relatively low energy, only about 10 kcal/mole less stable than the initial C–H bond.

When F replaces H, several changes prevent the oxidative cleavage of the C–F bond. First, the C–F bond is generally 5–8 kcal/mol stronger than the analogous C–H bond, making homolytic bond cleavage more difficult.² Second, the C–F bond possesses partial negative charge on the fluorine atom, which repels the electron rich oxygen of the iron-oxo species and raises the transition state energy of CYP₄₅₀ mediated oxidative cleavage. Finally, the resulting O–F bond is exceptionally weak, about 60 kcal/mol weaker than the C–F bond, making the intermediate far higher energy than the starting material (Figure 1-16b). Combined, these effects raise the activation barrier of CYP-mediated metabolism beyond an achievable level. Blocking CYP-mediated metabolism through fluorination has been exploited in many medicinal chemistry campaigns, such as the development of Bosentan²⁵ and Begacestat²⁶ (Figure 1-16c, Figure 1-17).
Figure 1-16: Fluorination Prevents CYP₄₅₀ Mediated Oxidation

a) Oxidative Metabolism of C–H Bond by CYP₄₅₀

\[
\text{Sub} - \text{H} \xrightarrow{\text{O}^+} \text{Sub} - \text{OH}
\]

\[
\begin{array}{ccc}
\text{Fe}^{IV} & \text{N} & \text{Cys} \\
\text{N} & \text{N} & \text{S} \\
\text{O} & \text{Cys} & \text{Sub}
\end{array}
\xrightarrow{\text{O}^+} 
\begin{array}{ccc}
\text{Fe}^{IV} & \text{N} & \text{Cys} \\
\text{N} & \text{N} & \text{S} \\
\text{O} & \text{Cys} & \text{Sub}
\end{array}
\xrightarrow{\text{O}^+} 
\begin{array}{ccc}
\text{Fe}^{III} & \text{N} & \text{Cys} \\
\text{N} & \text{N} & \text{S} \\
\text{O} & \text{Cys} & \text{Sub}
\end{array}
\]

b) Oxidative Metabolism of Analogous C–F Bond by CYP₄₅₀

\[
\text{Sub} - \text{F} \xrightarrow{\text{O}^+} \text{Sub} - \text{O}^-
\]

\[
\begin{array}{ccc}
\text{Fe}^{IV} & \text{N} & \text{Cys} \\
\text{N} & \text{N} & \text{S} \\
\text{O} & \text{Cys} & \text{Sub}
\end{array}
\xrightarrow{\text{O}^+} 
\begin{array}{ccc}
\text{Fe}^{IV} & \text{N} & \text{Cys} \\
\text{N} & \text{N} & \text{S} \\
\text{O} & \text{Cys} & \text{Sub}
\end{array}
\xrightarrow{\text{O}^+} 
\begin{array}{ccc}
\text{Fe}^{IV} & \text{N} & \text{Cys} \\
\text{N} & \text{N} & \text{S} \\
\text{O} & \text{Cys} & \text{Sub}
\end{array}
\]

\[
\begin{array}{cccc}
\text{Bond Strength}^2 \\
(\text{kcal/mol})
\end{array}
\]

<table>
<thead>
<tr>
<th>Bond</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C–H</td>
<td>104</td>
</tr>
<tr>
<td>C–F</td>
<td>110</td>
</tr>
<tr>
<td>C–O</td>
<td>90</td>
</tr>
<tr>
<td>O–H</td>
<td>102</td>
</tr>
<tr>
<td>O–F</td>
<td>53</td>
</tr>
</tbody>
</table>

c) Bosentan Metabolism

\[
\text{R} = \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\xrightarrow{\text{CYP 2C9}} \begin{array}{c}
\text{HO} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

\[
\begin{array}{ccc}
\text{HLM, 30 min Incubation} & \% \text{ Remaining} & \text{CYP2C9, 30 min Incubation} & \% \text{ Remaining} \\
\text{R} = \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{CF₃} \\
\text{CF₃} \\
\text{CF₃} \\
\text{CF₃} \\
\end{array} & 91.6\% & 75.8\% & 100\% \\
\text{R} = \begin{array}{c}
\text{CF₃} \\
\text{OH} \\
\text{CF₃} \\
\end{array} & 90.1\% & 100\% & 100\% \\
\text{R} = \begin{array}{c}
\text{CF₃} \\
\text{F} \\
\text{CF₃} \\
\text{CF₃} \\
\end{array} & 99\% & 100\% & 100\%
\end{array}
\]
Another example of fluorination inhibiting the oxidative activation of C–H bonds by CYP\textsubscript{450} enzymes is the development of Begacestat, as the half-life of the preclinical lead in microsomes precluded further use, necessitating further compound development (Figure 1-17).\textsuperscript{26} The compounds underwent both phase 1 aliphatic oxidation and phase 2 glucuronidation. To prevent phase 1 oxidation, the terminal methyl groups were replaced with trifluoromethyl groups, which shifted but did not sufficiently slow phase 1 metabolism. By decreasing the chain length between the sulfonamide and the trifluoromethyl groups, phase 1 metabolism was effectively stopped. Conversely, glucuronidation could not be prevented, as the free hydroxyl was necessary for activity. However, the vicinal trifluoromethyl groups withdraw electron density from the free alcohol, reducing the nucleophilicity of the alcohol and indirectly controlling phase 2 metabolism. Generally, phase 2 metabolism requires nucleophilic heteroatoms, especially alcohols, in order to undergo processes such as glucuronidation. The reduced electron density of the heteroatom is expected to slow or stop this metabolism.
**Figure 1-17:** Fluorination Pattern of Begacestat Perturbs Metabolism

<table>
<thead>
<tr>
<th>Initial Lead</th>
<th>Glucuronidation Cannot be Blocked</th>
<th>Glucuronidation</th>
<th>Fluorine Shifts Oxidative Met.</th>
<th>Fluorine Slows Glucuronidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO—Me—Me</td>
<td>Metabolism</td>
<td>Gluc—OH</td>
<td>Metabolism</td>
<td>Gluc—OH</td>
</tr>
<tr>
<td>HN—SO—Cl</td>
<td></td>
<td></td>
<td>Metabolism</td>
<td>Gluc—CF₃</td>
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<tr>
<td>CF₃</td>
<td></td>
<td></td>
<td></td>
<td>Gluc—CF₃</td>
</tr>
<tr>
<td>HO—Me—Me</td>
<td>Metabolism</td>
<td>Gluc—OH</td>
<td>Metabolism</td>
<td>Gluc—CF₃</td>
</tr>
<tr>
<td>HN—SO—Cl</td>
<td></td>
<td></td>
<td>Metabolism</td>
<td>Gluc—CF₃</td>
</tr>
<tr>
<td>CF₃</td>
<td></td>
<td></td>
<td>Metabolism</td>
<td>Gluc—CF₃</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microsome</th>
<th>t₁/₂ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>2</td>
</tr>
<tr>
<td>Rat</td>
<td>1</td>
</tr>
<tr>
<td>Human</td>
<td>8</td>
</tr>
<tr>
<td>Dog</td>
<td>–</td>
</tr>
<tr>
<td>Monkey</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>t₁/₂ (min)</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Rat</td>
<td>8</td>
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<tr>
<td>Human</td>
<td>8</td>
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<tr>
<td>Dog</td>
<td>13</td>
</tr>
<tr>
<td>Monkey</td>
<td>5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Microsome</th>
<th>t₁/₂ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>48</td>
</tr>
<tr>
<td>Rat</td>
<td>3</td>
</tr>
<tr>
<td>Human</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Dog</td>
<td>31</td>
</tr>
<tr>
<td>Monkey</td>
<td>26</td>
</tr>
</tbody>
</table>

In aromatic systems, fluorination alters the “NIH” hydride shift that occurs upon CYP₄₅₀-mediated aromatic oxidation reactions.²⁷ CYP₄₅₀ mediated aromatic metabolism generally requires electron-rich aromatic rings, as aromatic metabolism initiates via an epoxidation where the π-system of the aromatic ring acts as a nucleophile to react with the CYP₄₅₀ Fe–O species. The aromatic epoxide opens and undergoes the NIH-shift, a
1,2-hydride shift, to generate an aromatic alcohol (Figure 1-18a). Fluorination affects aromatic metabolism through two charge effects.

First, fluorine perturbs the distribution of electron density of an aromatic ring, which might decrease metabolism by slowing the initial reaction of the nucleophilic arene π-system on the CYP_{450} Fe–O species. Second, the dearomatized C–F bond is strong, and does not readily undergo 1,2-fluoride shifts, such as the “NIH” shift. Thus, when oxidation does occur, the site of oxidation changes, whether by the initial epoxide opening through a 1,2-hydride shift resulting in a different aromatic alcohol isomer, or a different initial oxidation site (Figure 1-18b).\textsuperscript{27} Thus, aromatic fluorination is frequently exploited in medicinal chemistry to either reduce, shift, or shut down aromatic oxidative metabolism, as in the development of Taranabant (Figure 1-18c).\textsuperscript{28} Aromatic oxidative metabolism of the electron-rich aryl ether of an early analog of Taranabant generated a glutathione adduct, which causes allergic reactions. To reduce this aromatic metabolism, the aryl ether was difluorinated; however, metabolism and formation of a glutathione adduct still occurred. To further reduce the electron density, the aryl ether was changed to an electron-deficient pyridine, which further reduced metabolism. Further reduction of the electron density of the ring by the addition of a trifluoromethyl substituent ultimately prevented this metabolism.
1.3. The Impact of Fluorine on the Reactivity of Organic Compounds

The aforementioned perturbations of biological properties make synthetic methods to access fluorine-containing molecules important to both biomedical and agricultural...
chemists. However, fluorination of a substrate can present distinct reactivity patterns in organic chemistry, making many synthetic transformations challenging to extrapolate to fluorinated systems. Often, standard organic reactions do not work in the presence of fluorinated reagents or with fluorinated substrates, which requires changes to the system or alternate synthetic strategies to provide the desired products.

For example, many standard transition metal-catalyzed reactions commonly employed to generate C–C and C–heteroatom bonds might fail when applied to the generation of C–C(F)ₙ or C–F bonds. To illustrate this type of challenge, consider the distinct conditions and mechanisms of Cu-catalyzed and -mediated 1,4-addition reactions of non-fluorinated and fluorinated groups to α,β-unsaturated carbonyl systems. Cu-catalyzed and -mediated 1,4-addition reactions of non-fluorinated substrates remain one of the most robust strategies in synthetic organic chemistry, compatible with a broad spectrum of organic nucleophiles, including simple methyl groups. While the first examples of the Cu-mediated 1,4-addition of a methyl group date back at least to 1941, the first examples of 1,4-addition of −CF₃ were only reported in 1988 and 1989, with the first general strategy reported in 2003.

In the non-fluorinated case, the reaction proceeds with catalytic quantities of Cu(I) at 0 °C or lower, with a mechanism that involves an oxidative addition of a higher-order cuprate to the β-position of the Michael acceptor to generate a Cu(III) intermediate, followed by reductive elimination of the new C(β)–Me bond (Figure 1-19). In contrast, similar reaction conditions do not promote conjugate addition reactions of −CF₃. Instead, reactions to generate a new C(β)–CF₃ bond require super-stoichiometric quantities of Cu.
at 60 °C, and proceed by a distinct mechanism involving addition of “free •CF₃” to the β-position unsaturated system with no indication of an analogous Cu(III) intermediate (Figure 1-19).³⁸

**Figure 1-19:** Different Mechanisms for Cu-Catalyzed 1,4-Additions of Methyl and Trifluoromethyl Nucleophiles³⁶-³⁸

As a second example, Pd-catalyzed cross-coupling reactions to generate C(aryl)–CF₃ bonds have proven challenging. The Pd–CF₃ bond resists reductive elimination, because the high electronegativity of the trifluoromethyl group³⁹ imparts strong ionic bond character to the Pd–C bond (Figure 1-20a).⁴⁰ This reductive elimination step requires ~22 kcal/mol to reach the transition state, with most of the energy required to break the Pd–CF₃ bond (Figure 1-20b).⁴¹ Since reductive elimination of the L₅(Ar)Pd–CF₃ bond is slow, other unexpected reaction pathways can occur.⁴² For instance, under the elevated temperatures necessary for the reductive elimination of the C(aryl)–CF₃ bond, the Ruppert-Prakash reagent (TMS–CF₃), the most common –CF₃ source, decomposes to :CF₂ and TMS–F, thus complicating transmetallation to Pd.⁴¹ As a result, most common catalyst systems that promote C–C bond-forming reactions fail to generate the C(aryl)–
CF₃ bond, which instead requires specialized ligands or higher oxidation states of Pd to promote reductive elimination.⁴¹,⁴²b,⁴³

**Figure 1-20:** Challenging Reductive Elimination of Pd–CF₃

*a) High electronegativity of CF₃ group resists red. elim. of Ar–R bond*⁴⁹

<table>
<thead>
<tr>
<th>R</th>
<th>σ⁺</th>
<th>Red. Elim. kᵣₑₐ₉ @ 110 °C</th>
<th>Red. Elim. t₁/₂ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>0.00</td>
<td>&gt;600</td>
<td>&lt;5 (90 °C)</td>
</tr>
<tr>
<td>CH₃Ph</td>
<td>0.22</td>
<td>&gt;250</td>
<td>&lt;5 (90 °C)</td>
</tr>
<tr>
<td>CH₂C(O)Ar</td>
<td>0.60</td>
<td>31</td>
<td>39 (90 °C)</td>
</tr>
<tr>
<td>CH₂CF₃</td>
<td>0.92</td>
<td>1.7</td>
<td>~720 (110 °C)</td>
</tr>
<tr>
<td>CH₂CN</td>
<td>1.30</td>
<td>1</td>
<td>~1,200 (110 °C)</td>
</tr>
<tr>
<td>CF₃</td>
<td>2.60</td>
<td>No Rxn</td>
<td>No Rxn (&gt;130 °C)</td>
</tr>
</tbody>
</table>

*b) High energy at TS for reductive elimination derives from lengthening and breaking of Pd–CF₃ bond*⁴⁰

The challenging reductive elimination from Pd can be avoided by employing other metal catalysts. For example, reductive elimination of CF₃ from a Cu(III) complex is facile, although oxidative addition of an aryl halide to Cu(I) to form a Cu(III) complex is slow, requiring weak C–X bonds or high temperatures. To address this issue, radical CF₃ addition to Cu(II) enables access to the Ar–Cu(III)–CF₃ complex that can undergo a more facile reductive elimination (Scheme 1-1a).⁴⁴ This strategy exploits a variety of •CF₃ precursors, from photocatalytic activation of an S–CF₃ reagent⁴⁴ or the direct one electron
transfer of •CF₃ to a Cu(I) catalyst from Togni or Umemoto’s reagent (Scheme 1-1b).\textsuperscript{45} Reductive elimination of Ar–CF₃ from Cu(III) is so facile that it is possible even at room temperature (Scheme 1-1c).\textsuperscript{46}

**Scheme 1-1: Facile Reductive Elimination from Cu(III)**

\begin{multicols}{2}
\begin{itemize}
\item[a)] Co-catalytic Photocatalysis Enables Facile CF₃ reductive elimination from Cu\textsuperscript{43}
\begin{align*}
\text{R} & \quad \text{Br} \\
\text{X} & \quad \text{OTf} \\
\text{Mes} & \quad \text{S-Mes} \\
\text{CF₃} & \quad \text{CuBr₂} \cdot 2\text{LiBr (20 mol\%)} \\
\text{Ir Photocat. (0.125–0.25 mol\%)} & \quad \text{(Me₃Si)₃SiOH, Inorganic Base} \\
\text{Acetone, Blue LED, 35 °C, Ar} & \quad \text{R} \quad \text{CF₃}
\end{align*}

\item[b)] Trifluoromethylation Reagents Enable CF₃ reductive elimination from Cu\textsuperscript{44}
\begin{align*}
\text{R} & \quad \text{CHCl₃, 60–120 °C, Ar} \\
\text{CF₃} & \quad \text{OCOAr} \\
\text{CuI (10 mol\%)} & \quad \text{R} \quad \text{CF₃}
\end{align*}

\item[c)] Oxidative Trifluoromethylation of Boronic Acids Mediated by Cu\textsuperscript{45}
\begin{align*}
\text{R} & \quad \text{B(OH)₂} \\
\text{TMS} & \quad \text{CF₃} \\
\text{Cu(OAc)₂ (1 equiv.)} & \quad \text{Phenanthroline (1.1 equiv)} \\
\text{CsF, 4 Å MS} & \quad \text{DCE, R.T., O₂} \\
\text{R} & \quad \text{CF₃}
\end{align*}
\end{itemize}

These two examples in which fluorinated reagents pose unique challenges relative to reactions of non-fluorinated reagents demonstrate why so much effort from the synthetic community has been devoted to finding new strategies for incorporating fluorinated substituents into organic molecules.\textsuperscript{29, 47}

While the presence of fluorine in a substrate poses challenges to standard synthetic transformations, fluorine can also open other avenues of reactivity by altering the energy barriers for transformations. For example, consider classical [3,3]-sigmatropic rearrangements. The thermal Claisen reaction of allyl cinnamyl ether requires forcing
conditions (190 °C, 6 h) to provide 75% yield of product. Presumably, this high temperature arises from the conjugated phenyl substitution at the terminal C6 position that removes π-electron density from allyl vinyl ether, disfavoring the bond-making event at the diyl transition state. However, when fluorinated at the α-position of the enol ether, the Claisen reaction occurs under more mild conditions (80 °C, 1 h). In this case, the gem-difluorinated carbon prefers an sp³-hybridized state rather than the sp²-hybridized state, thus providing a thermodynamic driving force that disfavors the reverse reaction (Figure 1-21a). This same effect also controls other sigmatropic rearrangements, such as the Cope rearrangement. For example, 1,1-difluoro-1,5-hexadiene prefers to rearrange to the 3,3-difluoro-1,5-hexadiene product (5 kcal/mol more stable), and the fluorinated substituents lower the activation barrier (2.5 kcal/mol) relative to the corresponding rearrangement of 1,5-hexadiene (Figure 1-21b).

Figure 1-21: The Presence of Fluorinate Facilitates [3,3]–Sigmatropic Rearrangements

Fluorination also affects the reactivity of carbonyl and other sp² hybridized functionalities via σ-withdrawing electronic effects. This perturbation is generally
explained through Bent’s rule, which states that atoms with more electron withdrawing substituents prefer hybrid orbitals with more p-character. This relieves electronic strain, as the p orbitals sit further from the nucleus than s orbitals and thus donate more electron density to the electron withdrawing substituents. Thus, fluorinated carbon atoms generally prefer sp\(^3\)-hybridization that can better release electron density to stabilize the partial cationic charge, thus driving some reactivity trends. For instance, \(\alpha\)-fluorinated carbonyls hydrate easily to hybridize from sp\(^2\) to sp\(^3\), allowing the carbonyl carbon to relieve the strain of the electron withdrawing fluorinated \(\alpha\)-carbon and the carbonyl oxygen (Figure 1-22a). This property has been exploited for developing therapeutically relevant agents, such as Lubiprostone, in which the \(\alpha,\alpha\)-difluoroketone prefers to rehybridize from the open ketone form (sp\(^2\)-hybridized) to the closed lactol form (sp\(^3\)-hybridized, Figure 1-22a).\(^{52}\) Additionally, medicinal chemists harness these physicochemical perturbations to facilitate inhibition of serine and aspartyl proteases (Figure 1-22b).\(^{1a, 1b, 53}\) Proteases cleave peptide bonds by adding oxygen-based nucleophiles to the amide carbonyl to generate a tetrahedral intermediate. This process involves an sp\(^2\) to sp\(^3\) rehybridization of the carbonyl carbon. When a peptide amide is replaced with an \(\alpha,\alpha\)-difluoroketone, two effects combine to inhibit proteases. First, the labile C–N bond is replaced with a stable C–C bond, preventing cleavage of the peptide bond isostere. Second, \(\alpha,\alpha\)-difluoroketones prefer sp\(^3\)-hybridization at the carbonyl carbon, thus stabilizing the tetrahedral intermediate and acting as a mechanism-based inhibitor.
**Figure 1-22: α,α-Difluoroketones Prefer sp³-Hybridization**

*a)* High electronegativity of fluorine encourages rehybridization of α,α-difluoroketones

\[
\begin{align*}
\text{sp}^2\text{-hybridization (more electronegative)} & \quad \text{sp}^3\text{-hybridization (less electronegative)} \\
R^1 \alpha \alpha & + \ H-OR^3 \\
\end{align*}
\]

α-withdrawing effect

Lubiprostone prefers the more stable cyclic lactol form\(^{51}\)

\[
\begin{align*}
\text{C}_{4}H_9 & \quad \text{OH} \\
\text{HO} & \quad \text{H} \\
\text{C}_6H_{12}CO_2H & \quad \text{C}_6H_{12}CO_2H \\
\end{align*}
\]

*b)* Fluorinated ketone-based protease inhibitors exploit stabilized tetrahedral intermediate\(^{1,a,b,52}\)

\[
\begin{align*}
\text{R}^1 \text{R}^2 & \quad \text{Enzyme-Ser-OH} \\
\text{R}^1 \text{R}^2 & \quad \text{Enzyme-Asp-CO}_2H \\
\text{R}^1 \text{R}^2 & \quad \text{H}_2\text{O} \\
\end{align*}
\]

Separately, α,α-difluoroketones possess low enolate reactivity driven by the inappropriate orbital alignment of fluorinated ketones. However, despite the electron-withdrawing effect of the difluoromethylene group, α,α-difluoroketones do not possess increased acidity relative to non-fluorinated ketones (Figure 1-23b). In order to deprotonate, the proton must align with the π orbital of the carbonyl\(^{54}\). Typically, electron withdrawing groups, such as carbonyls or nitro groups, increase acidity through π-
withdrawing effects that weaken the C–H bond, while deprotonation requires overlap between the $\alpha$-H and the $\pi$-orbitals. However, in this orientation, the F and O atoms would eclipse and cause unfavorable electrostatic repulsion. Thus, the F atoms likely reside in a conformation that minimizes C=O--F–C repulsion, and places the $\alpha$-H atom orthogonal to the $\pi$ system, which disfavors deprotonation (Figure 1-23a). As such, ketones bearing an $\alpha,\alpha$-difluoromethyl group and a simple alkyl group will preferentially generate the non-fluorinated enolate under both kinetic and thermodynamic conditions (Figure 1-23b). Thus, alternate strategies, such as Mg$^0$-mediated F$^-$ elimination from a trifluoromethyl ketone and subsequent trapping with TMS (Figure 1-23c), are required to access $\alpha,\alpha$-difluoroketone enolate derivatives.
Enolates typically exhibit strong nucleophilicity at the α-carbon, providing a functional handle for C–C bond formation via an S_N2 reaction between a ketone enolate and an sp^3-hybridized electrophile (Figure 1-23d)\(^{57}\) and are frequently exploited in complex molecule synthesis. Fluorinated enolates perturb this reactivity, as the strong inductive effect of two fluorine atoms lowers the electron density\(^{58}\) at the traditionally nucleophilic α-position\(^{59}\) thus shifting the reactive site to the O atom. As a result, alkylation occurs on O to produce β,β-difluorovinyl ethers (Figure 1-23e)\(^{60}\). Further, the α-carbon in α-
fluorinated enolates changes from a nucleophilic center to an electrophilic center. For example, C–F functionalization reactions of α,α-difluorinated enolates with strong nucleophiles generate various α-substituted-α-fluoroenols (Figure 1-23g).  

Nucleophilic C–C bond forming reactions of fluorinated enolates require metal catalysts and reactions strategies that activate the α,α-difluorinated carbon (Scheme 1-2). Specifically, this strategy enables regioselective formation of a Pd-enolate intermediate by the formation of an activated ester. Oxidative addition of Pd occurs at the activated ester, thus only the C-bound α,α-difluoroketone enolate forms, not the O-bound Pd species. Once Pd binds at the difluorinated position, reductive elimination enables C–C bond formation with the difluorinated carbon (Scheme 1-2).
**Scheme 1-2:** Metal Catalyzed Reactions Enable Nucleophilic Enolate Reactivity for \(\alpha,\alpha\)-Difluoroketones

---

*Decarboxylation generates the fluoroalkyl enolate*  
*Reductive elimination generates C–C Bond*

---

1.4. Fluorine-Induced Perturbations of Alkene Reactivity

Similar to the cases of \(\alpha,\alpha\)-difluorinated and non-fluorinated enolates, gem-difluoroalkenes demonstrate complementary reactivity to non-fluorinated alkenes. Both fluorinated and non-fluorinated alkenes can provide versatile building blocks for synthetic organic chemistry. Non-fluorinated alkene groups commonly react with electrophiles through the \(\pi\)-HOMO orbitals,\(^{30, 62}\) while also reacting with nucleophiles through the \(\pi^*\)-LUMO. To react with the \(\pi^*\) orbital, non-fluorinated alkenes require activation, typically
through incorporation of carbonyl, nitrile, and nitro groups that lower the LUMO through resonance effects. This activation restricts nucleophilic attack to the electrophilic β-carbon (Figure 1-24a), while functional groups that facilitate attack at the α-carbon are less common.

In contrast, fluorination of alkenes allows an alternate mode of reactivity, thus providing a distinct subset of products relative to classical 1,4-addition reactions (Figure 1-24a). For fluorinated alkenes, the inductive, σ-withdrawing effect of fluorine atoms activates the geminal carbon, while the resonance effect of fluorine disfavors attack of the β-position (Figure 1-24b). This regioselectivity is reinforced by the σ-withdrawing effect that stabilizes the β-fluorocarbanion intermediate after nucleophilic attack (Figure 1-24c).

Further, in gem-difluoroalkenes, the sp² hybridization of the difluorinated carbon increases the electrophilicity, as, according to Bent’s rule, a carbon center containing two electron deficient substitutions is more stable when the hybrid orbital bears more p-character (Figure 1-24c). Combined with the extreme electron deficiency of a difluorinated carbon, difluoroalkenes are exceptionally electrophilic at the difluorinated carbon, encouraging nucleophiles to the attack the α-carbon (Figure 1-24b). Overall, the fluorine-induced polarization of alkenes and enolates is sufficiently strong to overcome the intrinsic reactivity of non-fluorinated substrates and render electrophilic character at the typically nucleophilic site (Figure 1-24b).
Figure 1-24: Uncommon Reactivity of gem-Difluoroalkenes

Notably, C–F bond cleavage in gem-difluoroalkenes is easier than in other fluorinated systems due to the formation of the β-anionic intermediate enabling an addition / elimination mechanism (Figure 1-24c). Upon attack by a nucleophile, the reaction generates an unstable anionic intermediate vicinal to the fluorinated position. As a fluoride anion is more thermodynamically stable than a carbanion or other heteroatom centered anion, the elimination process eliminates fluoride rather than the recently incorporated nucleophile to relieve the disfavored anionic charge (Figure 1-24). Based on this reactivity, many net C–F functionalizations of difluoroalkenes are used to generate useful fluorinated moieties, enabling the synthesis of valuable fluorinated compounds. This reactivity has been exploited in intramolecular cyclizations (Scheme 1-3a) and intermolecular C–F functionalizations with amine, alcohol, thiol, and carbon nucleophiles (Scheme 1-3b). Previous efforts have not overridden this elimination step to deliver products bearing two fluorine atoms. Efforts that override this elimination step via protonation of the unstable intermediate form the basis of Chapter 2 and Chapter 3.
Scheme 1-3: C–F Functionalization Reactions of *gem*-Difluoroalkenes with Nucleophiles

Involves Nucleophilic Addition / F⁻ Elimination Mechanisms

*a) Intramolecular cyclizations by net C–F functionalization with nucleophiles*⁶⁸ᵃ,ᵇ

![Intramolecular cyclizations by net C–F functionalization with nucleophiles](image)

*b) Intermolecular net C–F functionalization with nucleophiles*⁶⁸ᶜ,ᵈ

![Intermolecular net C–F functionalization with nucleophiles](image)

The *gem*-difluoroalkene group also provides opportunities for developing new transition metal catalyzed reactions. For example, transition metals might be used to engage the anionic fluoroalkyl intermediate prior to elimination. This type of strategy would enable domino nucleophilic addition / metal catalyzed cross-coupling reactions, such as has been recently developed by the Loh⁷⁰ and Hu⁷¹ groups to form new C–C bonds and to produce highly functionalized β,β,β-trifluoroethylarenes (Figure 1-25a). Additionally, *gem*-difluoroalkenes can interact directly with metals, often by unexpected pathways (Figure 1-25b, c).⁶⁴ For these substrates the strong olefinic C–F bonds (120–129 kcal/mol)⁷² disfavor oxidative addition by most transition metals, except for recently...
reported Pd-based\textsuperscript{73} and Ni-based\textsuperscript{73d, 74} systems (Figure 1-25b). However, metal catalyst systems derived from Cu, Rh, Co, and alternate Pd complexes avoid oxidative addition to the C–F bond, and instead initiate the net C–F functionalization reaction by either olefin–metal coordination\textsuperscript{75} or C–H oxidative addition\textsuperscript{76} (in the presence of two vinylic C–X bonds), followed by regioselective insertion, and termination of the sequence through facile β-fluoride elimination to deliver mono-fluoroalkenes (Figure 1-25c). Current metal-catalyzed reactions of \textit{gem}-difluoroalkenes either undergo difunctionalization reactions using a fluoride nucleophile or cannot retain both fluorines when using other nucleophiles. This limitation of transition-metal catalyzed reactions with \textit{gem}-difluoroalkenes is addressed in Chapter 4 and Chapter 5.
Exploiting the reactivity of gem-difluoroalkenes is a valuable goal, as gem-difluoroalkenes are easily-accessible synthetic building blocks. These α,α-difluoroalkene substrates can be generated by a variety of methods, including cross coupling reactions of aryl halides and aryl boronic acids, and olefination reactions of diazo compounds, ketones, and aldehydes (Wittig and Julia-Kocienski reactions). The diverse strategies for generating gem-difluoroalkenes encourage the development of subsequent reactions for accessing a diverse subset of products, such as trifluoromethanes and fluoroalkylthioethers, and inspired the work within this dissertation.
1.5. References for Chapter 1


47. (a) Campbell, M. G.; Ritter, T., Late-stage formation of carbon-fluorine bonds. *Chem Rec* **2014**, *14* (3), 482-91; (b) Liang, T.; Neumann, C. N.; Ritter, T., Introduction of


63. (a) Sung, H. J.; Mang, J. Y.; Kim, D. Y., Catalytic asymmetric conjugate addition of α-fluoro β-ketophosphonates to nitroalkenes in the presence of nickel complexes. J.


Chapter 2 – Organocatalytic Reactions of Thiols with gem-Difluoroalkenes

2.1. Metal-Free Reactions of gem-Difluoroalkenes

Gem-difluoroalkenes are an easily accessed fluorinated functional group that can be elaborated into more complex fluorinated compounds. A variety of commercially available compounds bearing simple functional groups provide access to gem-difluoroalkenes (Scheme 2-1) including carbonyls through Wittig\textsuperscript{1a-f}, \textsuperscript{1n-p} or Julia-Kocienski\textsuperscript{1j, 1q, 1r} olefinations (Scheme 2-1i), alkenes through radical functionalization (Scheme 2-1ii),\textsuperscript{1s} and alkyl halides via nucleophilic addition reactions (Scheme 2-1iii).\textsuperscript{1t-v} Other methods to access gem-difluoroalkenes require synthesis of fluorinated intermediates, such as S_{N2}' reactions with vinyl trifluoromethanes (Scheme 2-1iv),\textsuperscript{1w-ac} or cross coupling with difluoroethylene derived compounds, such as difluorovinyl organo-zinc compounds,\textsuperscript{1g, 1af} difluorovinyl stannanes,\textsuperscript{1ad} and difluorovinyl tosylates (Scheme 2-1v).\textsuperscript{1ae} Due to the wide variety of methods and starting materials to access gem-difluoroalkenes, many functionalization reactions of this moiety have been developed.
The incorporation of fluorine in \textit{gem}-difluoroalkenes perturbs physicochemical properties thus enabling new reactivity that contrasts the reactivity of the non-fluorinated alkene.\textsuperscript{1h, 2} The $\sigma$-withdrawing effects of the fluorine substituents activate the difluorinated position for regioselective nucleophilic attack under both transition metal-catalyzed and non-catalyzed conditions (\textbf{Figure 2-2}).\textsuperscript{1h, 1x} The difluorinated carbon of the alkene is electrophilic, which activates \textit{gem}-difluoroalkenes for regioselective attack at the $\alpha$-position. This activation delivers a distinct regioselectivity from common alkene activating groups, such as carbonyls and nitro groups, which react at the $\beta$-position relative to the activating group. Combined, these physicochemical characteristics allow \textit{gem-}
difluoroalkenes to serve as mechanism-based inhibitors of enzymes with nucleophilic residues in the active sites (Figure 2-1).³

**Figure 2-1:** Mechanism Based Inhibitors Containing *gem*-Difluoroalkenes³⁵⁴
Many reactions that exploit the electrophilicity of the difluorinated position of gem-difluoroalkenes undergo a net addition / elimination process that defluorinates the substrate. Specifically, these reactions proceed through either unstable β-fluoroanions (Figure 2-2a)\(^{1x, 5}\) or β-fluoroorganometal intermediates (Figure 2-2b)\(^{6}\) that both undergo β-fluoride elimination and deliver monofluorinated products, specifically monofluoroalkenes.\(^{1h}\)

**Figure 2-2:** Types of Reactions of gem-Difluoroalkenes

The fluoroalkene products are lipophilic, conformationally locked mimics of peptide amide bonds,\(^{7}\) found in a variety of bioactive compounds. Typical fluoroalkene synthesis proceeds through the direct fluorination of non-fluorinated starting materials, including Shapiro fluorination,\(^{8}\) olefination reactions with mono-fluorinated ylides,\(^{9}\) or the electrophilic fluorination of alkenyl-metal species.\(^{10}\) Alternate methods of fluoroalkene
synthesis require fluorinated starting materials, such as elimination reactions of fluoroalkanes,¹¹ \( S_N2' \) reactions of allylic gem-difluorides,¹² or transition-metal catalyzed cross-coupling reactions.¹³ Fluoroalkene synthesis from gem-difluoroalkenes occurs via an orthogonal process, enabling access to otherwise hard to make compounds. For instance, intramolecular nucleophilic cyclizations of gem-difluoroalkenes enable access to five-member heterocycles fluorinated at the 2-position, such as 2-fluoro-indoles or -benzo[b]thiophenes (Scheme 2-2a).¹⁴ Other methods to provide the same fluorination pattern remain lacking. Similar reactions allow access to various fluorinated 6-member heterocycles (Scheme 2-2b).¹⁵ Such cyclization reactions generally do not require strong bases, as the proximity of the nucleophile to the electrophile enables facile nucleophilic addition.

**Scheme 2-2:** Representative Intramolecular Cyclization Reactions of gem-Difluoroalkenes

*a) Representative C–F Functionalization of gem-Difluoroalkenes: Synthesis of 2-F Substituted Five Member Heterocycles¹⁴*

\[
\begin{align*}
\text{Ph} & \quad \xrightarrow{\text{NaH, DMF, 80 °C}} \quad \text{Ph} \quad \xrightarrow{X = \text{NHR, SH}} \quad \text{Ph}
\end{align*}
\]

*b) Representative C–F Functionalization of gem-Difluoroalkenes: Synthesis of Six Member Heterocycles¹⁵*

\[
\begin{align*}
\text{Ph} & \quad \xrightarrow{\text{KCN, K}_2\text{CO}_3, \text{DMF, 80 °C}} \quad \text{Ph}
\end{align*}
\]
Intermolecular nucleophilic addition reactions to gem-difluoroalkenes exploit the same reactivity. However, the intermolecular attack of C-based nucleophiles to gem-difluoroalkenes requires strong bases, such as organolithium species.\textsuperscript{16} Aryl and alkyl lithium species efficiently react with TMS-containing gem-difluoroalkenes,\textsuperscript{16} while alkynyl lithium nucleophiles react with β,β-difluorostyrenes to generate β-fluoroenynes (Scheme 2-3a).\textsuperscript{17} More acidic, activated C-based nucleophiles, such as heterocycles\textsuperscript{18} (Scheme 2-3b) or malonates,\textsuperscript{19} require activation by slightly weaker bases, such as KHMDS or NaH, rather than an organolithium reagent. If the nucleophile is further activated, such as cyanide nucleophiles, C-F functionalization can occur with weak butoxide bases.\textsuperscript{20} Grignard reagents react without base, and preferentially react with gem-difluoroalkenes over carbonyls in an α,β-unsaturated system (Scheme 2-3c),\textsuperscript{21} highlighting the ability of the gem-difluoroalkenes to increase the “hardness” of the electrophile. Even nucleophilic substitution reaction of weak nucleophiles such as phenol to gem-difluoroalkenes occurs in the presence of the weak base K\textsubscript{3}PO\textsubscript{4}, providing fluorovinyl aryl ethers via a three component reaction from a boronic acid nucleophile and O\textsubscript{2} (Scheme 2-3d).\textsuperscript{22} Even under forcing conditions, using organolithium reagents, carbon-based nucleophiles undergo almost exclusively mono-addition, because the electrophilicity of the resulting fluoroalkene is significantly reduced, precluding further nucleophilic attack.
Scheme 2-3: C-Based Nucleophilic C–F Functionalization Reactions of \textit{gem-}Difluoroalkenes

\textit{a) C–F Functionalization Reactions of \textit{gem-}Difluoroalkenes with Alkynyl Lithium Nucleophiles}^{17}

\[
\begin{array}{c}
\text{MeO} \\ \text{Ph} \\ \text{Ph} \\ \text{H} \\ \text{H}
\end{array}
\begin{array}{c}
\text{MeO} \\ \text{Ph} \\ \text{Ph} \\ \text{H} \\ \text{H}
\end{array} + \begin{array}{c}
\text{Ph} \\ \text{N} \\ \text{N} \\ \text{Ph} \\ \text{Ph}
\end{array} \xrightarrow{\text{$^n$BuLi}} \begin{array}{c}
\text{MeO} \\ \text{Ph} \\ \text{Ph} \\ \text{H} \\ \text{H}
\end{array}
\]

\text{THF, 65 °C, Ar}

\textit{b) C–F Functionalization Reactions of \textit{gem-}Difluoroalkenes with Heterocycles}^{18}

\[
\begin{array}{c}
\text{Ph} \\ \text{F} \\ \text{F}
\end{array} + \begin{array}{c}
\text{N} \\ \text{N} \\ \text{O} \\ \text{Ph} \\ \text{Ph}
\end{array} \xrightarrow{\text{KHMDS}} \begin{array}{c}
\text{Ph} \\ \text{F}
\end{array}
\]

\text{DMSO, 25 °C, Ar}

\textit{c) C–F Functionalization Reactions of \textit{gem-}Difluoroalkenes with Grignard Reagents}^{21}

\[
\begin{array}{c}
\text{O} \\ \text{F} \\ \text{Ph}
\end{array} + \begin{array}{c}
\text{Me}
\end{array} \xrightarrow{\text{$^n$Bu$_3$N$^+$Br$^-$}} \begin{array}{c}
\text{Me}
\end{array}
\]

\text{THF, –25 °C, Ar}

\textit{d) Three Component C–F Functionalization Reaction of \textit{gem-}Difluoroalkenes}^{22}

\[
\begin{array}{c}
\text{Ph} \\ \text{F} \\ \text{F}
\end{array} + \begin{array}{c}
\text{Ph}
\end{array} \xrightarrow{\text{K$_3$PO$_4$}} \begin{array}{c}
\text{OPh}
\end{array}
\]

\text{NMP, 100 °C, Air}

For intermolecular reactions of N- or S-based nucleophiles with \textit{gem-}difluoroalkenes sequential nucleophilic addition / fluoride elimination reactions are facile, resulting in non-fluorinated products \textbf{(Scheme 2-4a)}.\textsuperscript{23} For these nucleophiles, achieving a single nucleophilic addition / fluoride elimination reaction requires control of nucleophile equivalents and reaction time \textbf{(Scheme 2-4b)}.\textsuperscript{24} However, mono-addition of a basic N-derived nucleophile results in a non-fluorinated product. When a basic nitrogen sits $\alpha$ to a C–F bond, the lone pair electrons of N eliminate fluoride to generate imines \textbf{(Scheme
This elimination makes the fluorine-retentive intermolecular functionalization of gem-difluoroalkenes with N-based nucleophiles to generate basic-nitrogen containing products an immense challenge.

Scheme 2-4: Representative C–F Functionalization Reactions of gem-Difluoroalkenes with Heteroatom-Based Nucleophiles

Uniquely, the addition of F\textsuperscript{−} to gem-difluoroalkenes to form trifluoromethanes\textsuperscript{26} never results in a defluorinated product; instead, the reaction follows a nucleophilic addition / protonation process. This uncommon reaction proceeds through a reversible equilibrium between the gem-difluoroalkene and an unstable \(\alpha\)-trifluoromethyl anion that is trapped with residual \(\text{H}_2\text{O}\) (Figure 2-3a). Initially, these reactions required the use of crown ethers and the explicit preparation, isolation, and purification of the gem-difluoroalkene.\textsuperscript{11} In 2014 a new, one-pot deoxytrifluoromethylation reaction of readily available aldehydes and
ketones to their respective trifluoromethanes proved that such reactions do not require additives to temporarily control the β-fluoroanion.\textsuperscript{26} Other reactions exploit this equilibrium process to intercept the β-fluoroanion with transition metals and further functionalizing \textit{gem}-difluoroalkenes.\textsuperscript{26-27} Unfortunately, if the β-fluoride elimination does not regenerate the starting material, no stable equilibrium forms, making the protonation of the unstable anionic intermediate more challenging (\textbf{Figure 2-3b}). Thus, general examples of such “fluorine-retentive” nucleophilic hydro-functionalization of \textit{gem}-difluoroalkenes remain elusive (\textbf{Figure 2-2d}).

\textbf{Figure 2-3:} Fluorinated Alkenes React \textit{via} Nucleophilic Addition / Protonation.

\begin{center}
\includegraphics[width=\textwidth]{fluorinated_alkenes.png}
\end{center}

Such an undeveloped general intermolecular “fluorine-retentive” nucleophilic functionalization of \textit{gem}-difluoroalkenes would allow access to underexplored fluorinated functional groups. Specifically, fluorine-retentive reactions with thiols would provide access to α,α-difluoroalkylthioethers from common, easily obtained materials. These
substructures alter the metabolism of the traditionally labile vicinal carbon of thioethers, and may reduce the oxidation of the thioether itself, and are thus important for medicinal and agricultural purposes, such as in anti-cancer\textsuperscript{28} and anti-inflammatory\textsuperscript{29} agents and agrichemicals (Figure 2-4a).\textsuperscript{30} Only a few suboptimal strategies exist to form $\alpha,\alpha$-difluoroalkylthioethers, leaving most of the potentially bioactive $\alpha,\alpha$-difluoroalkylthioethers prophetic in patents. Of these strategies, nucleophilic substitution reactions of silylated\textsuperscript{31} or halogenated (Figure 2-4bi)\textsuperscript{32} difluoroalkyl intermediates are the mildest methods, allowing for the broadest scope of compatible functional groups. However, the necessary starting materials require multi-step preparations, reducing the utility of these transformations. Radical processes to access $\alpha,\alpha$-difluoroalkylthioethers are more direct; however, the existing radical methods use a limited set of starting materials (Figure 2-4biii).\textsuperscript{32b, 32c, 33} For compounds containing simple alkyl or polyfluorinated alkyl substituents, gaseous fluorinated alkene electrophiles allow direct access to the difluorinated (thio)ether from thiols or alcohols. However, both the gaseous reagent and controlling the undesired fluoride elimination require cryogenic conditions (Figure 2-4bv).\textsuperscript{34} In a non-convergent method, oxidative methods that utilize harsh fluorinating reagents enable direct access to the desired $\alpha,\alpha$-difluoroalkylthioether substructure (Figure 2-4bii).\textsuperscript{35} The most common of these oxidative methods incorporates fluorine through deoxyfluorination, which precludes the presence of carbonyl and unprotected alcohol functionalities, and liberates toxic HF as a byproduct. Thus, a preparation of $\alpha,\alpha$-difluoroalkylthioethers via the base-catalyzed hydrofunctionalization of gem-difluoroalkenes with thiols, exploiting a nucleophilic addition / protonation mechanism,
complements existing methods to access α,α-difluoroalkythioethers, and should facilitate access to valuable, underexplored bioactive compounds.

**Figure 2-4**: β,β-Difluorophenethyl (Thio)ethers in Medicinal and Synthetic Chemistry

*a) Representative Structures of Bioactive β,β-Difluorophenethyl (Thio)ethers in Patents* 28–30

Cysteine Protease Inhibitor  
Cytochrome P450 Inhibitor  
HIF-2α Inhibitor

*b) Current Methods to Synthesize β,β-Difluorophenethyl (Thio)ethers* 31–35

2.2. Base Catalysis Enables Access to β,β-Difluorophenethyl Arylthioethers

Our initial studies focused on the addition / protonation reaction of aryl thiol nucleophiles with gem-difluorostyrene electrophiles. We envisioned that, since aryl thiols
are both highly nucleophilic (Swain-Scott = 9.92)\(^{36}\) and moderately acidic (pK\(_a\) = 6.52), aryl thiols subjected to catalytic amounts of weak base would rapidly deprotonate and add to the gem-difluoroalkene. We selected a styrene-derived difluoroalkene substrate to stabilize the proposed intermediate anion (Scheme 2-5A) after thiol addition through resonance, ideally speeding nucleophilic addition, while slowing \(\beta\)-fluoride elimination.

Once the unstable \(\beta\)-anionic intermediate would form, either the protonated catalyst or the remaining thiol pronucleophile would provide the proton to quench the reactive intermediate. Since the expected \(\beta,\beta\)-difluorophenethyl thioether product is significantly less acidic than either the protonated catalyst or thiol, proton transfer might occur faster than \(\beta\)-fluoride elimination, generating the desired product and closing the catalytic cycle (Scheme 2-5c). Following this hypothesis, we investigated the addition of thiophenol to difluoroalkenes.
After extensive optimization, we identified a general base-catalyzed protocol for adding aryl thiols to β,β-difluorostyrenes. Initial attempts to functionalize difluorostyrene 2.1 with thiophenol involved catalytic amounts of inorganic bases, which either generated non-fluorinated disubstituted alkene 2.3 (likely arising from sequential C–F functionalizations), or which did not react (Scheme 2-6). When higher quantities of inorganic base were employed, large amounts of α-fluorovinylthioethers formed. In contrast, catalytic quantities of organic bases generated the desired α,α-
difluoroalkylthioether in modest to excellent yield and selectivity. Of the bases evaluated, 1,1,3,3-tetramethylguanidine (TMG) provided the best yield and selectivity for product 2.2 over product 2.4 (Table 2-1, entries 1–4). Notably, the use of preformed PhSNa as a base only formed small amounts of desired product 2.2 or eliminated product 2.4 (Table 2-1, entry 5), which suggests that ArSH might not serve as the H⁺ donor, but rather TMG–H⁺. Subsequent evaluation of solvents revealed that chlorinated solvents provided the best yield and selectivity, with 1,2-dichloroethane (DCE) proving optimal (Table 2-1, entries 1, 5–11).

Scheme 2-6: Undesired Reactivity with Inorganic Bases

Table 2-1: Optimization of the Reaction Conditions[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>conv/yield [%][b]</th>
<th>2.2:2.4[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMG</td>
<td>DCE</td>
<td>&gt;99/96</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N</td>
<td>DCE</td>
<td>&gt;99/82</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>3</td>
<td>DMAP</td>
<td>DCE</td>
<td>&gt;99/67</td>
<td>&gt;25:1[e]</td>
</tr>
<tr>
<td>4</td>
<td>TBD</td>
<td>DCE</td>
<td>&gt;99/77</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>5[c]</td>
<td>PhSNa</td>
<td>DCE</td>
<td>15/&lt;1</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>TMG</td>
<td>PhNO₂</td>
<td>94/60</td>
<td>4:1</td>
</tr>
<tr>
<td>7</td>
<td>TMG</td>
<td>DMF</td>
<td>&gt;99/36</td>
<td>1:1.2</td>
</tr>
<tr>
<td>8</td>
<td>TMG</td>
<td>PhMe</td>
<td>56/8</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>9</td>
<td>TMG</td>
<td>MeCN</td>
<td>83/15</td>
<td>1:3.5</td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
<td>------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>10[d]</td>
<td>TMG</td>
<td>DCM</td>
<td>&gt;99/88</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>11[c]</td>
<td>TMG</td>
<td>DCE</td>
<td>&gt;99/91</td>
<td>&gt;25:1</td>
</tr>
</tbody>
</table>

[a] Standard conditions: 2.1 (1.0 equiv.), PhSH (2.0 equiv.), solvent (0.50 M), base (25 mol %), 80 °C, 4 h. [b] Determined by $^{19}$F NMR standardized with PhCF$_3$ (1.0 equiv.). [c] Solvent (0.25 M), base (5.0 mol %), 70 °C, 0.5 h. [d] 40 °C. [e] Reaction generated a sulfoxide side product. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

Of note, as the scale of the reaction increased, the optimized reaction conditions (5% TMG, 1.5 equiv. thiophenol, 70 °C, 0.5–4 h) showed reduced efficiency. Specifically, when the scale increase from a 0.1 mmol exploratory scale to a 0.5 mmol preparative scale, the reaction quickly approached completion (~80% conversion), but then stalled. This might be a result of worse heat transfer from the reaction block to the reaction mixture, as the increased volume of the reaction brings the total volume to the top of the heating element. Other possibilities include micro-aggregates of the TMG and thiophenolate in DCE that prevent the thiolate from reacting with the difluoroalkene, although as best we observed the reactions were homogenous. Complete conversion required either extended reaction times, elevated temperatures, or an additional equivalent of aryl thiol.

The optimized reaction conditions enabled coupling between thiophenol and a broad spectrum of functionalized β,β-difluorostyrenes (2.5a–n and 2.1), with selectivity generally exceeding 25:1 (Scheme 2-7). The reaction tolerated many useful functional groups on
the β,β-difluorostyrene, such as halides (2.6c, 2.6i, 2.6k), ethers (2.2, 2.6a–c, 2.6h), thioethers (2.6b), and nitrogenous functional groups (2.6d, 2.6e, 2.6i–n). Ortho-substituted β,β-difluorostyrenes required higher reaction temperatures (2.6c, 2.6g, 2.6i). Carbonyl-containing compounds were also tolerated (2.6j, 2.6l), and notably a substrate bearing an α,β-unsaturated ester reacted exclusively at the fluorinated position, with no evidence of irreversible Michael addition (2.6j) highlighting the high electrophilicity of the difluorinated position. Electron-rich and -neutral β,β-difluorostyrenes generally provided high yields and selectivities, and required low temperatures and short reaction times (2, 6a–e, 6h). In contrast, under standard reaction conditions, electron-deficient substrates reacted sluggishly, affording products in modest yields and selectivities. To reach full conversion, these reactions required higher temperatures and longer times (6k–n). However, these harsher conditions afforded more α-fluorovinythioether side product (6.6:1–13:1).
Scheme 2-7: Scope of Distinct β,β-Difluorostyrenes\textsuperscript{[a]}

\[
\text{PhSH} + \underset{2.5\text{a–n and 2.1}}{\text{R}} \xrightarrow{5\% \text{ TMG}} \text{DCE, 70–100 °C} \quad 0.5–20 \text{ h}
\]

Selectivity >25:1

2.6a, 76\% 70 °C, 0.5 h

2.6b, 59\%\textsuperscript{[b]} 90 °C, 5 h

2.6c, 87\% 70 °C, 0.5 h

2.6d, 77\%\textsuperscript{[b]} 90 °C, 5 h

2.6e, 79\% 70 °C, 14 h

2.6f, 75\%\textsuperscript{[b]} 90 °C, 5 h

2.6g, 90\%\textsuperscript{[b]} 90 °C, 5 h

2.6h, 88\% 80 °C, 0.5 h

2.6i, 72\%\textsuperscript{[b]} 90 °C, 5 h

2.6j, 73\%\textsuperscript{[b]} 90 °C, 5 h

2.6k, 60\%\textsuperscript{[b,c]} 100 °C, 20 h

2.6l, 83\%\textsuperscript{[b]} 90 °C, 5 h

2.6m, 57\%\textsuperscript{[b,d]} 100 °C, 20 h

2.6n, 54\%\textsuperscript{[b,e]} 100 °C, 20 h

5% TMG

DCE, 70–100 °C

0.5–20 h

2.5a–n and 2.1

2.6a–n and 2.2

\textsuperscript{[a]}
[a] Standard conditions: 2.5a–n (1.0 equiv.), PhSH (2.0 equiv.), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by $^{19}$F NMR analysis of the reaction mixture, unless otherwise indicated. Yields represent an average of two runs. [b] PhSH (3.0 equiv.). [c] Selectivity = 13:1. [d] Selectivity = 6.6:1. [e] Selectivity = 8:1. PMB = 4-methoxybenzyl, Tf = trifluoromethylsulfonate.

To determine whether the reduced selectivity arose from the instability of the product or of anionic intermediate A (Scheme 2-5c), purified products 2.2, 2.6d, and 2.6n were re-subjected to the reaction conditions (Scheme 2-8a). $^{19}$F NMR analysis of the reaction mixtures showed no evidence of degradation, which corroborates the fact that even with extended reaction times the selectivity is not reduced. Combined, these results suggest that β-fluoride elimination from A occurs more rapidly for electron-deficient species than for electron-rich or -neutral species, explaining the reduced selectivity (Scheme 2-8b).
Scheme 2-8: Decomposition of Anionic Intermediate A Reduces the Selectivity for e⁻-Deficient Substrates

Further, under the optimized conditions heteroaromatic gem-difluoroalkenes reacted smoothly (Scheme 2-9). Electron-rich and -deficient N-based heterocycles (indole 2.8a, pyridine 2.8b, pyrrole 2.8c), and S-based heterocycles (benzo[b]thiophene 2.8d, phenothiazine 2.8e, thiazole 2.8f) all provided good yield and selectivity, suggesting that the reaction conditions should apply to a broad spectrum of biologically relevant heteroaromatic compounds.
Scheme 2-9: Scope of Heteroaromatic $\beta,\beta$-Difluoro styrenes$^{[a]}$

[a] Standard conditions: 2.7a–n (1.0 equiv.), PhSH (2.0 equiv.), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity $>25:1$ as determined by $^{19}$F NMR analysis of the reaction mixture. Yields represent an average of two runs. [b] PhSH (3.0 equiv.). Ts = 4-toluenesulfonyl.

A broad scope of functionalized aryl thiol nucleophiles were also tolerated (Scheme 2-10). Aryl thiols bearing halides (2.10h, 2.10e), ethers (2.10a, 2.10b, 2.10f), trifluoromethane (2.10g), carbonyl groups (2.10b), and even a secondary amide (2.10c) afforded $\alpha,\alpha$-difluoroalkylthioether products, confirming that electron-rich, -neutral, and -weakly-deficient aryl thiols generally reacted smoothly. Thiols bearing strong electron-withdrawing groups (e.g. nitrile 2.10i) required higher temperatures and extended
reaction times. Notably, all reactions demonstrated excellent selectivity (>25:1) regardless of the nature of the nucleophile. However, under these conditions heteroaryl thiol nucleophiles did not add to β,β-difluorostyrenes electrophiles.

**Scheme 2-10: Scope of Distinct Aryl Thiols**

[arbol diagram]

[a] Standard conditions: 2.1 (1.0 equiv.), ArSH 2.9a–j (2.0 equiv.), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by $^{19}$F
NMR analysis of the reaction mixtures. Yields represent an average of two runs. [b] ArSH (3.0 equiv.).

Finally, the mild conditions tolerated many useful protecting groups, including a Ts-protected indole (2.8a), an acetal (2.8b), a Boc-protected amine (2.8f), benzyl- and p-methoxybenzyl-protected alcohols and amines (2.6c, 2.6h, 2.8e), and an acetyl-protected amine (2.10c), all potentially useful in multistep synthetic sequences.

While aryl thiol nucleophiles reacted efficiently, alkyl thiols reacted poorly, giving mainly addition / elimination products, presumably due to a mismatched thiol-base pair. To assess whether a system bearing two distinct nucleophiles could selectively react with the efficient aryl thiol nucleophile and avoid this undesired reactivity of alkyl thiols, an aryl thiol was reacted with 2.1 in the presence of an alkyl thiol under the harshest conditions explored (Scheme 2-11). Under these conditions, the aryl thiol selectively coupled to form aryl thioether 2.2 with <1% formation of alkyl thioether 2.11, likely because the increased acidity of the aryl thiol allows preferential deprotonation, and the resulting thiolate is more nucleophilic than the neutral thiol.

**Scheme 2-11:** Coupling of Aryl Thiol over Alkyl Thiol

\[
\begin{align*}
\text{Ph-SH} & \quad \text{(3.0 equiv)} \\
\text{\textit{n}_\text{oct}-\text{SH}} & \quad \text{(3.0 equiv)} \\
\text{Ph-S} & \quad \text{F} \quad \text{F} \quad \text{Ar} \\
\text{\textit{n}_\text{oct}-\text{S}} & \quad \text{F} \quad \text{F} \quad \text{Ar} \\
\text{100 °C, DCE, 20 h} & \quad 5\% \text{ TMG} \\
\text{Ar = 3,4,5-(OMe)}_{3}\text{-C}_{6}\text{H}_{2} & \quad 2.2 \\
\text{91%} & \quad 2.11 \\
\text{Not Observed}
\end{align*}
\]
2.3. Mechanistic Considerations

While we propose that the current reaction to achieve the hydrothiophenolation of gem-difluoroalkenes occurs via a base-catalyzed addition / protonation pathway, other mechanisms are possible. Thiols, especially aryl thiols, undergo facile one electron oxidation to thiol radicals, which are stable and competent at performing the same reaction. In fact, when difluoroalkene 2.1 was subjected to a strong radical initiator (AIBN) and thiophenol under similar conditions to the aforementioned base-catalyzed hydrothiophenolation reaction, the desired β,β-difluorophenethyl arylthioether was generated in high yield and selectivity. Thus, we set out to rule out the possibility that the current reaction proceeds via one-electron chemistry.

Several experiments support the proposed addition / protonation pathway over a mechanism involving S-based radicals. First, the reaction ran smoothly in the absence of light and O₂, which are known radical initiators of thiols (Table 2-2, entry 1–3). Second, although the reaction utilizes TMG (which can have inorganic impurities that can oxidize a thiolate), 37 other amine bases that lack such impurities (e.g. distilled Et₃N) are competent base catalysts (Table 2-1, entry 2). Third, when running the reaction in CD₂Cl₂ (which can transfer •D) 38 D was not incorporated into the product (Table 2-2, entry 4). Fourth, reactions run in presence of radical traps (e.g. 1,4-dicyanobenzene and BHT) proceed to full conversion and in comparable yields to the standard reaction conditions (Table 2-2, entries 5 and 6). In contrast, reactions run in the presence of TEMPO, both with and without TMG, gave no desired product and generated (PhS)₂, presumably by transfer of H• from PhSH to TEMPO and subsequent homocoupling of the resulting PhS•.
(Table 2-2, entry 7), although control reactions revealed that, in the presence of TEMPO, thiophenol formed the corresponding dithiane and thus cannot add to the gem-difluoroalkene. Thus, under our conditions, S-based radicals are not likely reactive intermediates.

Table 2-2: Experiments for Mechanistic Determination\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>conv/yield [%]\textsuperscript{[b]}</th>
<th>2.2:2.4\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{[c]}</td>
<td>O\textsubscript{2}</td>
<td>&gt;99/90</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>2\textsuperscript{[c]}</td>
<td>Dark</td>
<td>&gt;99/90</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>3\textsuperscript{[c]}</td>
<td>O\textsubscript{2} and Dark</td>
<td>&gt;99/95</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>4\textsuperscript{[d]}</td>
<td>DCM-D\textsubscript{2}</td>
<td>&gt;99/86</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>5</td>
<td>1,4-(CN)\textsubscript{2}-C\textsubscript{6}H\textsubscript{4}</td>
<td>&gt;99/88</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>6</td>
<td>BHT</td>
<td>&gt;99/82</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>7</td>
<td>TEMPO</td>
<td>&gt;0/0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Standard conditions: 2.1 (1.0 equiv.), PhSH (2.0 equiv.), additive (2.0 equiv.), DCE (0.50 M), TMG (5 mol %), 70 °C, 1 h. \textsuperscript{[b]} Determined by \textsuperscript{19}F NMR standardized with PhCF\textsubscript{3} (1.0 equiv.). \textsuperscript{[c]} Run at 80 °C. \textsuperscript{[d]} Run in DCM-D\textsubscript{2} instead of DCE for 4 h at 40 °C. BHT = Butylated Hydroxy Toluene.
2.4. Organocatalysis to Access $\beta,\beta$-Difluorophenethyl Alkylthioethers

As evidenced in Scheme 2-11, alkyl thiols are less competent nucleophiles than aryl thiols in the TMG catalyzed hydrothiolation of $\text{gem}$-difluoroalkenes. In fact, when subjected to TMG-catalysis in the absence of a competing aryl thiol nucleophile, reactions of alkyl thiol nucleophiles selectively formed the undesired $\alpha$-monofluorovinyl thioether side product (Scheme 2-12a). While not ideal, this result indicates that the reduced nucleophilicity of alkyl thiols (Swain-Scott = 6.95$^{39}$) relative to aryl thiols (Swain-Scott = 9.92$^{36}$) does not preclude nucleophilic attack under mild conditions with catalytic base. Unfortunately, the proton quench with alkyl thiols does not sufficiently outcompete the $\beta$-fluoride elimination, necessitating re-optimization of the reaction conditions.

Interestingly, when alkyl thiols were subjected to conditions utilizing the same inorganic bases that provided exclusive formation of the $\alpha$-monofluorovinyl thioether when using aryl thiols, the desired $\beta,\beta$-difluorophenethyl alkylthioether was formed in high yield and high selectivity (Scheme 2-12b). This result might indicate that the excess alkyl thiol provides the protons needed to quench the $\beta$-fluoroanionic intermediate, which explains the reduced protonation as alkyl thiols are less acidic ($pK_a = 10.86$) than aryl thiols ($pK_a = 6.61$).$^{40}$
Initial optimization of this reaction revealed that either catalytic NaH or catalytic pre-formed sodium alkylthiolate were ideal bases for electron rich and electron neutral gem-difluoroalkenes. However, under these reaction conditions, the substrate scope for selective hydrofunctionalization versus β-fluoride elimination was limited to electron-rich and neutral gem-difluoroalkenes. Reactions of electron-deficient gem-difluoroalkenes provided especially poor selectivity.

At this point a new graduate student, Jacob Sorrentino, joined the project. Under my mentorship, he performed extensive optimization to reveal the final optimized conditions; an organocatalytic catalyst mixture of pyridine, LiOTf, and 2-methoxyethanol. This optimized catalyst system provides high yields and high reactivity over a broad range of gem-difluoroalkenes and alkylthiols. My contributions to the substrate scope are summarized in Scheme 2-13.
**Scheme 2-13**: Scope of Aromatic and Heteroaromatic β,β-Difluorostyrenes

![Reaction Scheme]

- **2.5 or 2.7**
- **2.12 or 2.13**

[a] Standard conditions: 2.5 or 2.7 (1.0 equiv.), \(^{\text{n}}\)OctSH (1.5 equiv.), Pyridine (20.0 mol %), LiOTf (10.0 mol %), 2-OMe-EtOH (2.0 equiv.), \(\sigma\)-Xylene (0.33 M), 110 °C, 15 h, equipped with a balloon of air through a 16.5 G needle. Selectivity >25:1 as determined by \(^{19}\)F NMR analysis of the reaction mixtures. Yields represent an average of two runs.

[b] \(^{\text{n}}\)OctSH (3.0 equiv.).
2.5. Conclusions

In summary, we developed a new organo-catalytic strategy to generate \(\beta,\beta\)-difluorophenethyl thioethers by directly adding nucleophiles to \(\text{gem}\)-difluoroalkenes. In contrast to classical syntheses of such products that require multistep intermediate synthesis,\(^{31-32}\) harsh conditions,\(^{41}\) and/or gaseous reagents,\(^{34}\) and that many times rely on functional group interconversions\(^{31-32,35}\) to generate the fluorine-based substructure, our convergent method utilizes only catalytic quantities of a weak amine base to add thiol nucleophiles across \(\text{gem}\)-difluoroalkenes and deliver the desired products in moderate to good yields and selectivities. These reactions proceed via an unstable anionic intermediate that is prone to eliminate \(\text{F}^-\); however, the mild conditions avoid this undesired unimolecular elimination, contrasting the many reactions of \(\text{gem}\)-difluoroalkenes that selectively generate monofluoroalkene products.\(^1\)

The organocatalytic strategy enabled two reactions to access to a variety of functionalized \(\beta,\beta\)-difluorophenethyl thioethers in high yield and selectivity versus the \(\alpha\)-fluorovinylthioether. Using aryl thiols as a nucleophile, a simple, common, and commercially available guanidine base (TMG) was employed as catalyst in low loading and at moderate temperatures. This reaction is highly efficient and effective, providing the desired \(\beta,\beta\)-difluorophenethyl arylthioethers in high yield and generally >25:1 selectivity, although, as with \(\text{S}_\text{NAr}\) reactions, different substrates require minor reoptimization of reaction conditions. However, this reaction does suffer reduced selectivity when applied to electron deficient difluoroalkenes. When employing the less-acidic alkyl thiol nucleophiles, we developed a new reaction employing a unique organo-catalyst of
pyridine and LiOTf to affect the hydrothiolation of *gem*-difluoroalkenes, while similarly avoiding the formation of the undesired a-monofluorovinyl thioether. This reaction is broadly tolerant of substitutions to the *gem*-difluoroalkene electrophile, remaining highly selective.

This convergent organo-catalytic strategy to hydrofunctionalize *gem*-difluoroalkenes delivers a class of products that are underrepresented in synthetic and biomedical literature. Combined with direct preparations of β,β-difluorostyrenes,\textsuperscript{1h} the present reactions should facilitate access to this underutilized functional group in medicinal and agrichemistry. Further efforts aim to enable the addition of other nucleophiles, such as alkyl alcohols or C-based nucleophiles, to *gem*-difluoroalkenes, and to expand the scope of such reactions to include aliphatic and secondary *gem*-difluoroalkenes.
2.6. References for Chapter 2


37. We thank an unidentified reviewer for noting the potential of trace impurities to initiate radical reactivity.


Chapter 2 Appendix

Experimental Procedures and Spectra for Compounds in Chapter 2
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**General Considerations:**

Unless otherwise noted, reactions were performed under an atmosphere of air using oven-dried glassware. Coupling reactions with thiols and difluorostyrenes were performed in either 1-dram borosilicate glass vials sealed with a PTFE-lined silicone septa in a screw-top cap, or 5 mL pressure-resistant microwave vials sealed with a PTFE-lined silicone septa in a crimp-top cap. All other reactions were performed in round-bottom flasks sealed with rubber septa. Stainless steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by either $^{19}\text{F}$ NMR with an internal standard of $\alpha,\alpha,\alpha$-trifluorotoluene or by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualized by quenching of fluorescence. Column chromatography was conducted using a Teledyne Isco CombiFlash Rf 200 system utilizing gradient elution. Isolated yields reported in the manuscript represent an average of at least 2 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. 1,2 Dichloroethane (DCE, reagent grade, 99+%) and tetramethylguanidine (TMG) were purchased from Alfa Aesar. $N$-methylpyrrolidine (NMP, anhydrous) was purchased from Sigma Aldrich. Solvents, including dimethylformamide (DMF), toluene (PhMe), dichloromethane (DCM), methanol (MeOH), acetonitrile (MeCN), and tetrahydrofuran (THF) were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon. 30% hydrogen peroxide in water ($\text{H}_2\text{O}_2$) was purchased from Fisher Scientific. Other
chemical abbreviations utilized in this document include: α,α,α-Trifluorotoluene (TFT), sodium sulfate (Na₂SO₄), magnesium sulfate (MgSO₄), ethyl acetate (EtOAc), diethyl ether (Et₂O), ammonium chloride (NH₄Cl), n-butyl lithium (nBuLi), sodium hydroxide (NaOH), sodium metabisulfite (Na₂S₂O₅), Room Temperature (R.T.), 'butyl carbonate anhydride (Boc₂O), potassium carbonate (K₂CO₃), hydrochloric acid (HCl),

Proton nuclear magnetic resonance (¹H NMR) and fluorine nuclear magnetic resonance (¹⁹F NMR) were taken on a Bruker AVIIIHD 400 AVANCE spectrometer (400 and 376 MHz respectively). Proton and carbon nuclear magnetic resonance (¹³C NMR) were taken on an Bruker AVIII 500 Avance spectrometer with a CPDUL cryoprobe (500 and 126 MHz respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to the proton resonance of residual CHCl₃ in the NMR solvent (CHCl₃: δ = 7.26 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonance of the solvent residual peak (CDCl₃: δ = 77.16 ppm). Chemical shifts for fluorine 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 = pentet, 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, HAPCI) 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 on a Shimadzu FTIR-8400S Fourier Transform Infrared Spectrometer by
drying samples on a salt plate. Uncorrected melting points were measured on a Thomas Hoover Capillary Melting Point apparatus.

**Preparation of Compound SI-2.1:**

![Chemical Reaction Diagram]

2,2-difluoro-2-(triphenylphosphonio)acetate (SI-2.1): An oven-dried 2-neck 1000 mL round bottom flask, equipped with an internal thermometer and magnetic stirbar, was charged with 24.6 g (97.0 mmol) of triphenylphosphine and brought into the glovebox. In the glovebox, 20.0 g (97.0 mmol) of potassium bromodifluoroacetate (hygroscopic) was added. The vessel was sealed with a rubber septum, transferred out of the glovebox, and placed into a 0–10 °C water bath. Anhydrous DMF (250 mL) was added via cannula transfer, and the reaction was maintained at <18 °C for 21 h. At 21 h, the reaction was filtered, and the solid was washed 2X with 30 mL of DMF, 3X with 30 mL of H₂O, and 3X with 30 mL of Et₂O. The filtrate was placed into a 500 mL round bottom flask and dried overnight on high vacuum to afford 29.5 g (88%) of the compound SI-2.1 as a colorless solid. After drying, ¹H NMR in MeOD was used to assess the purity of the material. If impurities are present, the material was washed a second time. The ¹H NMR matches previous reports.¹
Note 1: Reaction times longer than 21 h decrease the yield of product. By 36 h, the yield will stabilize at ~60%. Product degradation is accompanied by the appearance of a yellow/brown color. If the color appears prior to 21 h, the reaction will not yet be complete. However, lowering the temperature will slow the degradation and allow the completion of the reaction.

Note 2: If the filtrate is not thoroughly washed, the material will be contaminated with either triphenylphosphine or water, and the subsequent reactions will have lower yields.

Note 3: Selection of reaction vessel size is important. For optimal yield, the volume of DMF should be approximately ¼ the volume of the reaction vessel.

Note 4: If the potassium bromodifluoroacetate is not a powder, presumably due to water, the yield will drop by ~10–15%.

**General Procedure for the Preparation of Gem-Difluoroalkenes (A1):** An oven dried round bottom flask was charged with 1 equivalent of aryl aldehyde and 1.75 equivalents of SI-2.1. The system was evacuated and backfilled with N₂ three times. Dry NMP or DMF was added via syringe (PTFE syringe with oven-dried stainless steel needle), and the system was immediately immersed in an oil bath at 60–90 °C for 1–3 hours. Upon completion, the reaction was quenched with aqueous NH₄Cl. Subsequently, 3 N HCl was added, and the aqueous layer was extracted 4X with EtOAc. The combined organic layers were washed 2X with 3 N HCl, 2X with H₂O, and 1X with a saturated brine solution. The
organic layers were dried over Na$_2$SO$_4$ or MgSO$_4$ and concentrated, and the residue was purified by flash chromatography using EtOAc and hexanes.

**General Procedure for the Preparation of Gem-Difluoroalkenes (A2):** An oven dried round bottom flask was charged with 1 equivalent of aryl aldehyde and 1.75 equivalents of SI-2.1. The system was evacuated and backfilled with N$_2$ three times. Dry NMP or DMF was added via syringe (PTFE syringe with oven-dried stainless steel needle), and the system was immediately immersed in an oil bath at 60–90 °C for 1–3 hours. Upon completion, the reaction was quenched with aqueous NH$_4$Cl. Subsequently, 3 N HCl was added, and the aqueous layer extracted 4X with EtOAc. The combined organic layers were washed 2X with 3 N HCl, 2X with H$_2$O, and 1X with a saturated brine solution. After extraction, the residual triphenylphosphine in the organic layers was subjected to oxidation by vigorously stirring with a 30% aqueous H$_2$O$_2$ solution for 15 min at R.T.. The aqueous layer was removed in a separatory funnel, and the organic layers were dried over Na$_2$SO$_4$ or MgSO$_4$, concentrated, and purified by flash chromatography using EtOAc and hexanes.

**Preparation and Characterization of Gem-Difluoroalkenes:**
5-(2,2-difluorovinyl)-1,2,3-trimethoxybenzene (2.1): Following General Procedure A1, 6.28 g (32.0 mmol) of 3,4,5-trimethoxybenzaldehyde was reacted with 20.0 g (56.0 mmol) of SI-2.1 in anhydrous NMP (48 mL) at 80 °C for 2 h. After workup, the compound was purified by flash chromatography, using 0–5–10% EtOAc in hexanes, furnishing 6.65 g (90% yield) of desired product 2.1 as a colorless solid, m.p. 37 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.55 (s, 2 H), 5.21 (dd, $J = 25.8$, 3.9 Hz, 1 H), 3.86–3.85 (m, 9 H);

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 156.2 (dd, $J = 297.6$, 287.8 Hz), 153.5, 137.3, 126.0 (t, $J = 5.8$ Hz), 15.0 (dd, $J = 6.7$, 3.5 Hz), 82.5 (dd, $J = 29.6$, 13.3 Hz), 61.1, 56.2;

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –82.91 (dd, $J = 33.4$, 25.8 Hz, 1 F), –84.72 (dd, $J = 33.4$, 3.9 Hz, 1 F);

IR (film): 2941, 2841, 2359, 1730, 1583, 1510, 1456, 1421, 1358, 1325, 1300, 1252, 1205, 1178, 1130, 1011, 901, 843, 712 cm$^{-1}$;

HRMS (HAPCI$^+$): calc. for C$_{11}$H$_{12}$F$_2$O$_3$ (M$^+$) 230.0755, found 230.0749, 2.6 ppm.
1-(2,2-difluorovinyl)-4-methoxybenzene (2.5a): Following General Procedure A2, 2.40 mL (20.0 mmol) of 4-anisealdehyde was reacted with 12.5 g (35.0 mmol) of Si-2.1 in of anhydrous NMP (80 mL) at 60 °C for 2 h. After workup, the compound was purified by flash chromatography, using 0–5% EtOAc in hexanes, furnishing 1.48 g (44% yield) of desired product 2.5a as a yellow oil, which turns purple after standing in the freezer.

**1H NMR (400 MHz, CDCl₃):** δ 7.27 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 5.23 (dd, J = 26.4, 3.8 Hz, 1 H), 3.82 (s, 3 H);

**13C NMR (126 MHz, CDCl₃):** δ 158.6 (t, J = 2.2 Hz), 155.9 (dd, J = 296.1, 286.9 Hz), 128.9 (dd, J = 6.3, 3.5 Hz), 122.8 (t, J = 6.2 Hz), 114.3, 81.7 (dd, J = 29.2, 14.2 Hz), 55.4;

**19F NMR (376 MHz, CDCl₃):** δ –84.67 (dd, J = 36.8, 26.4 Hz, 1 F), –86.47 (dd, J = 36.8, 3.9 Hz, 1 F);

**IR (film):** 2959, 2912, 2839, 1732, 1612, 1516, 1466, 1352, 1298, 1250, 1182, 1167, 1036, 937, 839, 609, 552, 523 cm⁻¹;

**HRMS (HAPCI⁺):** calc. for C₉H₈F₂O (M⁺) 170.0543, found 170.0538, 2.9 ppm.
(4-(2,2-difluorovinyl)phenyl)(methyl)sulfane (2.5b): Following General Procedure A2, 1.9 mL (13 mmol) of 4-methylthiobenzaldehyde was reacted with 8.4 g (24 mmol) of SI-2.1 in anhydrous DMF (52 mL) at 60 °C for 2 h. After workup, the compound was purified by flash chromatography, using 0–5% EtOAc in hexanes, to furnish 1.48 g (44% yield) of desired product 2.5b as a yellow-green semi-solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.26–7.21 (m, 4 H), 5.23 (dd, $J = 26.3$, 3.7 Hz, 1 H), 2.48 (s, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 156.2 (dd, $J = 298.0$, 288.1 Hz), 137.3 (t, $J = 2.3$ Hz), 128.0 (dd, $J = 6.4$, 3.5 Hz), 127.1 (t, $J = 6.4$ Hz), 126.7, 81.8 (dd, $J = 29.4$, 13.7 Hz), 15.8

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –82.26 (dd, $J = 32.1$, 26.2 Hz, 1 F), –84.45 (dd, $J = 32.1$, 3.8 Hz, 1 F)

IR (film): 3032, 2922, 1730, 1599, 1497, 1435, 1406, 1350, 1248, 1167, 1096, 937, 837, 729, 509 cm$^{-1}$

HRMS (HAPCI+): calc. for C$_9$H$_8$F$_2$S (M+) 186.0315, found 186.0302, 1.3 mmu.

Preparation of Compound 2.5c:
**5-bromo-2-((4-methoxybenzyl)oxy)benzaldehyde (2.5c-1):** Compound 2.5c-1 was prepared according to a previous report. The $^1$H NMR spectrum matched previous reports.²

**4-bromo-2-(2,2-difluorovinyl)-1-((4-methoxybenzyl)oxy)benzene (2.5c):** Following General Procedure A2, 2.50 g (7.80 mmol) of 2.5c-1 was reacted with 4.85 g (14.0 mmol) of SI-2.1 in anhydrous NMP (32 mL) at 80 °C for 2 h. After workup, the product was purified by flash chromatography, using 0–2.5–5% EtOAc in hexanes, to furnish 2.23 g (81% yield) of desired product 2.5c as a colorless solid, m.p. 65–67 °C.

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 7.59–7.58 (m, 1 H), 7.32 (d, $J = 8.4$ Hz, 2 H), 7.30–7.27 (m, 1 H), 6.93 (d, $J = 8.2$ Hz, 2 H), 6.80 (d, $J = 8.8$ Hz, 1 H), 5.63 (dd, $J = 25.9$, 4.8 Hz, 1 H), 4.98 (s, 2 H) 3.83 (s, 3 H)
$^{13}\text{C NMR (126 MHz, CDCl}_3\text{)}$: δ 159.7, 156.6 (dd, $J = 298.2, 288.6$ Hz), 155.0 (dd, $J = 4.7, 1.6$ Hz), 131.0 (dd, $J = 10.7, 2.0$ Hz), 130.8, 129.3, 128.4, 121.9 (t, $J = 6.4$ Hz), 114.2, 113.9, 113.4, 75.9 (dd, $J = 31.9, 12.5$ Hz), 70.6, 55.5

$^{19}\text{F NMR (376 MHz, CDCl}_3\text{)}$: δ –81.71 (dd, $J = 28.2, 5.0$ Hz, 1 F), –81.90 (dd, $J = 27.9, 25.9$ Hz, 1 F)

IR (film): 3043, 2955, 2835, 1726, 1614, 1587, 1514, 1487, 1464, 1406, 1381, 1344, 1300, 1285, 1248, 1223, 1173, 1117, 1034, 1005, 947, 878, 824, 802, 652, 581 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{16}$H$_{12}$BrF$_2$O$_2$ (M-H) 352.9989, found 352.9983, 1.7 ppm.

**Preparation of Compound 2.5d**

2-(3-bromophenyl)-1,3-dioxolane (2.5d-2):$^3$ Compound 2.5d-2 was prepared according to a previous report.
A 250 mL round-bottomed flask was charged with 5.8 mL (50 mmol) of 3-bromobenzaldehyde, 3.4 mL (60 mmol) of ethylene glycol, and 0.050 g (0.25 mmol) of p-toluenesulfonic acid. The reactants were dissolved in toluene (100 mL), and a Dean-Stark apparatus and reflux condenser was added to the top of the round-bottom flask. The reaction was placed in a preheated oil bath at 120 °C, and refluxed for 18 h. The reaction was washed with NaHCO₃, dried with MgSO₄, and concentrated. The product was used as is. The ¹H NMR spectrum matched previous reports.³

**3-morpholinobenzaldehyde (2.5d-1):**³ Compound 2.5d-1 was prepared according to a previous report. The ¹H NMR spectrum matched previous reports.³

**4-(3-(2,2-difluorovinyl)phenyl)morpholine (2.5d):** Following General Procedure A1, 0.62 g (3.0 mmol) of 2.5d-1 was reacted with 1.87 g (5.25 mmol) of Si-2.1 in anhydrous NMP (12 mL) at 60 °C for 3 h. After workup, the product was purified by flash chromatography, using 0–20% EtOAc in hexanes, to furnish 0.45 g (62% yield) of desired product 2.5d as a yellow oil.

**¹H NMR (400 MHz, CDCl₃):** δ 7.25 (t, J = 8.2 Hz, 1 H), 6.88–6.86 (m, 2 H), 6.81 (ddd, J = 8.3, 2.5, 1.0 Hz, 1 H), 5.24 (dd, J = 26.2, 4.0 Hz, 1 H), 3.88–3.85 (m, 4 H), 3.17–3.15 (m, 4 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): δ 156.4 (dd, $J = 298.1, 288.0$ Hz), 151.7, 131.3 (dd, $J = 7.0, 6.1$ Hz), 129.6, 119.6 (dd, $J = 6.4, 3.4$ Hz), 115.0 (dd, $J = 6.4, 3.6$ Hz), 114.7 (t, $J = 1.9$ Hz), 82.6 (dd, $J = 28.9, 13.1$ Hz), 67.0, 49.4

$^{19}$F NMR (376 MHz, CDCl$_3$): δ −82.05 (dd, $J = 31.7, 26.2$ Hz, 1 F), −84.21 (dd, $J = 31.6, 3.7$ Hz, 1 F)

IR (film): 2964, 2856, 2826, 2361, 2343, 1730, 1601, 1578, 1497, 1439, 1379, 1352, 1304, 1254, 1213, 1163, 1122, 1070, 999, 926, 885, 860, 820, 777, 744, 690, 644, 571, 527 cm$^{-1}$

HRMS (ESI+): calc. for C$_{12}$H$_{14}$F$_2$NO (M+H) 226.1043, found 226.1062, 1.9 mmu.

4-(2,2-difluorovinyl)-N,N-dimethylaniline (2.5e): Following General Procedure A2, 1.49 g (10.0 mmol) of 4-dimethylanaminobenzaldehyde was reacted with 6.24 g (17.5 mmol) of SI-2.1 in anhydrous DMF (20 mL) at 60 °C for 2 h. After workup, the product was purified by flash chromatography, using 0–10% EtOAc in hexanes, to furnish 1.09 g (60% yield) of desired product 2.5e as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.22–7.20 (m, 2 H), 6.71–6.69 (m, 2 H), 5.17 (dd, $J = 26.9, 4.0$ Hz), 2.96 (s, 6 H)
\(^{13}\text{C NMR} (126 \text{ MHz, CDCl}_3)\): \(\delta\) 155.7 (dd, \(J = 295.7, 285.3 \text{ Hz}\)), 149.5 (t, \(J = 1.8 \text{ Hz}\)), 128.6 (dd, \(J = 6.1, 3.5 \text{ Hz}\)), 118.3 (t, \(J = 5.9 \text{ Hz}\)), 112.7, 81.8 (dd, \(J = 28.7, 14.3 \text{ Hz}\)), 40.6

\(^{19}\text{F NMR} (376 \text{ MHz, CDCl}_3)\): \(\delta\) –85.89 (dd, \(J = 40.5, 26.8 \text{ Hz}\), 1 F), –88.03 (dd, \(J = 40.5, 4.0 \text{ Hz}\), 1 F)

IR (film): 2891, 2806, 2361, 2341, 1730, 1614, 1526, 1481, 1445, 1348, 1250, 1200, 1169, 1063, 933, 833, 810, 542, 521 cm\(^{-1}\)

HRMS (ESI\(^+\)): calc. for C\(_{10}\)H\(_{12}\)F\(_2\)N (M+H) 184.0938, found 184.0930, 0.8 mmu.

Preparation of Compound 2.5f

4-formylphenyl trifluoromethanesulfonate (2.5f-1): Compound 2.5f-1 was prepared according to a previous report. The \(^1\text{H NMR spectrum matched previous reports.}\)

4-(2,2-difluorovinyl)phenyl trifluoromethanesulfonate (2.5f): Following General Procedure A2, 3.67 g (14.4 mmol) of 2.5f-1 was reacted with 9.00 g (25.3 mmol) of SI-2.1 in anhydrous NMP (57 mL) at 80 °C for 2 h. After workup, the product was purified by
flash chromatography, using 0–10% EtOAc in hexanes, to furnish 1.51 g (36% yield) of desired product **2.5f** as a clear oil.

**1H NMR (400 MHz, CDCl₃):** δ 7.42–7.39 (m, 2 H), 7.27–7.23 (m, 2 H), 5.31 (dd, J = 25.6, 3.4 Hz, 1 H)

**13C NMR (126 MHz, CDCl₃):** δ 156.7 (dd, J = 299.2, 290.2 Hz), 148.2 (t, J = 2.7 Hz), 131.1 (dd, J = 7.3, 6.1 Hz), 129.4 (dd, J = 6.8, 3.6 Hz), 121.8, 118.9 (q, J = 320.9 Hz), 81.3 (dd, J = 30.4, 13.5 Hz)

**19F NMR (376 MHz, CDCl₃):** δ –72.80 (s, 3 F), –80.72 (dd, J = 26.7, 26.1 Hz, 1 F), –81.99 (dd, J = 26.7, 3.5 Hz, 1 F)

**IR (film):** 2361, 2344, 1732, 1505, 1427, 1356, 1252, 1213, 1173, 1140, 1018, 943, 889, 851, 741, 610, 525 cm⁻¹

**HRMS (HAPCI⁺):** calc. for C₉H₅F₅O₃S (M⁺) 287.9880, found 287.9872, 2.8 ppm.

**Preparation of Compound 2.5g**

![Diagram of the preparation process]
4’-(tert-butyl)-[1,1’-biphenyl]-2-carbaldehyde (2.5g-1): An oven dried 500 mL round bottom flask was charged with 2.9 mL (25 mmol) of 2-bromobenzaldehyde and 8.90 g (50.0 mmol) of 4-tert-butylphenylboronic acid and the system was moved to glovebox for the addition of 24.4 g (75.0 mmol) of Cs₂CO₃, 0.29 g (0.25 mmol) of Pd(PPh₃)₄ and anhydrous 1,4-dioxane (250 mL). After removal from the glovebox the system was immediately immersed in an oil bath at 80 °C and stirred overnight. The reaction was diluted with water and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic layers were dried over MgSO₄ and concentrated. Chromatography on silica gel (hexanes/EtOAc) afforded 5.11 g (86%) of desired product 2.5g-1 as a colorless solid, m.p. 55 °C.

1H NMR (400 MHz, CDCl₃): δ 10.01 (d, J = 0.9 Hz, 1 H), 8.02 (dd, J = 7.4, 1.2 Hz, 1 H), 7.63 (td, J = 7.5, 1.5 Hz, 1 H), 7.52–7.44 (m, 4 H), 7.32 (d, J = 8.3 Hz, 2 H), 1.38 (s, 9 H).

4’-(tert-butyl)-2-(2,2-difluorovinyl)-1,1’-biphenyl (2.5g): Following General Procedure A1, 5.11 g (21.4 mmol) of 5g-1 was reacted with 13.0 g (36.4 mmol) of SI-2.1 in anhydrous DMF (85 mL) at 60 °C for 2 h. After workup, the product was purified by flash chromatography, using 0–10% EtOAc in hexanes, to furnish 4.67 g (80% yield) of desired product 2.5g as a colorless solid, m.p. 46–48 °C.

1H NMR (500 MHz, CDCl₃): δ 7.59 (d, J = 8.1 Hz, 1 H), 7.43 (d, J = 8.5 Hz, 2 H), 7.34 (dd, J = 6.8, 3.5 Hz, 1 H), 7.32 (dd, J = 8.1, 5.4 Hz, 1 H), 7.29 (dd, J = 6.1, 1.3 Hz, 2 H),
7.26 (d, \( J = 2.0 \) Hz, 1 H), 7.24 (d, \( J = 1.3 \) Hz, 1 H), 5.27 (dd, \( J = 26.2, 4.3 \) Hz, 1 H), 1.37 (s, 9 H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 156.4 (dd, \( J = 297.6, 286.8 \) Hz), 150.3, 141.3 (dd, \( J = 4.9, 1.6 \) Hz), 137.8, 130.4, 129.4, 128.2 (dd, \( J = 9.6, 1.5 \) Hz), 128.1 (d, \( J = 6.3 \) Hz), 127.5, 127.2, 125.3, 80.9 (dd, \( J = 30.4, 12.3 \) Hz), 34.7, 31.5

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –83.28 (dd, \( J = 32.5, 4.3 \) Hz, 1 F), –85.14 (ddd, \( J = 32.6, 26.1, 1.8 \) Hz, 1 F)

IR (film): 2964, 1726, 1483, 1398, 1348, 1269, 1232, 1173, 1117, 939, 835, 762 cm\(^{-1}\)

HRMS (HAPCI\(^{+}\)): calc. for C\(_{18}\)H\(_{19}\)F\(_2\) (M+H) 273.1455, found 273.1452, 1.1 ppm.

1-(benzyloxy)-4-(2,2-difluorovinyl)-2-methoxybenzene (2.5h): Following General Procedure A2, 2.42 g (10.0 mmol) of 5h-1 was reacted with 6.24 g (17.5 mmol) of Si-2.1 in anhydrous DMF (40 mL) at 60 °C for 2 h. After workup, the product was purified by flash chromatography, using 0–10% EtOAc in hexanes, to furnish 2.18 g (79% yield) of desired product 2.5h as a colorless solid, m.p. 50 °C.
\[^{1}\text{H NMR (400 MHz, CDCl}_3\text{)}\]: \(\delta 7.43 (d, J = 7.6 \text{ Hz}, 2 \text{ H}), 7.39–7.35 \text{ Hz (m, 2 H)}, 7.32–7.28 \text{ (m, 1 H)}, 6.90 (d, J = 1.9 \text{ Hz}, 1 \text{ H}), 6.84 (d, J = 8.3 \text{ Hz}, 1 \text{ H}), 6.80 (dd, J = 8.4, 2.0 \text{ Hz}, 1 \text{ H}), 5.21 (dd, J = 26.2, 3.9 \text{ Hz}, 1 \text{ H}), 5.17 (s, 2 \text{ H}), 3.89 (s, 3 \text{ H})\)

\[^{13}\text{C NMR (126 MHz, CDCl}_3\text{)}\]: \(\delta 156.0 \text{ (dd, } J = 296.8, 286.9 \text{ Hz), 149.8, 147.4 (t, } J = 2.2 \text{ Hz), 137.1, 128.7, 128.0, 127.4, 123.7 (t, } J = 6.3 \text{ Hz), 120.5 (dd, } J = 6.1, 4.0 \text{ Hz), 114.2, 111.2 (dd, } J = 6.9, 3.1 \text{ Hz), 82.0 (dd, } J = 29.4, 13.7 \text{ Hz), 71.1, 56.1}\)

\[^{19}\text{F NMR (376 MHz, CDCl}_3\text{)}\]: \(\delta -84.07 \text{ (dd, } J = 35.9, 26.2 \text{ Hz, 1 F), -85.90 (dd, } J = 36.0, 3.8 \text{ Hz, 1 F)}\)

\textbf{IR (film): } 3410, 2359, 2341, 1734, 1520, 1472, 1456, 1421, 1340, 1265, 1211, 1182, 1142, 1030, 1003, 858, 798, 744, 696, 681, 650, 440, 417 \text{ cm}^{-1}

\textbf{HRMS (HAPCI\textsuperscript{+}): } \text{calc. for C}_{16}\text{H}_{14}\text{F}_{2}\text{O}_{2} \text{ (M\textsuperscript{+}) 276.0962, found 276.0953, 3.3 ppm.}

\textbf{Preparation of Compound 2.5i}

(2-iodophenyl)methanol (2.5i-2):\textsuperscript{6} Compound 2.5i-2 was prepared according to a previous report.\textsuperscript{6} An oven-dried 250 mL round bottom flask was charged with a magnetic stirbar and 4.97 g (20.0 mmol) of 4-iodobenzoic acid. Anhydrous THF (40 mL) was added,
and the solution cooled to 0 °C. At 0 °C, 22 mL of BH₃•THF (22 mmol, 1 M in THF) was added dropwise. The reaction was allowed to warm to ambient temperature and stir overnight. The reaction was quenched with 50 mL of a solution of 1:1 THF:H₂O. The THF was removed in vacuo, and 50 mL of a saturated aq. solution of K₂CO₃ added. The resulting solution was extracted 3X with 25 mL of Et₂O, and the combined organic layers dried over MgSO₄ and concentrated in vacuo. The resulting compound was of sufficient purity to use for the next step, and the reaction afforded 4.50 g (96%) of desired product 2.5i-2 as a colorless solid. The ¹H NMR spectrum matched previous reports.

2-iodobenzaldehyde (2.5i-1): Compound 2.5i-1 was prepared according to a previous report. An oven-dried 500 mL flask was charged with a magnetic stirbar, 4.50 g (19.0 mmol) of 5i-2, and 12.32 g (29.0 mmol) of Dess-Martin periodinane. The system was evacuated and backfilled with N₂ 3X, and then anhydrous DCM (200 mL) was added at R.T.. The reaction was stirred overnight at ambient temperature, and quenched with approximately 50 mL of H₂O. Upon the addition of H₂O, a white precipitate formed, and the reaction was filtered. The precipitate was loaded on silica gel and purified by flash chromatography with 20% EtOAc in hexanes. The reaction furnished 3.34 g (75%) of desired product 2.5i-1 as a colorless solid. The ¹H NMR spectrum matched previous reports.

1-(2,2-difluorovinyl)-2-iodobenzene (2.5i): Following General Procedure A1, 3.00 g (13.0 mmol) of 2.5i-1 was reacted with 8.11 g (23.0 mmol) of SI-2.1 in anhydrous NMP
(52 mL) at 80 °C for 2 h. After workup, the product was purified by flash chromatography, using a very slow gradient of 0–5% EtOAc in hexanes, to furnish 2.16 g (63% yield) of desired product 2.5i as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 (dd, $J = 7.9, 1.2$ Hz, 1 H), 7.47 (dt, $J = 7.9, 1.7$ Hz, 1 H), 7.34 (J = 7.9, 7.3, 1.3 Hz, 1 H), 6.95 (td, 7.7, 1.7 Hz, 1 H), 5.57 (dd, $J = 25.0, 3.7$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 156.7 (dd, $J = 298.6, 289.0$ Hz), 139.6, 134.0 (dd, $J = 8.0, 5.6$ Hz), 128.9 (d, $J = 1.6$ Hz), 128.85 (dd, $J = 8.7, 1.4$ Hz), 128.5, 99.7 (dd, $J = 5.7, 2.0$ Hz), 86.5 (32.1, 12.6 Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –82.34 (dd, $J = 26.7, 3.6$ Hz, 1 F), –83.88 (dd, $J = 26.7, 24.9$ Hz, 1 F)

IR (film): 1729, 1468, 1433, 1348, 1275, 1244, 1175, 1113, 1013, 941, 810, 748, 712, 665, 635, 571 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_8$H$_5$F$_2$I (M+) 265.9404, found 265.9400, 1.5 ppm.

**Preparation of Compound 2.5j**
ethyl (E)-3-(3-formylphenyl)acrylate (2.5j-1): Compound 2.5j-1 was prepared according to a previous report. A flame dried 500 mL round bottom flask was equipped with a magnetic stirbar and charged with Pd(OAc)$_2$ (0.112 g, 0.500 mmol) of and (o-MeC$_6$H$_4$)$_3$P (0.305 g, 1.00 mmol). The system was evacuated and backfilled 3X with N$_2$, and anhydrous DMF (125 mL) was added via cannula. By syringe, 3.33 mL (31.3 mmol) of ethyl acrylate and 3.0 mL (25 mmol) of 3-bromobenzaldehyde were added, followed by 7.0 mL (50 mmol) of anhydrous Et$_3$N. The system was immediately submerged in a preheated 125 ºC oil bath and stirred for 18 h. After returning to ambient temperature, the reaction was quenched with H$_2$O and extracted 3X with DCM. The combined organic layers were washed 2X with 1 N aq. HCl and 2X with saturated brine solution. The organic layers were then dried over MgSO$_4$, concentrated, and purified by flash chromatography on silica gel (0–20% EtOAc in hexanes), to furnish 3.19 (63%) of desired product 2.5j-1 as a clear oil. The $^1$H NMR spectrum matched reference.

ethyl (E)-3-(3-(2,2-difluorovinyl)phenyl)acrylate (2.5j): Following General Procedure A2, 3.07 g (15.0 mmol) of 2.5j-1 was reacted with 9.08 g (25.5 mmol) of SI-2.1 in anhydrous NMP (30 mL) at 80 ºC for 2 h. After workup, the product was purified by flash chromatography using 0–10–20% EtOAc in hexanes, to furnish 2.32 g (65% yield) of desired product 2.5j as a colorless solid, m.p. 24 ºC.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.69 (d, $J = 16.0$ Hz, 1 H), 7.49 (s, 1 H), 7.43 (td, $J = 6.2$, 3.3 Hz, 1 H), 7.38 (d, $J = 6.1$ Hz, 1 H), 6.47 (d, $J = 16.0$ Hz, 1 H), 5.31 (dd, $J = 26.0$, 3.6 Hz, 1 H), 4.30 (q, $J = 7.1$ Hz, 2 H), 1.37 (t, $J = 7.1$ Hz, 3 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 167.0, 156.56 (dd, $J = 298.8$, 289.3 Hz), 144.2, 135.0, 131.2 (t, $J = 7.1$, 6.1 Hz), 129.4, 127.3 (dd, $J = 6.4$, 3.6 Hz), 126.6, 119.0, 81.9 (dd, $J = 29.5$, 13.3 Hz), 60.7, 14.5

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.17 (dd, $J = 29.2$, 25.9 Hz, 1 F), –82.99 (dd, $J = 29.0$, 3.7 Hz, 1 F)

IR (film): 2982, 2361, 2343, 1730, 1713, 1639, 1431, 1367, 1352, 1312, 1267, 1248, 1178, 1038, 980, 922, 897, 862, 824, 791, 685 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{13}$H$_{13}$F$_2$O$_2$ (M+H) 239.0884, found 239.0879, 2.1 ppm.

$^{1,3}$-dichloro-5-(2,2-difluorovinyl)benzene (2.5k): Following General Procedure A2, 1.61 g (10.0 mmol) of 3,5-dichlorobenzaldehyde was reacted with 5.70 g (17.5 mmol) of SI-2.1 in anhydrous NMP (40 mL) at 80 °C for 2 h. After workup, the product was purified by flash chromatography using 0–10% EtOAc in hexanes, to furnish 0.99 g (52% yield) of desired product 2.5k as a pale oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24 (t, $J = 1.9$ Hz, 1 H), 7.21 (d, $J = 1.9$ Hz, 2 H), 5.21 (dd, $J = 25.2$, 3.3 Hz, 1 H)
\(^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\):} \delta 156.9 (dd, J = 300.2, 291.1 Hz), 135.4, 133.5 (dd, J = 7.7, 6.1 Hz), 127.2 \text{ t, } J = 2.0 \text{ Hz}, 126.0 (dd, J = 6.9, 3.6 Hz), 81.1 \text{ (dd, } J = 31.0, 13.1 \text{ Hz)}

\(^{19}\text{F NMR (376 MHz, CDCl}_3\):} \delta -78.72 \text{ (dd, } J = 25.2, 23.8 \text{ Hz, 1 F)}, -80.80 \text{ (dd, } J = 23.8, 3.3 \text{ Hz, 1 F)}

\text{IR (film):} \text{ 2361, 2341, 1728, 1589, 1560, 1419, 1350, 1254, 1177, 1124, 1105, 980, 899, 876, 856, 802, 690, 669 cm}^{-1}

\text{HRMS (HAPCI\(^+\):} \text{ calc. for C}_8\text{H}_4\text{Cl}_2\text{F}_2 (M\(^+\)) 207.9658, \text{ found 207.9648, 4.8 ppm.}

\text{Preparation of Compound 2.5l}

\text{4-formyl-\textit{N,\textit{N-dipropylbenzamide} (2.5l-1):} }^9 \text{ Compound 2.5l-1 was prepared according to a previous report. The } ^1\text{H NMR spectrum matched previous reports.}^9

\text{4-(2,2-difluorovinyl)-\textit{N,\textit{N-dipropylbenzamide} (2.5l):} Following General Procedure A1, 2.06 g (8.60 mmol) of 5l-1 was reacted with 5.35 g (15.0 mmol) of SI-2.1 in anhydrous NMP (34.4 mL) at 80 \text{ °C for 2 h. After workup, the product was purified by flash}
chromatography, using 0–20–50% EtOAc in hexanes, to furnish 1.84 g (80% yield) of desired product **2.5l** as a yellow oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.36–7.31 (m, 4 H), 5.29 (dd, J = 26.1, 3.6 Hz, 1 H), 3.45 (bs, 2 H), 3.18 (bs, 2 H), 1.68 (bs, 2 H), 1.53 (bs, 2 H), 0.97 (bs, 3 H), 0.75 (bs, 3 H)

**<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):** δ 171.4, 156.6 (dd, J = 299.2, 289.3 Hz), 136.0 (t, J = 2.1 Hz), 131.3 (t, J = 6.7 Hz), 127.6 (dd, J = 6.4, 3.5 Hz), 127.1, 82.0 (dd, J = 29.5, 13.5 Hz), 50.8, 46.5, 22.1, 20.8, 11.6, 11.2

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ –81.03 (dd, J = 28.6, 26.2, 1 F), –82.96 (dd, J = 28.6, 3.7, 1 F)

**IR (film):** 2966, 2935, 2876, 2361, 2343, 1730, 1634, 1514, 1464, 1425, 1381, 1352, 1246, 1169, 1099, 939, 856, 762, 586 cm<sup>-1</sup>

**HRMS (ESI+):** calc. for C<sub>15</sub>H<sub>20</sub>F<sub>2</sub>NO (M+H) 268.1513, found 268.1517, 0.4 mmu.

![2.5m](image)

**4-(2,2-difluorovinyl)benzonitrile (2.5m):** Following General Procedure A2, 2.17 g (16.6 mmol) of 4-cyanobenzaldehyde was reacted with 10.3 g (29.0 mmol) of **SI-2.1** in anhydrous NMP (92 mL) at 80 °C for 0.25 h. After workup, the product was purified by
flash chromatography, using 0–10% EtOAc in hexanes, to furnish 1.20 g (44% yield) of desired product 2.5m as a colorless solid, m.p. 66–67 °C.

\(^1\text{H NMR (400 MHz, CDCl}_3\): } \delta 7.55 (d, J = 8.4 \text{ Hz, 2 F}), 7.36 (d, J = 8.4, 2 \text{ H}), 5.27 (dd, J = 25.6, 3.4 \text{ Hz, 1 H})

\(^{13}\text{C NMR (126 MHz, CDCl}_3\): } \delta 157.1 (dd, J = 301.3, 292.3 \text{ Hz}), 135.5 (dd, J = 7.4, 6.4 \text{ Hz}), 132.6, 128.2 (dd, J = 6.9, 3.6 \text{ Hz}), 118.8, 110.7 (t, J = 2.4 \text{ Hz}), 82.0 (dd, J = 30.5, 12.9 \text{ Hz})

\(^{19}\text{F NMR (376 MHz, CDCl}_3\): } \delta -77.77 (dd, J = 25.5, 20.4 \text{ Hz, 1 F}), -79.44 (dd, J = 20.5, 3.3 \text{ Hz, 1 F})

\text{IR (film): } 3423, 3406, 2361, 2341, 2228, 1732, 1610, 1514, 1244, 1173, 945, 856, 746, 548 \text{ cm}^{-1}

\text{HRMS (HAPCI+): } \text{calc. for } C_9H_6F_2N (M+H) 166.0468, \text{ found } 166.0462, 3.6 \text{ ppm.}

\begin{figure}
\includegraphics[width=\textwidth]{2.5n.png}
\end{figure}

\textbf{1-(2,2-difluorovinyl)-3-nitrobenzene (2.5n):} Following General Procedure A2, 3.03 g (20.0 mmol) of 3-nitrobenzaldehyde was reacted with 12.5 g (35.0 mmol) of \textbf{SI-2.1} in anhydrous NMP (80 mL) at 120 °C for 0.5 h. After workup, the product was purified by
flash chromatography, using 0–5% EtOAc in hexanes, to furnish 2.38 g (64% yield) of desired product 2.5n as a pale yellow solid, m.p. 30–32 °C.

**1H NMR (400 MHz, CDCl₃):** δ 8.20 (s, 1 H), 8.10 (d, J = 8.7 Hz, 1 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.52 (t, J = 8.0 Hz, 1 H), 5.39 (dd, J = 25.3, 3.1 Hz, 1 H)

**13C NMR (126 MHz, CDCl₃):** δ 157.1 (dd, J = 299.8, 291.5 Hz), 148.7, 133.4 (dd, J = 6.7, 3.6 Hz), 132.4 (dd, J = 7.8, 6.1 Hz), 129.8, 122.5 (dd, J = 6.8, 3.7 Hz), 122.0 (t, J = 2.0 Hz), 81.3 (dd, J = 30.9, 13.3 Hz)

**19F NMR (376 MHz, CDCl₃):** δ –78.94 (dd, J = 25.2, 23.7 Hz, 1 F), –80.67 (dd, J = 23.8, 3.2 Hz, 1 F)

**IR (film):** 3101, 2361, 2341, 1730, 1531, 1350, 1296, 1248, 1177, 972, 914, 901, 824, 735, 706, 677 cm⁻¹

**HRMS (HAPCI+):** calc. for C₈H₆F₂NO₂ (M+H) 186.0367, found 186.0359, 4.3 ppm.

**Preparation of Compound 2.7a**

![Reaction Scheme](image)

**1-tosyl-1H-indole-3-carbaldehyde (2.7a-1):**¹⁰ Compound 2.7a-1 was prepared according to a previous report. The ¹H NMR spectrum matched previous reports.¹⁰
3-(2,2-difluorovinyl)-1-tosyl-1H-indole (2.7a): Following General Procedure A1, 1.80 g (6.00 mmol) of 2.7a-1 was reacted with 3.77 g (10.5 mmol) of SI-2.1 in anhydrous DMF (24 mL) at 80 °C for 2 h. After workup, the product was purified by flash chromatography, using hexanes, increasing to 5% DCM in hexanes, then 5% EtOAc in hexanes, and then increasing to 10% EtOAc in hexanes, to furnish 1.59 g (79% yield) of desired product 2.7a as a colorless solid, m.p. 106–108 °C.

1H NMR (400 MHz, CDCl3): δ 8.04 (d, J = 8.3 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 2 H), 7.65 (s, 1 H), 7.48 (d, J = 7.9 Hz, 1 H), 7.36 (t, J = 7.8 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 7.20 (d, J = 8.0 Hz, 2 H), 5.39 (d, 26.7 Hz, 1 H), 2.31 (s, 3 H)

13C NMR (126 MHz, CDCl3): δ 156.8 (dd, J = 296.1, 289.9 Hz), 145.2, 135.0, 134.7, 130.0, 129.4 (d, J = 3.3 Hz), 126.9, 125.3, 123.5, 123.3 (dd, J = 9.8, 3.9 Hz), 119.1 (d, J = 1.3 Hz), 113.8, 111.9 (J = 6.6, 5.2 Hz), 72.5 (dd, J = 32.1, 18.4 Hz), 21.6

19F NMR (376 MHz, CDCl3): δ –78.18 (t, 26.4 Hz, 1 F), –84.63 (d, J = 26.3 Hz, 1 F)

IR (film): 2361, 2341, 1732, 1597, 1558, 1448, 1375, 1323, 1286, 1175, 1134, 1094, 980, 918, 837, 814, 760, 744, 702, 677, 656, 590, 573, 538 cm⁻¹

HRMS (ESI+): calc. for C₁₇H₁₄F₂NO₂S (M+H) 334.0713, found 334.0733, 2.0 mmu.

Preparation of Compound 2.7b
2-bromo-5-(1,3-dioxolan-2-yl)pyridine (2.7b-2): Compound 2.7b-2 was prepared according to a previous report. A 1 L round-bottom flask was charged with 10.1 g (54.0 mmol) of 6-bromonicotinaldehyde, PhMe (540 mL), 13.2 mL (220 mmol) of ethylene glycol, and 1.17 g (5.40 mmol) of PTSA-H$_2$O were sequentially added. The system was equipped with a Dean-Stark apparatus and a reflux condenser, placed in a 120 °C oil bath, and stirred for 18 h. The resulting solution was washed with saturated NaHCO$_3$ (3X 100 mL) followed by brine (2X 100 mL). The organic layer was dried with Na$_2$SO$_4$ and concentrated under reduced pressure to afford 8.87 g (71% yield) of desired product 2.7b-2 as a clear oil. The $^1$H NMR spectrum matched previous reports.

3-(5-(1,3-dioxolan-2-yl)pyridin-2-yl)benzaldehyde (2.7b-1): An oven-dried 1 L round bottom flask was charged with 8.87 g (39.0 mmol) of 7b-2, 8.71 g (58.0 mmol) of 3-boronobenzaldehyde, 1.31 g (5.80 mmol) of Pd(OAc)$_2$, and 26.1 g (77.0 mmol) of K$_3$PO$_4$-7H$_2$O. The flask was sealed with a rubber septum and evacuated and backfilled with N$_2$ three times. The reagents were dissolved in 200 mL of IPA (sparged for 20 min with N$_2$)
and 200 mL of H$_2$O (freshly distilled under N$_2$ gas). The reaction vessel was submerged in an 80 °C oil bath for 13 h. At R.T., brine (100 mL) was added to the reaction, followed by an extraction with EtOAc (3X 150 mL). The organic layer was concentrated with Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography using a gradient from 0–20–50% EtOAc in hexanes, to furnish 4.81 g (49% yield) of desired product 2.7b-1 as a yellow/white solid, m.p. 57–59 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.12 (s, 1 H), 8.81 (d, $J = 2.1$ Hz, 1 H), 8.52 (t, $J = 1.7$ Hz, 1 H), 8.31 (ddd, $J = 7.9$, 1.9, 1.1 Hz, 1 H), 7.95 (dt, $J = 7.7$, 1.4 Hz, 1 H), 7.92 (dd, $J = 8.2$, 2.2 Hz, 1 H), 7.83 (dd, 8.2, 0.9 Hz, 1 H), 7.66 (t, $J = 7.7$ Hz, 1 H), 5.93 (s, 1 H), 4.19–4.07 (m, 4 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 192.4, 156.8, 148.6, 140.1, 137.0, 135.5, 133.0, 132.8, 130.1, 129.7, 128.7, 120.4, 102.0, 65.6

IR (film): 2959, 2888, 2729, 1697, 1601, 1474, 1342, 1182, 1086, 1024, 982, 941, 837, 800, 764, 689, 652, 403 cm$^{-1}$

HRMS (ESI+): calc. for C$_{15}$H$_{14}$NO$_3$ (M+H) 256.0974, found 256.0996, 2.2 mmu.

2-(3-(2,2-difluorovinyl)phenyl)-5-(1,3-dioxolan-2-yl)pyridine (2.7b): Following General Procedure A1, 4.56 g (18.0 mmol) of 2.7b-1 was reacted with 11.0 g (31.0 mmol) of SI-2.1 in anhydrous NMP (38 mL) at 60 °C for 1 h. After workup, the product was
purified by flash chromatography on silica gel, using a gradient from 0–20–50% EtOAc in hexanes, to furnish 3.95 g (76% yield) of desired product **2.7b** as a tan solid, m.p. 35 °C.

**1H NMR (400 MHz, CDCl3):** δ 8.78 (dt, *J* = 2.2, 0.7 Hz, 1 H), 7.95 (t, *J* = 1.8 Hz, 1 H), 7.87 (dd, *J* = 8.3, 2.3 Hz, 1 H), 7.84 (dt, *J* = 7.2, 1.7 Hz, 1 H), 7.74 (dd, *J* = 8.2, 0.8 Hz, 1 H), 7.47–7.41 (m, 2 H), 5.91 (s, 1 H), 5.38 (dd, *J* = 26.1, 3.8 Hz, 1 H), 4.18–4.06 (m, 4 H)

**13C NMR (126 MHz, CDCl3):** δ 158.0, 156.5 (dd, *J* = 298.5, 288.6 Hz), 148.4, 139.6, 135.2, 132.2, 131.1 (t, *J* = 6.5 Hz), 129.3, 128.3 (dd, *J* = 6.9, 3.2 Hz), 126.6 (dd, *J* = 5.8, 3.8 Hz), 125.8 (t, *J* = 2.0 Hz), 120.4, 102.1, 82.3 (dd, *J* = 29.4, 13.3 Hz), 65.6

**19F NMR (376 MHz, CDCl3):** δ –81.56 (dd, *J* = 30.3, 26.1 Hz, 1 F), –83.63 (dd, *J* = 30.3, 3.8 Hz, 1 F)

**IR (film):** 2982, 2888, 1728, 1601, 1566, 1474, 1427, 1410, 1352, 1296, 1227, 1165, 1138, 1088, 1024, 982, 951, 891, 856, 833, 797, 766, 692, 571 cm⁻¹

**HRMS (ESI+):** calc. for C₁₆H₁₄F₂NO₂ (M+H) 290.0993, found 290.0996, 1.0 ppm.

![2.7c](image)

**4-(2,2-difluorovinyl)-1-phenyl-1H-pyrazole (2.7c):** Following General Procedure A1, 1.51 g (8.70 mmol) of 1-phenyl-1H-pyrazole-4-carbaldehyde was reacted with 5.44 g
(15.0 mmol) of \textbf{SI-2.1} in anhydrous NMP (17.4 mL) at 60 °C for 1 h. After workup, the product was purified by flash chromatography, using hexanes, increasing to 10% DCM in hexanes, then 5% EtOAc in hexanes, and then increasing to 10% EtOAc in hexanes, to furnish 1.18 g (66% yield) of desired product \textbf{2.7c} as a colorless solid, m.p. 70–71 °C.

\textbf{1H NMR (400 MHz, CDCl$_3$):} $\delta$ 7.88 (s, 1 H), 7.70 (s, 1 H), 7.67 (d, $J = 7.9$ Hz, 2 H), 7.44 (t, $J = 7.7$ Hz, 2 H), 7.29 (t, $J = 7.2$ Hz, 1 H), 5.22 (dd, $J = 26.9$, 1.7 Hz, 1 H)

\textbf{13C NMR (126 MHz, CDCl$_3$):} $\delta$ 156.3 (dd, $J = 293.6$, 287.3 Hz), 140.0 (dd, $J = 4.3$, 3.0 Hz), 139.9, 129.5, 126.7, 124.5 (t, $J = 4.9$ Hz), 119.1, 113.2 (dd, $J = 7.2$, 4.9 Hz), 72.9 (dd, $J = 32.0$, 18.7 Hz)

\textbf{19F NMR (376 MHz, CDCl$_3$):} $\delta$ –82.09 (dd, $J = 34.7$, 27.0 Hz, 1 F), –88.03 (dd, $J = 34.8$, 1.7 Hz, 1 F)

\textbf{IR (film):} 2361, 2341, 1741, 1466, 1398, 1317, 1238, 1165, 1074, 1018, 825, 751, 689, 656 cm$^{-1}$

\textbf{HRMS (ESI+):} calc. for C$_{11}$H$_9$F$_2$N$_2$ (M+H) 207.0734, found 207.0720, 1.4 mmu.

\textbf{Preparation of Compound 2.7d}

\[
\begin{align*}
\text{Ph$_3$P}^+\text{CF$_2$CO}_2^- & \rightarrow \text{Ph$_3$P}^+\text{CF$_2$CO}_2^- \\
\text{NMP, 80 °C, 2 h} & \rightarrow \text{2.7d}
\end{align*}
\]
dibenzo[\textit{b},d\textit{]}thiophene-4-carbaldehyde (2.7d-1): An oven dried 100 mL round bottom flask was equipped with a magnetic stirbar and charged with 1.87 g (10.0 mmol) of dibenzothiophene. The system was evacuated and backfilled with N\textsubscript{2}, and then anhydrous THF (30 mL) was added. The system was cooled to 0 °C, and 7.45 mL (10.0 mmol) of freshly titrated \textit{n}-BuLi (titrated at 1.38 M in hexanes) was added dropwise to the reaction. The reaction was stirred 1.5 h at 0 °C, and then 1.60 mL (20.0 mmol) of anhydrous DMF was added dropwise at 0 °C, and the reaction was stirred for 2.5 h at 0 °C. The reaction was poured into 50 mL of ice water to quench the reaction, and the resulting solution was extracted 3X with 20 mL of EtOAc, dried over MgSO\textsubscript{4}, and concentrated. After workup, the product was purified by flash chromatography on silica gel using a gradient from 0–20% EtOAc in hexanes, to furnish 1.41 g (66%) of desired product 2.7d-1 was isolated as a colorless solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 10.31 (s, 1 H), 8.45 (d, \(J = 7.8\) Hz, 1 H), 8.25–8.23 (m, 1 H), 8.01 (dd, \(J = 7.5, 1.1\) Hz, 1 H), 7.99–7.96 (m, 1 H), 7.69 (t, \(J = 7.6\) Hz, 1 H), 7.54 (td, \(J = 6.5, 5.7, 3.6\) Hz, 2 H).

4-(2,2-difluorovinyl)dibenzo[\textit{b},d\textit{]}thiophene (2.7d): Following General Procedure A2, 1.37 g (5.70 mmol) of 2.7d-1 was reacted with 3.59 g (9.99 mmol) of SI-2.1 in anhydrous NMP (23 mL) at 80 °C for 2 h. After workup, the product was purified by flash chromatography on silica gel, using a gradient from 0–10–20% EtOAc in hexanes, to furnish 0.97 g (61%) of desired product 2.7d as a colorless solid, m.p. 79–80 °C.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.18–8.13 (m, 1 H), 8.07 (dd, $J = 7.8, 1.1$ Hz, 1 H), 7.90–7.86 (m, 1 H), 7.59 (dt, $J = 7.7, 1.5$ Hz, 1 H), 7.51–7.46 (m, 3 H), 5.54 (dd, $J = 25.1, 3.2$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 157.1 (dd, $J = 299.2, 290.2$ Hz), 138.8, 136.02, 135.99, 127.1, 125.5 (dd, $J = 8.9, 1.9$ Hz), 125.1, 125.0, 124.8, 123, 122, 120.5 (t, $J = 1.6$ Hz), 80.1 (dd, $J = 30.4, 14.6$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –80.64 (dd, $J = 25.0, 1.7$ Hz, 1 F), –81.64 (dd, $J = 24.7, 3.2$ Hz, 1 F)

IR (film): 2361, 2341, 1728, 1394, 1354, 1265, 1205, 1167, 955, 820, 750, 667, 424 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{14}$H$_8$F$_2$S (M+) 246.0315, found 246.0304, 4.5 ppm.

Preparation of Compound 2.7e
10-benzyl-10H-phenothiazine (2.7e-2): Compound 2.7e-2 was prepared according to a previous report. An oven dried 500 mL round bottom flask was charged with 3.03 g (126 mmol) of NaH in a glovebox. Upon removal from the glovebox, the NaH was suspended in anhydrous THF (60 mL). In a separate 100 mL round bottom flask, 5.97 g (30.0 mmol) of phenothiazine was dissolved in anhydrous THF (30 mL) and transferred by cannula to the 500 mL round bottom flask. The system was immediately immersed in an oil bath at 60 °C for 4 h or until the appearance of a yellow/orange color. The reaction was cooled to ambient temperature, and 6.07 mL (51.0 mmol) of benzyl bromide was added dropwise. The solution was stirred for 18 h, and then heated at 60 °C for 1 h or until the color faded. The reaction was quenched with cold 1 N HCl, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 1 M HCl, dried over Na₂SO₄ and concentrated. Chromatography on silica gel (hexanes/EtOAc) afforded 5.37 g (62%) of desired product 2.7e-2 as a colorless solid, m.p. 87–88 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.32–7.23 (m, 5 H), 7.03 (dd, J = 7.6, 1.6 Hz, 2 H), 6.92 (td, J = 7.4, 1.6 Hz, 2 H), 6.80 (td, J = 7.5, 1.2 Hz, 2 H), 6.58 (dd, J = 8.1, 1.2 Hz, 2 H), 5.04 (s, 2 H).

10-benzyl-10H-phenothiazine-3-carbaldehyde (2.7e-1): Compound 2.7e-1 was prepared according to a previous report. An oven dried 100 mL 3-necked round bottom flask with reflux condenser was charged with 2.90 g (10.0 mmol) of 2.7e-2, and the system was evacuated and backfilled with N₂ three times. Anhydrous DCE (50 mL) was added
via cannula followed by the addition of 3.10 mL (40.0 mmol) of DMF. The system was cooled to 0 °C, and 3.70 mL (40.0 mmol) of POCl$_3$ was added dropwise. The system was immediately immersed in an oil bath at 80 °C and refluxed overnight. The reaction was cooled to 0 °C, quenched slowly with 5 mL of water while stirring, and the aqueous layer was extracted DCM (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated. Chromatography on silica gel (hexanes/EtOAc) afforded 1.00 g (31%) of **2.7e-1** as a yellow solid, m.p. 99–102 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.75 (s, 1 H), 7.56 (d, $J = 1.9$ Hz, 1 H), 7.45 (dd, $J = 8.4$, 2.0 Hz, 1 H), 7.40–7.26 (m, 5 H), 7.08 (dd, $J = 7.5$, 1.7 Hz, 1 H), 7.00 (td, $J = 7.8$, 1.7 Hz, 1 H), 6.92 (td, $J = 7.4$, 1.3 Hz, 1 H), 6.67 (dd, $J = 8.1$, 1.3 Hz, 1 H), 6.65 (d, $J = 8.4$ Hz, 1 H), 5.13 (s, 2 H).

**10-benzyl-3-(2,2-difluorovinyl)-10H-phenothiazine (2.7e):** Following General Procedure A2, 1.10 g (3.40 mmol) of **2.7e-1** was reacted with 2.07 g (5.80 mmol) of SI-2.1 in anhydrous DMF (14 mL) at 60 °C for 2 h. After workup, the product was purified by flash chromatography, using 0–20% EtOAc in hexanes, to furnish 1.00 g (84% yield) of desired product **2.7e** as a yellow/orange semisolid.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.38–7.33 (m, 2 H), 7.32–7.27 (m, 3 H), 7.10 (dd, $J = 7.6$, 1.6 Hz, 1 H), 7.08 (d, $J = 2.2$ Hz, 1 H), 7.03–6.95 (m, 1 H), 6.92 (dd, $J = 8.5$, 2.2 Hz, 1 H), 6.88 (td, $J = 7.5$, 1.2 Hz, 1 H), 6.64 (dd, $J = 8.2$, 1.2 Hz, 1 H), 6.58 (d, $J = 8.5$ Hz, 1 H), 5.12 (dd, $J = 26.3$, 3.7 Hz, 1 H), 5.08 (s, 2 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 156.0 (dd, $J = 297.6$, 287.7 Hz), 144.2, 143.3 (t, $J = 2.2$ Hz), 136.5, 128.9, 127.5, 127.2, 127.0, 126.6, 125.7 (dd, $J = 6.6$, 3.4 Hz), 124.7 (t, $J = 6.3$ Hz), 123.5, 122.8, 122.6, 115.5, 81.2 (dd, $J = 29.6$, 13.8 Hz), 52.7

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –83.09 (dd, $J = 33.9$, 26.4 Hz, 1 F), –85.21 (dd, $J = 34.0$, 3.5 Hz, 1 F)

IR (film): 3061, 3030, 2922, 2853, 1728, 1603, 1578, 1497, 1470, 1454, 1445, 1366, 1344, 1259, 1238, 1173, 955, 879, 825, 746, 735, 696

HRMS (ESI+): calc. for C$_{21}$H$_{16}$F$_2$NS (M+H) 352.0972, found 352.0989, 1.7 mmu.

Preparation of Compound 2.7f

2-(piperazin-1-yl)thiazole (2.7f-3):$^{15}$ Compound 2.7f-3 was prepared according to a previous report.$^{15}$ A 250 mL 2-neck round bottom flask, equipped with a magnetic stirbar and reflux condenser, was charged with 1.80 mL (20.0 mmol) of 2-bromothiazole and
6.03 g (70.0 mmol) of piperazine. The system was dissolved in 1-butanol (60 mL) and immersed in an oil bath at 125 °C and refluxed for 5 h. The reaction was cooled to ambient temperature and stirred for an additional 15 h. The system was filtered, the filtrate concentrated in vacuo, combined with sat. aq. Na$_2$CO$_3$, and extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and concentrated. Flash chromatography on silica gel (1:1 MeOH/EtOAc) afforded 2.20 g (65% yield) of desired product 2.7f-3 as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.19 (d, $J = 3.7$ Hz, 1 H), 6.56 (d, $J = 3.7$ Hz, 1 H), 3.45 (dd, $J = 6.6$, 3.5 Hz, 4 H), 2.98 (dd, $J = 6.7$, 3.5 Hz, 4 H), 1.69 (s, 1 H).

tert-butyl 4-(thiazol-2-yl)piperazine-1-carboxylate (2.7f-2):$^{16}$ Compound 2.7f-2 was prepared according to a previous report.$^{16}$ A flame dried 250 mL round bottom flask was charged with 2.15 g (12.7 mmol) of 7f-3 and 0.16 g (1.3 mmol) of 4-dimethylaminopyridine, and the system was evacuated and backfilled with N$_2$ three times. Anhydrous CH$_3$CN (65 mL) was added via cannula transfer followed by the addition of 4.40 mL (31.8 mmol) of Et$_3$N. The system was cooled to 0 °C for the addition of 5.80 mL (25.4 mmol) of Boc$_2$O and stirred at ambient temperature overnight. The reaction was quenched with water, and the aqueous layer was extracted EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated. Flash chromatography on silica gel (1:1 MeOH/EtOAc) afforded 3.29 g (96%) of desired product 2.7f-2 as a yellow solid, m.p. 110–111 °C.
$^1$H NMR (400 MHz, CDCl$_3$): δ 7.21 (d, $J = 3.6$ Hz, 1 H), 6.60 (d, $J = 3.6$ Hz, 1 H), 3.56 (dd, $J = 6.5$, 3.9 Hz, 4 H), 3.47 (dd, $J = 6.5$, 3.8 Hz, 4 H), 1.48 (s, 9 H).

tert-butyl 4-(5-formylthiazol-2-yl)piperazine-1-carboxylate (2.7f-1): A flame dried 100 mL round bottom flask was charged with 3.18 g (11.8 mmol) of 2.7f-2, and the system was evacuated and backfilled with N$_2$ three times. Anhydrous THF (35 mL) was added via cannula transfer and the system was cooled to –78 °C for the addition of 9.02 mL (14.2 mmol) of freshly titrated n-BuLi. The reaction was stirred at –78 °C for 0.5 h followed by the dropwise addition of 1.80 mL (23.6 mmol) of anhydrous DMF. The system was stirred for an additional hour at –78 °C before being quenched with cold isopropanol and moved to 0 ºC ice bath for a H$_2$O quench. The aqueous layer was extracted EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated. Flash chromatography on silica gel by a gradient from 0–20–50–100% EtOAc in hexanes afforded 2.68 g (76%) of desired product 2.7f-1 as a tan solid, m.p. 135 ºC.

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.72 (s, 1 H), 7.87 (s, 1 H), 3.72–3.44 (m, 8 H), 1.49 (s, 9 H).

tert-butyl 4-(5-(2,2-difluorovinyl)thiazol-2-yl)piperazine-1-carboxylate (2.7f): Following General Procedure A1, 1.5 g (5.0 mmol) of 2.7f-1 was reacted with 3.0 g (8.5 mmol) of SI-2.1 in anhydrous DMF (20 mL) at 80 ºC for 2 h. After workup, the product
was purified by flash chromatography on silica gel, using a gradient from 0–20–100% EtOAc in hexanes, to furnish 1.2 g (74% yield) of desired product 2.7f as a tan solid, m.p. 112 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.20 (s, 1 H), 5.55 (dd, $J = 25.9$, 1.9 Hz, 1 H), 3.71 (dd, $J =$ 6.5, 3.9 Hz, 4 H), 3.62 (dd, $J =$ 6.5, 3.8 Hz, 4 H), 2.33 (s, 1 H), 1.64 (s, 9 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 171.6 (dd, $J = 5.1$, 2.8 Hz), 155.3 (dd, $J =$ 294.2, 288.0 Hz), 154.8, 138.3 (dd, $J =$ 8.0, 3.4 Hz), 116.1 (dd, $J =$ 8.1, 5.4 Hz), 80.6, 75.5 (dd, $J =$ 34.3, 18.7 Hz), 48.4, 43.1 (d, $J =$ 11.8 Hz), 28.6

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –83.42 (dd, $J =$ 34.9, 25.8 Hz, 1 F), –89.90 (d, $J =$ 34.4 Hz, 1 F)

IR (film): 3468, 2978, 2930, 2868, 2359, 2342, 1732, 1688, 1530, 1476, 1456, 1422, 1366, 1341, 1323, 1285, 1269, 1231, 1177, 1142, 1126, 1045, 1001, 974, 918, 851, 804, 775, 739, 667, 652 cm$^{-1}$

HRMS (ESI+): calc. for C$_{14}$H$_{20}$F$_2$N$_3$O$_2$S (M+H) 332.1244, found 332.1257, 1.3 mmu.

General Procedure for the Coupling Reaction of Arylthiols and Difluoroalkenes (B):
An oven-dried 1-dram vial was charged with difluoroalkene (0.50 mmol) and a magnetic stirbar. The substrate was dissolved in DCE (2.0 mL), and aryl-thiol (1.0–1.5 mmol) was added via a 250 µL micro syringe. Tetramethylguanidine (TMG) (3.1 µL, 0.025 mmol) was added via a 10 µL micro syringe. The vial was sealed with a screw top cap with a PTFE
septum and stirred for 3 min at ambient temperature. Subsequently, the vial was placed on a pre-heated reaction block, and stirred at 70–90 °C for 0.5–20 h. The vial was cooled to R.T., and 60 µL of \( \alpha,\alpha,\alpha \)-trifluorotoluene was added by microsyringe. The solution was stirred at ambient temperature for 10 min to ensure mixing, after which an aliquot was taken from the vial and analyzed by \(^{19}\)F NMR. The NMR sample was then returned to the vial, 2 mL of water was added, and the reaction mixture was extracted 3X with 5 mL DCM and 5 mL \( \text{H}_2\text{O} \). After extraction, the organic layer was dried with \( \text{MgSO}_4 \) or \( \text{Na}_2\text{SO}_4 \) and concentrated, and the crude mixture was purified by flash chromatography.

**General Procedure for the Coupling Reaction of Arylthiols and Difluoroalkenes (C):**

An oven-dried 10 mL microwave vial was charged with difluoroalkene (0.50 mmol) and a magnetic stirbar. The substrate was dissolved in DCE (2.0 mL), and aryl-thiol (1.0–1.5 mmol) was added via a 250 µL micro syringe. Tetramethylguanidine (TMG) (3.1 µL, 0.025 mmol) was added via a 10 µL micro syringe. The vial was sealed with a crimp-top cap with a PTFE septum and stirred for 3 min at ambient temperature. Subsequently, the vial was placed in a pre-heated oil bath, and stirred at 100 °C for 5–20 h. The vial was cooled to R.T., and 60 µL of \( \alpha,\alpha,\alpha \)-trifluorotoluene was added by microsyringe. The solution was stirred at ambient temperature for 10 min to ensure mixing, after which an aliquot was taken from the vial and analyzed by \(^{19}\)F NMR. The NMR sample was then returned to the vial, 2 mL of water was added, and the reaction mixture was extracted 3X with 5 mL DCM and 5 mL \( \text{H}_2\text{O} \). After extraction, the organic layer was dried with \( \text{MgSO}_4 \) or \( \text{Na}_2\text{SO}_4 \) and concentrated, and the crude mixture was purified by flash chromatography.
General Procedure for the Coupling Reaction of Alkylthiols and Difluoroalkenes (D): An oven-dried 1 dram vial was charged with difluoroalkene (0.50 mmol) and a magnetic stirbar. The compound was brought into the glovebox, and lithium triflate (0.05 mmol) was added, then pyridine (0.1 mmol) was added via 10 µL glass microsyringe, and the mixture was dissolved in o-xylene (1.5 mL). The 1 dram vial was sealed with a screw-top cap equipped with a PTFE-lined silicon septum, and removed from the glovebox. The reaction mixture was exposed to air, and alkyl-thiol (0.75 mmol) was added via a 1.0 mL PTFE syringe. The vial was sealed with the same screw-top cap lined with a PTFE-lined silicon septum, and a balloon of air was equipped through a 16.5 G needle. Subsequently, the vial was placed in a pre-heated reaction plate and stirred at 110 °C for 15 h. The vial was cooled to R.T., and 50 µL of α,α,α-trifluorotoluene was added by microsyringe. The solution was diluted with EtOAc, and stirred at ambient temperature for 10 min to ensure mixing, after which an aliquot was taken from the vial and analyzed by 19F NMR. The NMR sample was then returned to the vial, 2 mL of water was added, and the reaction mixture was extracted 3X with 5 mL EtOAc and 5 mL saturated NaHCO3 (aq). After extraction, the organic layer was dried with Na2SO4 and concentrated, and the crude mixture was purified by flash chromatography.

Preparation and Characterization of Compounds in Scheme 2-6:

Undesired Reactivity with Inorganic Bases
Reactions were performed following General Procedure C, with the following modifications:

- Reactions were run with 0.1 mmol of compound 2.1.
- The bases used were inorganic in nature. Representative bases include: NaH, K$_2$CO$_3$, KO$^-$Bu.
- All reactions were run at 80 °C for 4 h, standardized with 12 µL (0.10 mmol) of TFT, and analyzed by $^{19}$F NMR through relative integration to the TFT resonance.

Preparation and Characterization of Compounds Described in Table 2-1

Following a modified General Procedure C, 0.023 g (0.10 mmol) of compound 2.1 was added to an oven-dried 1 dram screw-top vial. In the case of solid bases (DMAP, TBD, preformed thiolate), the base (0.025 mmol) was added, and the mixture dissolved in solvent (0.4 mL). Subsequently, 0.020 mL (0.20 mmol) of thiophenol was added, followed
by the addition of 0.025 mmol of liquid bases (Et₃N, TMG). The solution was stirred for 3 min at R.T., and then stirred at 80 °C for 4 h (except where marked as different). After returning to R.T., the reaction was standardized with 12 µL (0.10 mmol) of TFT, diluted with DCM, and stirred for 10 min. The reaction was then added to an NMR tube and analyzed by ¹⁹F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 were determined by relative integration vs. the TFT resonance.

**Synthesis of Sodium Phenylthiolate:** An oven dried, 25 mL round bottomed flask equipped with a magnetic stirbar was transferred into the glovebox, and 95% sodium hydride (0.049 g, 2.0 mmol) was added. The flask was sealed with a rubber septum, transferred to a fume hood, and immersed in an ice bath under a nitrogen atmosphere. Anhydrous THF (10 mL) was added, and the suspension was stirred vigorously. Anhydrous thiophenol (0.20 mL, 2.0 mmol) was added dropwise at 0 °C, and the resulting suspension was stirred at R.T. After 5 h, the solvent was removed *in vacuo*, and the resulting white solid was used without further purification.
(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)(phenyl)sulfane (22): Following General Procedure B, 0.12 g (0.50 mmol) of compound 2.1 was reacted with 0.105 mL (1.00 mmol) of thiophenol at 70 °C for 1 h. After workup, the product was purified by flash chromatography using 0–10% Et₂O in PhMe, furnishing 0.14 g (83% yield) of desired product 2.2 as a colorless solid, m.p. 57–58 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, J = 7.4 Hz, 2 H), 7.44–7.35 (m, 3 H), 6.49 (s, 2 H), 3.86 (s, 9 H), 3.37 (t, J = 14.7 Hz, 2 H);

¹³C NMR (126 MHz, CDCl₃): δ 153.2, 137.7, 136.3, 129.9, 129.2, 128.8 (t, J = 279.8 Hz), 127.6 (t, J = 3.3 Hz), 127.0 (t, J = 2.5 Hz), 107.7, 61.0, 56.3, 45.6 (t, 24.4 Hz);

¹⁹F NMR (376 MHz, CDCl₃): δ −71.50 (t, J = 14.8, 2 F);

IR (film): 3065, 2939, 2839, 2361, 2341, 1591, 1508, 1462, 1423, 1346, 1315, 1246, 1225, 1151, 1128, 1036, 1014, 947, 924, 874, 831, 777, 750, 706, 692, 667, 436 cm⁻¹;

HRMS (HAPCI⁺): calc. for C₁₇H₁₉F₂O₃S (M+H) 341.1023, found 341.1007, 4.7 ppm.

(E)-(1-fluoro-2-(3,4,5-trimethoxyphenyl)vinyl)(phenyl)sulfane (2.4): To an oven-dried 1 dram vial equipped with a magnetic stirbar were added 0.12 g (0.50 mmol) of compound
2.1, 0.50 mL of nitrobenzene, 0.26 mL (2.5 mmol) of thiophenol, and 16 µL (0.125 mmol) of TMG. The resulting yellow solution was stirred for 3 min at R.T., and then stirred for 4 h at 100 °C. A 60 µL (0.50 mmol) aliquot of TFT was added as an internal standard to determine the amount of α–monofluorovinylthioether formed. Analysis of the crude reaction mixture by \(^{19}\)F NMR (376 MHz, no deuterated solvent) showed a ratio of 1.5:1 compounds 2.2:2.4. After workup, water was added, and the reaction mixture extracted 3X with 5 mL of DCM and 5 mL of H\(_2\)O. Chromatographic purification by a gradient elution from 0% EtOAc in hexanes to 50% EtOAc in hexanes (removal of PhNO\(_2\)) followed by a gradient elution from 0% Et\(_2\)O in PhMe to 5% Et\(_2\)O in PhMe afforded a 6.3:1 mixture of compound 2.4 (2.9:1 diastereoselectivity):compound 2.2.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ Major isomer 7.46–7.43 (m, 2 H), 7.37–7.28 (m, 3 H), 6.83 (s, 2 H), 6.71 (d, \(J = 16.5\) Hz, 1 H), 3.86 (s, 6 H), 3.83 (s, 3 H); Minor isomer 7.48–7.46 (m, 2 H), 7.37–7.28 (m, 3 H), 6.78 (s, 2 H), 6.23 (d, \(J = 31.9\) Hz, 1 H), 3.86 (s, 6 H), 3.83 (s, 3 H);

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): δ –80.15 (d, \(J = 16.5\) Hz, integration 2.85 - major diasteromer), –86.59 (d, \(J = 31.9\) Hz, integration 1 – minor diastereomer).

**Experimental Procedures for Mechanistic Determination**

*Experiments in the Absence of Oxygen:* Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 was added to a 1 dram vial and sealed with a screw-top cap containing a PTFE lined septum. The system was evacuated and backfilled
3X with N\textsubscript{2}, and subsequently dissolved in anhydrous DCE (0.4 mL, sparged with N\textsubscript{2} for 1 h prior to use). Anhydrous thiophenol (0.030 mL, 0.30 mmol) was added, and then TMG (0.6 \mu L, 0.005 mmol, sparged with N\textsubscript{2} for 1 h prior to use). The reaction was stirred for 3 min at R.T., and then for 1 h at 80 °C. Once returned to R.T., the reaction was standardized with 12 \mu L of TFT (0.10 mmol), diluted with DCM, and analyzed by \textsuperscript{19}F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 were determined by relative integration vs. the TFT resonance. Compound 2.1 conversion: >99%, compound 2.2 yield: 90%, compound 2.4 yield: 0%.

A second reaction was run following the above procedure, modified to exclude light by wrapping the 1 dram vial in aluminum foil before evacuation and backfill with N\textsubscript{2}. Compound 2.2 yield: 95%, conversion: >99%, compound 2.4 yield: 0%.

Experiments in the Absence of Light: Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 was added to a 1 dram vial. The compound was dissolved in DCE (0.4 mL), and the 1 dram vial was wrapped in aluminum foil to exclude light. Thiophenol (0.030 mL, 0.30 mmol) was added, and then TMG (0.6 \mu L, 0.005 mmol). The reaction was stirred for 3 min at R.T., and then for 1 h at 80 °C. Once returned to R.T., the reaction was standardized with 12 \mu L of TFT (0.10 mmol), diluted with DCM, and analyzed by \textsuperscript{19}F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 were determined by relative integration vs. the TFT resonance. Compound 2.1 conversion: >99%, compound 2.2 yield: 90%, compound 2.4 yield: 0%.
Experiments with Radical Scavengers

Using 1,4-dicyanobenzene: Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 and 0.026 g (0.20 mmol) of 1,4-dicyanobenzene were added to a 1 dram vial. The compound was dissolved in DCE (0.4 mL). Thiophenol (0.020 mL, 0.20 mmol) was added, and then TMG (0.6 µL, 0.005 mmol). The reaction was stirred for 3 min at R.T., and then for 1 h at 70 °C. Once returned to R.T., the reaction was standardized with 12 µL of TFT (0.10 mmol), diluted with DCM, and analyzed by $^{19}$F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 were determined by relative integration vs. the TFT resonance. Compound 2.1 conversion: >99%, compound 2.2 yield: 88%, compound 2.4 yield: 0%. The presence of non-fluorinated adducts was evaluated by GC-MS (EI+). GC-MS analysis showed 1,4-dinitrobenzene and compound 2.2 with no evidence of dithiane formation.

Using Butylated Hydroxytoluene (BHT): Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 and 0.044 g (0.20 mmol) of BHT were added to a 1 dram vial. The compound was dissolved in DCE (0.4 mL). Thiophenol (0.020 mL, 0.20 mmol) was added, and then TMG (0.6 µL, 0.005 mmol). The reaction was stirred for 3 min at R.T., and then for 1 h at 70 °C. Once returned to R.T., the reaction was standardized with 12 µL of TFT (0.10 mmol), diluted with DCM, and analyzed by $^{19}$F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 were determined by relative integration vs. the TFT resonance. Compound 2.1 conversion: 99%, compound 2.2 yield: 82%, compound 2.4 yield: 0%. The presence of non-fluorinated adducts was evaluated
by GC-MS (EI+). GC-MS analysis showed BHT and compound 2.2 with no evidence of dithiane formation.

**Using TEMPO:** Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 and 0.031 g (0.20 mmol) of TEMPO were added to a 1 dram vial. The compound was dissolved in DCE (0.4 mL). Thiophenol (0.020 mL, 0.20 mmol) was added, and then TMG (0.6 µL, 0.005 mmol). The reaction was stirred for 3 min at R.T., and then for 1 h at 70 °C. Once returned to R.T., the reaction was standardized with 12 µL of TFT (0.10 mmol), diluted with DCM, and analyzed by $^{19}$F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 were determined by relative integration vs. the TFT resonance. Compound 2.1 conversion: 0%, compound 2.2 yield: 0%, compound 2.4 yield: 0%. The presence of non-fluorinated adducts was evaluated by GC-MS (EI+). GC-MS analysis showed TEMPO, TEMPO-H, compound 2.1 and dithiane.

**Control Reactions with TEMPO:** Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 and 0.031 g (0.20 mmol) of TEMPO were added to a 1 dram vial. The compound was dissolved in DCE (0.4 mL). TMG (0.6 µL, 0.005 mmol) was added to the solution. The reaction was stirred for 3 min at R.T., and then for 1 h at 70 °C. Once returned to R.T., the reaction was standardized with 12 µL of TFT (0.10 mmol), diluted with DCM, and analyzed by $^{19}$F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 were determined by relative integration vs. the TFT resonance. Compound 2.1 conversion: 0%, compound 2.2 yield: 0%, compound 2.4 yield: 0%. The presence of
non-fluorinated adducts was evaluated by GC-MS (EI+). GC-MS analysis showed TEMPO and compound 2.1.

Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 and 0.031 g (0.20 mmol) of TEMPO were added to a 1 dram vial. The compound was dissolved in DCE (0.4 mL). The reaction was stirred for 3 min at R.T., and then for 1 h at 70 °C. Once returned to R.T., the reaction was standardized with 12 µL of TFT (0.10 mmol), diluted with DCM, and analyzed by \(^{19}\)F NMR. The conversion of 2.1, the yield of 2.2, and the yield of 2.4 was determined by relative integration vs. the TFT resonance. Compound 2.1 conversion: 0%, compound 2.2 yield: 0%, compound 2.4 yield: 0%. The presence of non-fluorinated adducts was evaluated by GC-MS (EI+). GC-MS analysis showed TEMPO and compound 2.1.

Following a modified General Procedure C 0.031 g (0.20 mmol) of TEMPO was added to a 1 dram vial and dissolved in DCE (0.4 mL). Thiophenol (0.020 mL, 0.20 mmol) and then TMG (0.6 µL, 0.005 mmol) was added to the solution. The reaction was stirred for 3 min at R.T., and then for 1 h at 70 °C. Once returned to R.T., the reaction was diluted with DCM, and analyzed by GC-MS (EI+). GC-MS analysis showed TEMPO, TEMPO-H, and dithiane.
Following a modified General Procedure C 0.031 g (0.20 mmol) of TEMPO was added to a 1 dram vial and dissolved in DCE (0.4 mL). Thiophenol (0.020 mL, 0.20 mmol) was added to the solution. The reaction was stirred for 3 min at R.T., and then for 1 h at 70 °C. Once returned to R.T., the reaction was diluted with DCM, and analyzed by GC-MS (EI+). GC-MS analysis showed TEMPO, TEMPO-H, and dithiane.

Experiment with DCM-D₂: Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound 2.1 was added to a 1 dram vial and dissolved in DCM-D₂ (0.4 mL). Thiophenol (0.020 mL, 0.20 mmol) was added, and then TMG (0.6 µL, 0.005 mmol). The reaction was stirred for 3 min at R.T., and then for 4 h at 40 °C. Once returned to R.T., the reaction was standardized with 12 µL of TFT (0.10 mmol), diluted with DCM, and analyzed by ¹⁹F NMR. Conversion, yield of 2.2, and yield of 2.4 was determined by relative integration vs. the TFT resonance. The presence or absence of deuterium was evaluated by GC-MS and by analysis the ²D NMR spectrum. Compound 2.2 yield: 86%, conversion: >99%. No evidence of compound 2.4. Analysis of the ²D NMR revealed no deuterated resonances (other than DCM-D₂). GC-MS analysis showed no deuterated product. The chromatogram and spectrum were identical to an analogous reaction run in DCM.
(1,1-difluoro-2-(4-methoxyphenyl)ethyl)(phenyl)sulfane (2.6a): Following General Procedure B, 0.085 g (0.50 mmol) of compound 2.5a was reacted with 0.105 mL (1.00 mmol) of thiophenol at 70 °C for 0.5 h. After workup, the product was purified by flash chromatography using 0–10% EtOAc in hexanes, furnishing 0.104 g (74% yield) of desired product 2.6a as a pale oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.58 (d, $J = 7.3$ Hz, 2 H), 7.43–7.34 (m, 3 H), 7.22 (d, $J = 8.4$ Hz, 2 H), 6.88 (d, $J = 8.3$ Hz, 2 H), 3.81 (s, 3 H), 3.37 (t, $J = 14.3$ Hz, 2 H);

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 159.3, 136.3, 131.7, 129.8, 129.1, 129.0 (t, $J = 279.8$ Hz), 127.1 (t, $J = 2.1$ Hz), 124.1 (t, $J = 3.5$ Hz), 114.0, 55.4, 44.5 (t, $J = 24.3$ Hz);

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ −71.85 (t, $J = 14.8$ Hz, 2 F);

IR (film): 3433, 3063, 2934, 2837, 1612, 1514, 1474, 1441, 1304, 1254, 1221, 1180, 1153, 1113, 1032, 1007, 976, 872, 822, 781, 748, 690, 646, 606, 422 cm$^{-1}$;

HRMS (HAPCI$^+$): calc. for C$_{15}$H$_{14}$F$_2$OS (M$^+$) 280.0733, found 280.0725, 2.9 ppm.
(1,1-difluoro-2-(4-(methylthio)phenyl)ethyl)(phenyl)sulfane (2.6b): Following General Procedure B, 0.093 g (0.50 mmol) of compound 2.5b was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90°C for 5 h. After workup, the product was purified by flash chromatography using 0–5–10% EtOAc in hexanes, to furnish 0.099 g (66% yield) of desired product 2.6b in 97% purity (as determined by 1H and 19F NMR) as a pale oil.

1H NMR (400 MHz, CDCl3): δ 7.57 (d, J = 7.6 Hz, 2 H), 7.43–7.34 (m, 3 H), 7.24–7.19 (m, 4 H), 3.38 (t, J = 14.7 Hz, 2 H), 2.49 (s, 3 H)

13C NMR (126 MHz, CDCl3): δ 138.2, 136.3, 131.1, 129.9, 129.1, 128.75 (t, J = 279.7 Hz), 128.74 (t, J = 3.5 Hz), 127.0 (t, J = 2.1 Hz), 126.5, 44.7 (t, J = 24.4 Hz), 15.8

19F NMR (376 MHz, CDCl3): δ −71.76 (t, J = 14.7 Hz, 2 F)

IR (film): 3059, 3024, 2920, 1601, 1584, 1495, 1476, 1441, 1408, 1325, 1279, 1219, 1155, 1094, 1036, 1009, 976, 874, 843, 808, 768, 750, 704, 691, 638, 596, 575, 505 cm⁻¹

HRMS (HAPCI⁺): calc for C₁₅H₁₄F₂S₂ (M⁺) 296.0505, found 296.0508, 1.0 ppm.
(2-(5-bromo-2-((4-methoxybenzyl)oxy)phenyl)-1,1-difluoroethyl)(phenyl)sulfane

(2.6c): Following General Procedure B, 0.18 g (0.50 mmol) of compound 2.5c was reacted with 0.105 mL (1.00 mmol) of thiophenol at 70°C for 0.5 h. After workup, the product was purified by flash chromatography using 0–10% EtOAc in hexanes, to furnish 0.204 g (88% yield) of desired product 2.6c as a yellow oil.

1H NMR (400 MHz, CDCl3): δ 7.58 (d, J = 7.5 Hz, 2 H), 7.42–7.32 (m, 7 H), 6.93 (d, J = 8.3 Hz, 2 H), 6.83 (d, J = 8.7 Hz, 1 H), 5.00 (s, 2 H), 3.83 (s, 3 H), 3.51 (t, J = 14.9 Hz, 2 H)

13C NMR (126 MHz, CDCl3): δ 159.4, 156.3, 136.2, 134.8, 131.7, 129.7, 129.0, 128.7 (t, J = 280.4 Hz), 128.5, 127.0 (t, J = 2.0 Hz), 123.3 (t, J = 2.8 Hz), 114.0, 113.8, 112.7, 70.3, 55.3, 38.0 (t, J = 24.8 Hz)

19F NMR (376 MHz, CDCl3): δ –71.10 (t, J = 14.9 Hz, 2 F)

IR (film): 2934, 2835, 1612, 1585, 1514, 1489, 1464, 1302, 1281, 1246, 1175, 1153, 1130, 1032, 1009, 982, 862, 810, 750, 690, 642 cm⁻¹

LRMS (EI+): calc. for C22H19BrF2O2S (M+) 464.03, found 464.0.
**4-(3-(2,2-difluoro-2-(phenylthio)ethyl)phenyl)morpholine (2.6d):** Following General Procedure B, 0.11 g (0.50 mmol) of compound 2.5d was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90 °C for 5 h. After workup, the product was purified by flash chromatography using 0–5–10–20% EtOAc in hexanes, to furnish 0.13 g (77% yield) of desired product 2.6d as a tan solid, m.p. 42–44 °C.

**1H NMR (400 MHz, CDCl₃):** δ 7.58 (d, J = 6.9 Hz, 2 H), 7.43–7.34 (m, 3 H), 7.25 (t, J = 7.7 Hz, 1 H), 6.88 (d, J = 8.3 Hz, 1 H), 6.83 (d, J = 8.2 Hz, 2 H), 3.87 (t, J = 4.8 Hz, 4 H), 3.39 (t, J = 14.8 Hz, 2 H), 3.17 (t, J = 4.9 Hz, 4 H)

**13C NMR (126 MHz, CDCl₃):** δ 151.4, 136.3, 133.1 (t, J = 3.2 Hz), 129.8, 129.3, 129.1, 128.8 (t, J = 280.1 Hz), 127.1 (t, J = 2.0 Hz), 122.3, 118.0, 115.1, 67.0, 49.4, 45.6 (t, J = 24.1 Hz)

**19F NMR (376 MHz, CDCl₃):** δ –71.35 (t, J = 14.8 Hz, 2 F)

**IR (film):** 3059, 2963, 2855, 2824, 2359, 2342, 1603, 1584, 1495, 1476, 1449, 1379, 1337, 1304, 1265, 1244, 1227, 1155, 1123, 1036, 1017, 986, 887, 764, 750, 693, 667, 571, 550, 498 cm⁻¹

**HRMS (ESI+):** calc for C₁₈H₂₀F₂NOS (M+H) 336.1234, found 336.1251, 1.7 mmu.
4-(2,2-difluoro-2-(phenylthio)ethyl)-N,N-dimethylaniline (2.6e): Following General Procedure B, 0.092 g (0.50 mmol) of compound 2.5e was reacted with 0.105 mL (1.00 mmol) of thiophenol at 70˚C for 14 h. After workup, the product was purified by flash chromatography using 0–10–20% EtOAc in hexanes, to furnish 0.12 g (81% yield) of desired product 2.6e as an off-white solid, m.p. 57 ºC.

\[ \text{IR (film): } 2903, 2806, 2361, 2341, 1616, 1524, 1354, 1234, 1151, 1034, 1007, 974, 810, 748, 690, 667 \text{ cm}^{-1} \]

\[ \text{HRMS (ESI+): } \text{calc. for } C_{16}H_{18}F_{2}NS (M+H) 294.1128, \text{ found } 294.1123, 1.7 \text{ ppm.} \]
4-(2,2-difluoro-2-(phenylthio)ethyl)phenyl trifluoromethanesulfonate (2.6f):
Following General Procedure C, 0.145 g (0.500 mmol) of compound 2.5f was reacted with 0.16 mL (1.5 mmol) of thiophenol. After workup, the product was purified by flash chromatography using 0–10% EtOAc in hexanes, to furnish 0.152 g (76% yield) of desired compound 2.6f as a clear oil in 97% purity (as determined by $^1$H and $^{19}$F NMR).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.59–7.56 (m, 2 H), 7.45–7.35 (m, 5 H), 7.27–7.23 (m, 2 H), 3.45 (t, $J$ = 14.6 Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.3, 136.3, 132.8 (t, $J$ = 3.1 Hz), 132.5, 130.1, 129.3, 128.2 (t, $J$ = 279.9 Hz), 126.6 (t, $J$ = 2.2 Hz), 121.5, 118.9 (q, $J$ = 320.8 Hz), 44.5 (t, $J$ = 24.8 Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –72.12 (t, $J$ = 14.6 Hz, 2 F), –72.84 (s, 3 F)

IR (film): 3065, 2359, 2342, 1599, 1505, 1476, 1425, 1331, 1250, 1215, 1182, 1140, 1109, 1036, 1018, 982, 943, 889, 854, 835, 750, 727, 691, 638, 608, 519, 498 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{15}$H$_{11}$F$_5$O$_3$S$_2$ (M$^+$) 398.0070, found 398.0060, 2.5 ppm.
(2-(4’-(tert-butyl)-1,1’-biphenyl)-2-yl)-1, 1-difluoroethyl)(phenyl)sulfane (2.6g):
Following General Procedure B, 0.14 g (0.50 mmol) of compound 2.5g was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90 °C for 5 h. After workup, the product was purified by flash chromatography using 0–2.5–5–10–20% EtOAc in hexanes, to furnish 0.18 g (93% yield) of desired product 2.6g as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.51 (d, $J$ = 7.8 Hz, 2 H), 7.40 (d, $J$ = 8.3 Hz, 2 H), 7.37 (d, $J$ = 7.4 Hz, 1 H), 7.36–7.33 (m, 1 H), 7.32 (d, $J$ = 8.3 Hz, 2 H), 7.29 (d, $J$ = 13.3 Hz, 1 H), 7.21 (d, $J$ = 7.9 Hz, 2 H), 3.51 (t, $J$ = 15.4 Hz, 2 H), 1.38 (d, $J$ = 0.7 Hz, 9 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 149.9, 143.6, 138.2, 136.2, 131.1 (t, $J$ = 1.9 Hz), 130.8, 129.7, 129.10 (t, $J$ = 280.4 Hz), 129.06, 127.6, 127.3, 127.2 (t, $J$ = 2.3 Hz), 125.2, 41.5 (t, $J$ = 23.8 Hz), 34.7, 31.6

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –70.08 (t, $J$ = 15.36 Hz, 2 F)

IR (film): 3061, 3026, 2962, 2905, 2868, 2361, 2330, 1485, 1441, 1398, 1364, 1329, 1269, 1223, 1155, 1107, 1024, 1007, 978, 839, 766, 750, 690, 545 cm$^{-1}$

HRMS (HAPCI+): calc. for C$_{24}$H$_{24}$F$_2$S (M+) 382.1567, found 382.1563, 1.0 ppm.
(2-(4-(benzyloxy)-3-methoxyphenyl)-1,1-difluoroethyl)(phenyl)sulfane (2.6h):

Following General Procedure B, 0.14 g (0.50 mmol) of compound 2.5h was reacted with 0.105 mL (1.00 mmol) of thiophenol at 80 °C for 0.5 h. After workup, the product was purified by flash chromatography using 0–2.5–5–10–20% EtOAc in hexanes, to furnish 0.17 g (87% yield) of desired product 2.6h as a colorless solid, m.p. 52–53 °C.

$^1$H NMR (400 MHz, CDCl$_3$): \( \delta \) 7.59–7.57 (m, 2 H), 7.45–7.44 (m, 2 H), 7.42–7.40 (m, 1 H), 7.39–7.35 (m, 4 H), 7.32–7.29 (m, 1 H), 6.85 (d, \( J = 8.2 \) Hz, 1 H), 6.83 (d, \( J = 2.0 \) Hz, 1 H), 6.77 (dd, \( J = 8.3, 2.0 \) Hz, 1 H), 5.16 (s, 2 H), 3.89 (s, 3 H), 3.36 (t, \( J = 14.6 \) Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): \( \delta \) 149.5, 148.0, 137.2, 136.3, 129.8, 129.1, 129.0 (t, \( J = 279.9 \) Hz), 128.7, 128.0, 127.4, 127.1 (t, \( J = 2.0 \) Hz), 125.0 (t, \( J = 3.4 \) Hz), 123.0, 114.2, 113.7, 71.1, 56.1, 44.9 (t, \( J = 24.3 \) Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): \( \delta \) –71.63 (t, \( J = 14.7 \) Hz, 2 F)

IR (film): 3060, 2933, 1591, 1514, 1454, 1265, 1223, 1144, 1036, 1014, 984, 746, 694, 660 cm$^{-1}$

HRMS (HAPCl+): calc. for C$_{22}$H$_{20}$F$_2$O$_2$S (M+) 386.1152, found 386.1153, 0.3 ppm.
(1,1-difluoro-2-(2-iodophenyl)ethyl)(phenyl)sulfane (2.6i): Following General Procedure B, 0.13 g (0.50 mmol) of compound 2.5i was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90°C for 5 h. After workup, the product was purified by flash chromatography using 0–5% EtOAc in hexanes, to furnish 0.14 g (74% yield) of compound 2.6i in 99% purity (as determined by $^1$H and $^{19}$F NMR) as a colorless solid, m.p. 34 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.87 (dd, $J = 7.9$, 1.3 Hz, 1 H), 7.63–7.61 (m, 2 H), 7.45–7.35 (m, 4 H), 7.33 (td, $J = 7.5$, 1.3 Hz, 1 H), 6.99 (td, $J = 7.7$, 1.8 Hz, 1 H), 3.69 (t, $J = 15.0$ Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 140.0, 136.5, 135.7 (t, $J = 2.3$ Hz), 131.6 (d, $J = 1.6$ Hz), 130.0, 129.5, 129.2, 128.7 (t, $J = 280.9$ Hz), 128.4, 126.9 (t, $J = 2.2$ Hz), 102.3, 49.1 (t, $J = 24.1$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): δ −71.31 (t, $J = 15.0$ Hz, 2 F)

IR (film): 3059, 2359, 2340, 1474, 1439, 1329, 1296, 1219, 1153, 1119, 1032, 1018, 978, 885, 868, 745, 719, 691 cm$^{-1}$

HRMS (HAPCI⁺): calc. for C$_{14}$H$_{11}$F$_2$S (M–I) 249.0550, found 249.0547, 1.2 ppm.
ethyl (E)-3-(3,2-difluoro-2-(phenylthio)ethyl)phenyl)acrylate (2.6j): Following General Procedure B, 0.12 g (0.50 mmol) of compound 2.5j was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90 °C for 5 h. After workup, the product was purified by flash chromatography using 0–2.5–5–10–20% EtOAc in hexanes, to furnish 0.14 g (79% yield) of desired product 2.6j as a colorless solid, m.p. 58 °C.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.68 (d, $J = 16.0$ Hz, 1 H), 7.60–7.55 (m, 2 H), 7.49 (dd, $J = 7.8, 1.5$ Hz, 1 H), 7.46–7.39 (m, 2 H), 7.40–7.35 (m, 3 H), 7.33–7.29 (m, 1 H), 6.45 (d, $J = 16.0$ Hz, 1 H), 4.27 (q, $J = 7.2$ Hz, 2 H), 3.44 (t, $J = 14.7$ Hz, 2 H), 1.34 (t, $J = 7.1$ Hz, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 167.0, 144.3, 136.3, 134.8, 132.9 (t, $J = 3.2$ Hz), 132.5, 130.3, 130.0, 129.2, 129.1, 128.6 (t, $J = 279.9$ Hz), 127.5, 126.8 (t, $J = 2.2$ Hz), 60.7, 45.1 (t, $J = 24.5$ Hz), 14.5

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –71.71 (t, $J = 14.7$ Hz, 2 F)

IR (film): 3063, 2982, 2935, 1713, 1639, 1475, 1441, 1367, 1312, 1265, 1231, 1180, 1161, 1094, 1036, 984, 943, 866, 750, 690 cm$^{-1}$

HRMS (HAPCI+): calc. for C$_{19}$H$_{19}$F$_2$O$_2$S (M+H) 349.1074, found 349.1064, 2.9 ppm.
(2-(3,5-dichlorophenyl)-1,1-difluoroethyl)(phenyl)sulfane (2.6k): Following General Procedure C, 0.11 g (0.50 mmol) of compound 2.5k was reacted with 0.16 mL (1.5 mmol) of thiophenol at 100 °C for 20 h. After extraction from a mixture of 1 N NaOH and saturated aq. Na$_2$S$_2$O$_5$ (a mixture designed to remove residual thiophenol and small amounts of diphenyl sulfide that are difficult to remove by flash chromatography) with DCM, the product was purified by flash chromatography using 0–5% EtOAc in hexanes, to furnish 0.11 g (68% yield) of desired product 2.6k as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.60–7.57 (m, 2 H), 7.46–7.37 (m, 3 H), 7.33 (t, $J = 1.9$ Hz, 1 H), 7.18 (d, $J = 1.9$ Hz, 2 H), 3.36 (t, $J = 14.5$ Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 136.3, 135.2 (t, $J = 3.0$ Hz), 135.0, 130.2, 129.3, 129.1, 128.2, 128.0 (t, $J = 280.0$ Hz), 126.5 (t, $J = 2.2$ Hz), 44.5 (t, $J = 25.0$ Hz)

$^{19}$F NMR (356 MHz, CDCl$_3$): $\delta$ –71.91 (t, $J = 14.5$ Hz, 2 F)

IR (film): 3075, 3063, 2359, 2332, 1589, 1570, 1476, 1435, 1387, 1327, 1260, 1213, 1153, 1121, 1103, 1038, 1017, 984, 901, 880, 858, 799, 779, 741, 691, 667, 575 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{14}$H$_{10}$Cl$_2$F$_2$S (M$^+$) 317.9848, found 317.9841, 2.2 ppm.
4-(2,2-difluoro-2-(phenylthio)ethyl)-N,N-dipropylbenzamide (2.6l): Following General Procedure B, 0.13 g (0.50 mmol) of compound 2.5l was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90 °C for 5 h. After workup, the product was purified by flash chromatography using 0–10–20–30% EtOAc in hexanes, to furnish 0.17g (88% yield) of desired product 2.6l in 95% purity (as determined by $^1$H and $^{19}$F NMR) as a pale yellow solid, m.p. 25 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.57 (d, $J = 7.7$ Hz, 2 H), 7.42–7.29 (m, 7 H), 3.44 (bs, 2 H), 3.43 (t, $J = 14.8$ Hz, 2 H), 3.16 (bs, 2 H), 1.68 (bs, 2 H), 1.53 (bs, 2 H), 0.97 (bs, 3 H), 0.75 (bs, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 171.6, 136.9 (d, $J = 2.9$ Hz), 136.3, 133.1 (t, $J = 3.1$ Hz), 130.7, 129.9, 129.2, 128.6 (t, $J = 280.0$ Hz), 126.9, 126.8, 50.8, 46.5, 45.0 (t, $J = 24.5$ Hz), 22.1, 20.8, 11.6, 11.2

$^{19}$F NMR (376 MHz, CDCl$_3$): δ −71.79 (t, $J = 14.8$ Hz, 2 F)

IR (film): 3061, 2965, 2934, 2874, 1634, 1514, 1464, 1427, 1381, 1306, 1258, 1221, 1155, 1099, 1036, 1011, 980, 893, 876, 853, 750, 704, 692, 640, 557 cm$^{-1}$

HRMS (ESI+): calc. for C$_{21}$H$_{25}$F$_2$NOSNa (M+Na) 400.1523, found 400.1519, 1.0 ppm.
4-(2,2-difluoro-2-(phenylthio)ethyl)benzonitrile (2.6m): Following General Procedure C, 0.082 g (0.50 mmol) of compound 2.5m was reacted with 0.155 mL (1.5 mmol) of thiophenol at 100 °C for 20 h. After workup, the product was purified by flash chromatography using 0–5–20% EtOAc in hexanes, to furnish 0.080 g (58% yield) of desired compound 2.6m as a colorless solid, m.p. 63–64 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.64 (d, J = 8.0 \text{ Hz}, 2 \text{ H}), 7.56 (d, J = 7.5 \text{ Hz}, 2 \text{ H}), 7.46–7.36 (m, 5 \text{ H}), 3.47 (t, J = 14.5 \text{ Hz}, 2 \text{ H})\)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta 137.5 (t, J = 3.1 \text{ Hz}), 136.3, 132.3, 131.5, 130.2, 129.3, 128.1 (t, J = 280.2 \text{ Hz}), 126.4 (t, J = 2.2 \text{ Hz}), 118.7, 112.0, 45.2 (t, J = 24.8 \text{ Hz})\)

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta -71.85 (t, J = 14.5 \text{ Hz}, 2 \text{ F})\)

IR (film): 2359, 2342, 2228, 1611, 1505, 1474, 1441, 1429, 1416, 1321, 1211, 1144, 1013, 988, 959, 891, 853, 824, 775, 752, 708, 691, 577, 548, 498 cm\(^{-1}\)

HRMS (HAPCI\(+\)): calc. for C\(_{15}\)H\(_{12}\)F\(_2\)NS (M+H) 276.0659, found 276.0654, 1.8 ppm.
(1,1-difluoro-2-(3-nitrophenyl)ethyl)(phenyl)sulfane (2.6n): Following General Procedure C, 0.093 g (0.50 mmol) of compound 2.5n was reacted with 0.16 mL (1.5 mmol) of thiophenol at 100 °C for 20 h. After workup, the product was purified by flash chromatography using 0–5–10–20% EtOAc in hexanes, to furnish 0.081 g (55% yield) of desired product 2.6m as a colorless solid, m.p. 49–50 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20 (ddd, $J = 8.2, 2.3, 1.1$ Hz, 1 H), 8.16 (t, $J = 1.9$ Hz, 1 H), 7.63 (d, $J = 7.7$ Hz, 1 H), 7.59–7.57 (m, 2 H), 7.53 (t, $J = 7.9$ Hz, 1 H), 7.46–7.37 (m, 3 H), 3.52 (t, $J = 14.5$ Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 148.4, 136.8, 136.3, 134.1 (t, $J = 3.1$ Hz), 130.2, 129.6, 129.4, 128.1 (t, $J = 280.0$ Hz), 126.4 (t, $J = 2.3$ Hz), 125.6, 123.1, 44.7 (t, $J = 25.1$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –72.17 (t, $J = 14.5$ Hz, 2 F)

IR (film): 3077, 2359, 2342, 1531, 1476, 1441, 1435, 1350, 1319, 1298, 1223, 1153, 1084, 1034, 1015, 984, 916, 870, 820, 804, 750, 727, 692, 679, 652, 569, 422 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{14}$H$_{11}$F$_2$NO$_2$S (M$^+$) 295.0479, found 295.0473, 2.0 ppm.
Experimental Procedures and Characterization of Compounds in Scheme 2-9

3-(2,2-difluoro-2-(phenylthio)ethyl)-1-tosyl-1H-indole (2.8a): Following General Procedure B, 0.17 g (0.50 mmol) of compound 2.7a was reacted with 0.11 mL (1.0 mmol) of thiophenol at 70 °C for 0.5 h. After workup, the product was purified by flash chromatography using 0–10% EtOAc in hexanes, to furnish 0.16 g (72% yield) of desired product 2.8a in 98% purity (as determined by $^1$H and $^{19}$F NMR) as a translucent crystalline solid, m.p. 121–124 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.98 (d, $J = 8.3$ Hz, 1 H), 7.76 (d, $J = 8.0$ Hz, 2 H), 7.58 (s, 1 H), 7.54 (d, $J = 7.5$ Hz, 2 H), 7.48 (d, $J = 7.8$ Hz, 1 H), 7.41 (q, $J = 7.1$ Hz, 1 H), 7.34 (dt, $J = 14.7$, 7.6 Hz, 3 H), 7.25 (s, 1 H), 7.21 (d, $J = 8.0$ Hz, 2 H), 3.50 (t, $J = 14.3$ Hz, 2 H), 2.32 (s, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 207.2, 145.1, 136.3, 135.2, 135.1, 130.8, 130.02, 129.99, 129.2, 128.8 (t, $J = 280.0$ Hz), 127.0, 126.8 (t, $J = 1.8$ Hz), 125.0, 123.5, 119.8 (d, $J = 1.8$ Hz), 113.8, 113.5 (J = 3.7 Hz), 35.1 (t, $J = 26.4$ Hz), 30.1

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –70.94 (t, $J = 14.4$ Hz, 2 F)

IR (film): 3109, 3061, 2924, 2359, 2341, 1597, 1474, 1447, 1367, 1281, 1229, 1217,
1175, 1134, 1121, 1099, 1084, 1038, 1018, 991, 962, 878, 812, 785, 744, 704, 690, 669, 602, 571, 536, 494 cm⁻¹

HRMS (ESI⁺): calc. for C₂₃H₂₀F₂NO₂S₂Na (M+Na) 466.0723, found 466.0722, 0.6 ppm.

2-(3-(2,2-difluoro-2-(phenylthio)ethyl)phenyl)-5-(1,3-dioxolan-2-yl)pyridine (2.8b):
Following General Procedure C, 0.14 g (0.50 mmol) of compound 2.7b was reacted with 0.16 mL (1.5 mmol) of thiophenol at 100 °C for 20 h. After workup, the product was purified by flash chromatography on silica gel using a gradient from 0–10–30% EtOAc in hexanes, to furnish 0.15 g (73% yield) of desired product 2.8b in 97% purity (as determined by ¹H and ¹⁹F NMR) as a pale solid, m.p. 77–80 °C.

¹H NMR (400 MHz, CDCl₃): δ 8.78 (d, J = 1.7 Hz, 1 H), 7.95–7.93 (m, 2 H), 7.86 (dd, J = 8.2, 2.2 Hz, 1 H), 7.75 (dd, J = 8.2, 0.9 Hz, 1 H), 7.60–7.58 (m, 2 H), 7.46 (dd, J = 8.4, 7.6 Hz, 1 H), 7.43–7.34 (4 H), 5.91 (s, 1 H), 4.18–4.06 (m, 4 H), 3.52 (t, J = 14.8 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 158.0, 148.4, 139.4, 136.3, 135.2, 132.7 (t, J = 3.2 Hz), 132.1, 131.4, 129.9, 129.4, 129.2, 129.0, 128.8 (t, J = 280.0 Hz), 127.0 (t, J = 2.2 Hz), 126.6, 120.4, 102.1, 65.6, 45.3 (t, J = 24.4 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ –71.60 (t, J = 14.8 Hz, 2 F)
IR (film): 3059, 2989, 2888, 1722, 1601, 1568, 1474, 1441, 1414, 1356, 1223, 1155, 1088, 1057, 1024, 980, 941, 862, 839, 800, 750, 692, 658, 658, 573 cm⁻¹

HRMS (ESI⁺): calc. for C₂₂H₂₀F₂N₂O₂S (M+H) 400.1183, found 400.1175, 2.0 ppm.

4-(2,2-difluoro-2-(phenylthio)ethyl)-1-phenyl-1H-pyrazole (2.8c): Following General Procedure B, 0.10 g (0.50 mmol) of compound 2.7c was reacted with 0.11 mL (1.0 mmol) of thiophenol at 70 °C for 0.5 h. After workup, the product was purified by flash chromatography using 0–10% EtOAc in hexanes, to furnish 0.14 g (85% yield) of desired product 2.8c in 98% purity (as determined by ¹H and ¹⁹F NMR) as a colorless solid, m.p. 65 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.88 (s, 1 H), 7.69 (d, J = 8.0 Hz, 2 H), 7.65 (s, 1 H), 7.60 (d, J = 7.4 Hz, 2 H), 7.45 (dd, J = 8.3, 7.8 Hz, 3 H), 7.39 (dd, J = 7.2, 6.7 Hz, 2 H), 7.29 (t, J = 7.5 Hz, 1 H), 3.38 (t, J = 14.5 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 142.1, 140.1, 136.3, 130.0, 129.6, 129.2, 128.7 (t, J = 279.1 Hz), 127.1, 126.9 (t, J = 2.2 Hz), 126.7, 119.2, 113.7 (t, J = 3.8 Hz), 34.8 (t, J = 26.4 Hz)
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –72.51 (t, $J = 14.6$ Hz, 2 F)

IR (film): 3055, 2924, 2359, 2341, 1599, 1574, 1504, 1474, 1441, 1400, 1329, 1238, 1211, 1157, 1040, 1018, 1007, 972, 955, 906, 860, 752, 690, 667, 577, 501, 474 cm$^{-1}$

HRMS (ESI+): calc. for C$_{17}$H$_{15}$F$_2$N$_2$S (M+H) 317.0924, found 317.0911, 4.1 ppm.

4-(2,2-difluoro-2-(phenylthio)ethyl)dibenzo[b,d]thiophene (2.8d): Following General Procedure B, 0.12 g (0.50 mmol) of compound 2.7d was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90 °C for 5 h. After workup, the product was purified by flash chromatography on silica gel using a gradient from 0–5–10% EtOAc in hexanes, to furnish 0.16 g (88% yield) of desired product 2.8d in 97% purity (as determined by $^1$H and $^{19}$F NMR) as a yellow-green solid, m.p. 84–87 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.15 (ddd, $J = 8.6, 6.5, 2.8$ Hz, 2 H), 7.88–7.86 (m, 1 H), 7.60 (d, $J = 7.0$ Hz, 2 H), 7.49–7.46 (m, 4 H), 7.39 (ddd, $J = 14.7, 8.2, 6.7$ Hz, 3 H), 3.74 (t, $J = 14.7$ Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 141.2, 139.1, 136.4, 136.2, 136.0, 130.0, 129.21, 129.18, 129.0 (t, $J = 280.9$ Hz), 127.0, 126.84 (m), 126.82 (t, $J = 3.0$ Hz), 124.9, 124.7, 122.9, 121.9, 121.3, 44.4 (t, $J = 25.1$ Hz)
\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta -70.29\) (t, \(J = 14.7\) Hz, 2 F)

**IR (film):** 3061, 2359, 1586, 1474, 1443, 1402, 1333, 1317, 1260, 1219, 1155, 1096, 1055, 1022, 980, 905, 870, 748, 723, 704, 691, 652, 586, 498 cm\(^{-1}\)

**HRMS (HAPCl\(^+\)):** calc. for C\(_{20}\)H\(_{14}\)F\(_2\)S\(_2\) (M\(^+\)) 356.0505, found 356.0516, 3.1 ppm.

![Structural formula of 2.8e](image)

**10-benzyl-3-(2,2-difluoro-2-(phenylthio)ethyl)-10\(H\)-phenothiazine (2.8e):** Following General Procedure B, 0.18 g (0.50 mmol) of compound 2.7e was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90 °C for 5 h. After workup, the product was purified by flash chromatography using 0–5–10–20% EtOAc in hexanes, to furnish 0.19 g (83% yield) of desired product 2.8e as a yellow semisolid.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.61–7.55\) (m, 2 H), 7.34 (dtd, \(J = 24.1, 12.3, 11.9, 6.0\) Hz, 9 H), 7.08 (dd, \(J = 7.6, 1.5\) Hz, 1 H), 7.01–6.93 (m, 2 H), 6.89–6.83 (m, 2 H), 6.60 (dd, \(J = 17.9, 8.2\) Hz, 2 H), 5.08 (s, 2 H), 3.26 (t, \(J = 14.7\) Hz, 2 H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta 144.3\) (d, \(J = 26.6\) Hz), 136.6, 136.3, 129.8, 129.5, 129.1, 128.9, 128.8, 128.7 (t, \(J = 279.7\) Hz), 128.4, 127.4, 127.1 (d, \(J = 25.6\) Hz), 126.7, 126.2 (t, \(J = 3.2\) Hz), 123.1 (d, \(J = 55.6\) Hz), 122.7, 115.6, 115.23, 52.9, 44.2 (t, \(J = 24.6\) Hz)
\(^{19}\text{F NMR (376 MHz, CDCl}_3\): \(\delta -71.72 \text{ (t, } J = 14.7 \text{ Hz, 2 F)}\)

\textbf{IR (film):} 3430, 2388, 2288, 1647, 1578, 1495, 1470, 1443, 1366, 1288, 1258, 1223, 1153, 1034, 1028, 1013, 912, 746, 692

\textbf{HRMS (ESI+):} calc. for C\(_{27}\)H\(_{22}\)F\(_2\)NS\(_2\) (M+H) 462.1162, found 462.1182, 2.0 mmu.

tert-butyl 4-(5-(2,2-difluoro-2-(phenylthio)ethyl)thiazol-2-yl)piperazine-1-carboxylate (2.8f): Following General Procedure B, 0.17 g (0.50 mmol) of compound 2.7f was reacted with 0.16 mL (1.5 mmol) of thiophenol at 90 °C for 5 h. After workup, the product was purified by flash chromatography on silica gel using a gradient from 0–20–50% EtOAc in hexanes, to furnish 0.19 g (86% yield) of desired product 2.8f as a yellow solid, m.p. 82 °C.

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \(\delta 7.61–7.58 \text{ (m, 2 H), 7.45–7.35 (m, 3 H), 7.00 (d, } J = 1.0 \text{ Hz, 1 H), 3.55 (dd, } J = 6.7, 3.8 \text{ Hz, 4 H), 3.48–3.41 (m, 6 H), 1.48 (s, 9 H)}\)

\(^{13}\text{C NMR (126 MHz, CDCl}_3\):} \(\delta 172.4, 154.7, 140.3, 136.4, 130.1, 129.3, 128.3 \text{ (t, } J = 280.0 \text{ Hz), 126.7, 116.1 (t, } J = 3.5 \text{ Hz), 80.5, 48.2, 43.0 (bs), 37.3 (t, } J = 27.1 \text{ Hz), 28.5}\)

\(^{19}\text{F NMR (376 MHz, CDCl}_3\):} \(\delta -72.51 \text{ (t, } J = 13.7 \text{ Hz, 2 F)}\)
IR (film): 2976, 2926, 2859, 2361, 1697, 1522, 1452, 1420, 1366, 1285, 1254, 1238, 1167, 1140, 1034, 1009, 999, 968, 897, 750, 691, 669 cm\(^{-1}\)

HRMS (ESI+): calc. for C\(_{20}\)H\(_{25}\)F\(_2\)N\(_3\)S\(_2\)Na (M+Na) 464.1254, found 464.1263, 1.9 ppm.

Experimental Procedures and Characterization of Compounds in Scheme 2-10

(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)(4-methoxyphenyl)sulfane (2.10a):

Following General Procedure B, 0.115 g (0.500 mmol) of compound 2.1 was reacted with 0.125 mL (1.00 mmol) of 4-methoxythiophenol at 70 °C for 30 min. After workup, the product was purified by flash chromatography using 0–5% Et\(_2\)O in PhMe, to furnish 0.148 g (80% yield) of desired product 2.10a as a colorless solid, m.p. 66–67 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.50 (d, \(J = 8.4\) Hz, 2 H), 6.89 (d, \(J = 8.4\) Hz, 2 H), 6.49 (s, 2 H), 3.85 (s, 9 H), 3.82 (s, 3 H), 3.34 (t, \(J = 14.7\) Hz, 2 H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 161.2, 153.2, 138.2, 137.6, 128.6 (t, \(J = 279.4\) Hz), 127.7 (t, \(J = 3.2\) Hz), 117.4 (t, \(J = 2.3\) Hz), 114.7, 107.7, 61.0, 56.3, 55.5, 45.4 (t, 24.4 Hz)

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) –72.57 (t, \(J = 14.7\) Hz, 2 F)
IR (film): 2999, 2939, 2839, 2361, 2339, 1591, 1508, 1495, 1462, 1423, 1346, 1315, 1290, 1250, 1225, 1175, 1151, 1128, 1028, 1007, 995, 947, 924, 874, 829, 777, 692, 667, 646, 528 cm⁻¹

HRMS (HAPCI⁺): calc. for C₁₈H₂₁F₂O₄S (M+H) 371.1129, found 371.1114, 4.9 ppm.

Preparation of Compound 2.9b

ethyl 2-(o-tolyloxy)acetate (2.9b-2):¹⁸ Compound 2.9b-2 was prepared according to a previous report.¹⁸ An oven-dried 250 mL two-neck round-bottom flask equipped with a magnetic stirbar and reflux condenser was charged with 10.4 g (75.0 mmol) of anhydrous grade K₂CO₃, and evacuated and backfilled with N₂ 3X. o-Cresol (5.80 mL, 56.0 mmol) was added, and the mixture dissolved in anhydrous MeCN (100 mL). The mixture was stirred for 15 min at R.T., and then 7.0 mL (63 mmol) of ethyl bromoacetate was added. The reaction vessel was submerged in a 90 °C oil bath, and the reaction refluxed overnight. At R.T., the reaction was filtered, and the filtrate concentrated to dryness to
give 10.6 g (97%) of desired product 2.9b-2 as a yellow oil. 2.9b-2 was of sufficient purity to use in the next step.

\( ^1 \text{H NMR (400 MHz, CDCl}_3) \): \( \delta \) 7.17–7.11 (m, 2 H), 6.90 (td, \( J = 7.4, 1.1 \) Hz, 1 H), 6.71 (d, \( J = 8.3 \) Hz, 1H), 4.64 (s, 2 H), 4.27 (q, \( J = 7.1 \) Hz, 2 H), 2.30 (s, 3 H), 1.30 (t, \( J = 7.2 \) Hz, 3 H).

Note: The reaction can be run without utilizing anhydrous solvents or dry glassware. However, the yield will be lower and purification will be necessary. The most important component is the quality of \( \text{K}_2\text{CO}_3 \). For full conversion, we recommend anhydrous grade \( \text{K}_2\text{CO}_3 \).

**ethyl 2-(4-(chlorosulfonyl)-2-methylphenoxy)acetate (2.9b-1):**\(^{18} \) Compound 2.9b-1 was prepared according to a previous report.\(^{18} \) An oven-dried 25 mL round bottom flask equipped with a magnetic stirbar was sealed with a rubber septum. To the round bottom flask was added 7.00 mL (105 mmol) of chlorosulfonic acid. The round bottom flask was submerged in a 0 °C ice bath, and the chlorosulfonic acid stirred rapidly, to which 3.90 g (20.0 mmol) of 2.9b-2 was added dropwise. Once all 2.9b-2 was added, the reaction was warmed to ambient temperature over 1 h and stirred for another 2 h. The reaction was then carefully poured over ice (caution: the reaction with the ice can cause splatter). After drying on high vacuum, 4.60 g (78%) of desired product 2.9b-1 was recovered as a grey solid and used without further purification.
methyl 2-(4-mercapto-2-methylphenoxy)acetate (2.9b):\textsuperscript{18} Compound 2.9b was prepared according to a previous report.\textsuperscript{18} A 3-neck flask was equipped with a magnetic stirbar and a reflux condenser and charged with 4.60 g (15.7 mmol) of 2.9b-1 and 9.36 g (78.6 mmol) of powdered tin metal. The mixture was suspended in MeOH (150 mL), and the side-arms sealed with rubber septa. Concentrated HCl (20 mL) was added dropwise while the mixture was rapidly stirring. During the addition of the HCl, the exotherm caused the reaction to begin refluxing. Once all HCl was added, the reaction vessel was submerged in a 90 °C oil bath, and the mixture refluxed overnight. The reaction was returned to ambient temperature, and then quenched by pouring the reaction over ice. The reaction was extracted with ether (3X 50 mL), and the organic layer washed 2X with 20 mL of H\textsubscript{2}O. The organic layer was dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated \textit{in vacuo}. The crude product was purified by flash chromatography on silica gel by 30\% EtOAc in hexanes. The reaction afforded 1.89 g (57\%) of desired product 2.9b as a clear oil. The \textsuperscript{1}H NMR spectrum matches previous reports.\textsuperscript{18}

![Chemical structure of 2.10b]

methyl 2-(4-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)thio)-2-methylphenoxy)acetate (2.10b): Following General Procedure B, 0.12 g (0.50 mmol) of
compound 2.1 was reacted with 0.21 g (1.0 mmol) of compound 10b at 70 °C for 0.5 h. After workup, the product was purified by flash chromatography using 0–30% EtOAc in hexanes, to furnish 0.19 g (81% yield) of desired product 2.10b in 97% purity (assessed by ¹H and ¹⁹F NMR) as an off-white solid, m.p. 60–63 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.38–7.35 (m, 2 H), 6.66 (d, J = 8.4 Hz, 1 H), 6.49 (s, 2 H), 4.67 (s, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.34 (t, J = 14.7 Hz, 2 H), 2.28 (s, 3 H)

¹³C NMR (126 MHz, CDCl₃): δ 169.3, 157.7, 153.2, 139.2, 137.6, 135.5, 128.7 (t, J = 279.4 Hz), 128.4, 127.7 (t, J = 3.1 Hz), 118.2, 111.4, 107.7, 65.5, 61.0 (d, J = 2.5 Hz), 56.3 (d, J = 2.4 Hz), 52.5 (d, J = 2.3 Hz), 45.4 (t, J = 24.4 Hz), 16.3

¹⁹F NMR (376 MHz, CDCl₃): δ –72.36 (t, J = 14.8 Hz, 2 F)

IR (film): 2922, 1761, 1591, 1508, 1491, 1460, 1423, 1311, 1240, 1213, 1126, 1040, 1005, 881, 806, 771, 702, 663 cm⁻¹

HRMS (ESI+): calc. for C₂₁H₂₄F₂O₆Na (M+Na) 465.1159, found 465.1141, 3.9 ppm.
**N-(4-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)thio)phenyl)acetamide (2.10c):**

Following General Procedure C, 0.12 g (0.50 mmol) of compound 2.1 was reacted with 0.25 g (1.5 mmol) of 4-acetamidothiophenol at 100 °C for 20 h. After workup, the product was purified by flash chromatography on silica gel using a gradient of 0–40–70–100% EtOAc in hexanes with 1% Et₃N, to furnish 0.18 g (88% yield) of desired product 2.10c in 98% purity (as determined by ^1^H and ^1⁹^F NMR) as a colorless solid, m.p. 120–121 °C.

**^1^H NMR (400 MHz, CDCl₃):** δ 7.53 (s, 4 H), 7.22 (bs, 1 H), 6.49 (s, 2 H), 3.86 (s, 6H), 3.85 (s, 3 H), 3.34 (t, J = 14.7 Hz, 2 H), 2.19 (s, 3 H)

**^1³^C NMR (126 MHz, CDCl₃):** δ 168.5, 153.2, 139.6, 137.7, 137.4, 128.65 (t, J = 279.9 Hz), 127.6 (t, J = 3.2 Hz), 121.6, 120.0, 107.7, 61.0, 56.3, 45.5 (t, J = 24.3 Hz), 24.9

**^1⁹^F NMR (376 MHz, CDCl₃):** δ –72.05 (t, J = 14.8 Hz, 2 F)

**IR (film):** 3318, 2999, 2940, 2839, 1694, 1682, 1591, 1530, 1510, 1462, 1424, 1397, 1371, 1346, 1314, 1292, 1248, 1225, 1180, 1150, 1126, 1036, 1011, 995, 945, 874, 833, 777, 737, 692, 665, 590, 525 cm⁻¹

**HRMS (ESI+):** calc. for C₁⁹H₂₁F₂NO₄SK (M+K) 436.0796, found 436.0792, 0.9 ppm.
3-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)thio)aniline (2.10d): Following General Procedure B, 0.12 g (0.50 mmol) of compound 2.1 was reacted with 0.11 mL (1.0 mmol) of 3-aminothiophenol at 90 °C for 20 h. After extraction from 1 N NaOH (to remove the residual 3-aminothiophenol that is difficult to remove by normal-phase chromatography) with DCM, the product was purified by flash chromatography using 0–30–40–70% EtOAc in hexanes, to furnish 0.13 g (71% yield) of desired product 2.10d in 95% purity (by ¹H and ¹⁹F NMR) as an orange/pink solid, m.p. 87–90 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.14 (t, J = 7.8 Hz, 1 H), 6.96 (dt, J = 7.7, 1.2 Hz, 1 H), 6.91 (t, J = 2.0 Hz, 1 H), 6.71 (ddd, J = 8.0, 2.4, 1.0 Hz, 1 H), 6.49 (s, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.72 (bs, 2 H), 3.35 (t, J = 14.8 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.1, 147.0, 137.6, 129.9, 128.9 (t, J = 279.5 Hz), 127.75 (t, J = 2.1 Hz), 127.69 (t, J = 3.2 Hz), 126.0, 122.1, 116.5, 107.7, 61.0, 56.2, 45.5 (t, J = 24.6 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ –71.50 (t, J = 14.8 Hz, 2 F)

IR (film): 3462, 3372, 3231, 2999, 2940, 2837, 2359, 1622, 1593, 1508, 1481, 1460, 1424, 1344, 1316, 1225, 1150, 1126, 1001, 990, 872, 777, 689, 667, 405 cm⁻¹

HRMS (ESI+): calc. for C₁₇H₁₉F₂NO₃SNa (M+Na) 378.0951, found 378.0958, 1.9 ppm.
(2-bromophenyl)(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)sulfane (2.10e):
Following General Procedure B, 0.12 g (0.50 mmol) of compound 2.1 was reacted with 0.12 mL (1.0 mmol) of 2-bromothiophenol at 70 °C for 2 h. After workup, the product was purified by flash chromatography using 0–10% Et₂O in PhMe, to furnish 0.18 g (84% yield) of desired product 2.10e as a colorless solid, m.p. 57–58 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J = 7.7 Hz, 1 H), 7.67 (dd, J = 8.0 Hz, 1.6 Hz, 1 H), 7.26-7.24 (m, 1 H), 6.52 (s, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.42 (t, J = 14.8 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.2, 137.84, 137.76, 133.7, 131.1, 130.3, 129.0, 128.9 (t, J = 281.5 Hz), 128.0, 127.3 (t, J = 3.1 Hz), 107.7, 61.0, 56.3, 45.7 (t, J = 23.9 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ -71.03 (t, J = 14.9 Hz, 2 F)

IR (film): 2997, 2937, 2837, 2359, 2341, 1591, 1506, 1462, 1423, 1346, 1315, 1246, 1225, 1151, 1126, 1038, 1009, 993, 945, 926, 874, 829, 777, 756, 690, 667, 646, 633, 581, 563, 525 cm⁻¹

HRMS (HAPCI⁺): calc. for C₁₇H₁₇BrF₂O₃S (M⁺) 418.0050, found 418.0050, 0.0 ppm.

Preparation of Compound 2.9f
**ethyl 2-(4-mercapto-2-methylphenoxy)acetate (2.9f-1):** A three-neck, 250 mL round bottom flask was equipped with a magnetic stirbar, an internal thermometer, and a reflux condenser and then charged with 3.51 g (53.0 mmol) of zinc dust. The zinc dust was suspended in 54 mL of EtOAc, and rapidly stirred. The reaction vessel was submerged in a 40 °C oil bath, and the temperature modulated to achieve an internal reaction temperature of 40 °C. At this temperature, 1.80 mL (31.0 mmol) of glacial acetic acid and 0.56 mL (31 mmol) of deionized H₂O were added to the suspension. Subsequently 4.47 g (15.3 mmol) of 9b-1 were added in portions, maintaining an internal reaction temperature less than 60 °C. After all 2.9b-1 was added, the reaction was stirred at 40 °C for 1 h. Subsequently, 12.0 mL (91.0 mmol) of TMS-Cl was added dropwise, maintaining an internal temperature less than 55 °C. Once all of the TMS-Cl was added, the reaction was brought to reflux, which requires an internal temperature of approximately 77 °C, and refluxed overnight. At ambient temperature, the reaction was quenched with saturated aq. NH₄Cl and extracted with EtOAc (3X 50 mL). The organic layer was dried with Na₂SO₄ and concentrated in vacuo, and the crude product was purified by flash chromatography on silica gel using a gradient of 0–10–30% EtOAc in hexanes. The reaction afforded 1.74 g (50%) of desired product 2.9f-1 as a clear oil.
**1H NMR (400 MHz, CDCl₃):** δ 7.14 (d, J = 2.4 Hz, 1 H), 7.09 (dd, J = 8.5, 2.3 Hz, 1 H), 6.59 (d, J = 8.4 Hz, 1 H), 4.60 (s, 2 H), 4.25 (q, J = 7.1 Hz, 2 H), 3.33 (s, 1 H), 2.24 (s, 3 H), 1.29 (t, J = 7.1 Hz, 3 H).

**2-(4-mercapto-2-methylphenoxy)ethan-1-ol (2.9f):** An oven-dried 100 mL round bottom flask, equipped with a magnetic stirbar, was charged with 0.29 g (7.5 mmol) of lithium aluminum hydride in the glovebox and sealed with a rubber septum. The reaction vessel was removed from the glovebox and submerged in a 0 °C ice bath, and the lithium aluminum hydride was suspended in anhydrous THF (32 mL). 0.65 g (3.0 mmol) of 9f-1 was added to the reaction at 0 °C. The reaction solidified, so additional anhydrous THF (approx. 10 mL) was added, and the temperature was allowed to rise to R.T., and subsequently stirred for 3 h. The reaction was cooled to 0 °C in an ice bath and quenched by the addition of 10 mL of EtOAc. Then, a saturated solution of Rochelle's salt (20 mL) was added, and the reaction was stirred overnight at R.T. The reaction was extracted with EtOAc (3X 20 mL), and the organic layer dried over Na$_2$SO$_4$ and concentrated in vacuo to provide 0.320 g (60%) of desired product 2.9f as a colorless solid, m.p. 74–76 °C. Note, if contaminated with a disulfide impurity, purification on silica gel by a gradient from 0% EtOAc in hexanes to 40% EtOAc in hexanes furnishes pure product, albeit in lower yield.

**1H NMR (400 MHz, CDCl₃):** δ 7.13–7.10 (m, 2 H), 6.70 (d, J = 8.8 Hz, 1 H), 4.03 (dd, J = 5.2, 3.8 Hz, 2 H), 3.97–3.95 (m, 2 H), 3.34 (s, 1 H), 2.21 (s, 1 H), 2.18 (s, 3 H)
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 155.7, 133.6, 129.5, 128.0, 120.2, 112.1, 69.6, 61.7, 16.2

IR (film): 3196, 2938, 2872, 2552, 2359, 2342, 1595, 1493, 1454, 1400, 1294, 1246, 1196, 1138, 1101, 1086, 1049, 928, 914, 897, 876, 866, 804, 658 cm\(^{-1}\)

HRMS (ESI-): calc. for C\(_9\)H\(_{11}\)O\(_2\)S (M-H) 183.0480, found 183.0443, 3.7 mmu.

2-(4-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)thio)-2-methylphenoxy)ethan-1-ol (2.10f): Following General Procedure B, 0.12 g (0.50 mmol) of compound 2.1 was reacted with 0.26 g (1.5 mmol) of 10f at 90 °C for 5 h. After workup, the product was purified by flash chromatography on silica gel using a gradient from 0–10–30–60% EtOAc in hexanes, to furnish 0.21 g (99% yield) of desired product 2.10f in 96% purity (determined by \(^1\)H and \(^{19}\)F NMR) as a colorless solid, m.p. 55–57 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.40–7.35 (m, 2 H), 6.81 (d, \(J = 8.2\) Hz, 1 H), 6.50 (s, 2 H), 4.11 (dd, \(J = 5.2, 3.8\) Hz, 2 H), 4.02–3.98 (m, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.34 (t, \(J = 14.7\) Hz, 2 H), 2.23 (s, 3 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 158.4, 153.2, 139.0, 137.6, 135.7, 128.7 (t, $J = 279.3$ Hz), 127.8, 127.7 (t, $J = 3.0$ Hz), 117.3, 111.5, 107.7, 69.5, 61.6, 61.0, 56.3, 45.4 (t, $J = 24.4$ Hz), 16.3

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –72.49 (t, $J = 14.7$ Hz, 2 F)

IR (film): 3457, 2938, 2839, 2359, 2332, 1593, 1506, 1493, 1456, 1424, 1346, 1316, 1298, 1250, 1225, 1194, 1126, 1103, 1034, 997, 922, 889, 872, 810, 692, 667, 581, 530 cm$^{-1}$

HRMS (ESI+): calc. for C$_{20}$H$_{24}$F$_2$O$_5$SNa (M+Na) 437.1210, found 437.1221, 2.5 ppm.

(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)(3-(trifluoromethyl)phenyl)sulfane (2.10g): Following General Procedure B, 0.12 g (0.50 mmol) of compound 2.1 was reacted with 0.14 mL (1.0 mmol) of 3-trifluoromethyl thiophenol at 70 °C for 0.5 h. After workup, the product was purified by flash chromatography using 0–5% Et$_2$O in PhMe, to furnish 0.16 g (78% yield) of desired product 2.10g as a colorless solid, m.p. 59–60 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.84 (s, 1 H), 7.77 (d, $J = 7.8$ Hz, 1 H), 7.67 (d, $J = 7.9$ Hz, 1 H), 7.50 (t, $J = 7.8$ Hz, 1 H), 6.50 (s, 2 H), 3.87–3.86 (m, 9 H), 3.40 (t, $J = 14.6$ Hz)
$^{13}$C NMR (126 MHz, CDCl$_3$): δ 153.3, 139.3, 137.9, 132.7 (q, $J = 3.8$ Hz), 131.6 (q, $J = 32.6$ Hz), 129.6, 128.6 (t, $J = 281.1$ Hz), 128.3 (d, $J = 2.1$ Hz), 127.1 (t, $J = 3.4$ Hz), 126.7 (q, $J = 3.7$ Hz), 122.6 (q, $J = 273.2$ Hz), 107.7, 61.0, 56.3, 45.6 (t, $J = 23.9$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –62.77 (s, 3 F), –70.77 (t, $J = 14.5$ Hz, 2 F)

IR (film): 2999, 2941, 2841, 1591, 1508, 1462, 1423, 1346, 1325, 1304, 1275, 1246, 1225, 1169, 1151, 1128, 1070, 1041, 1013, 947, 926, 876, 800, 777, 714, 696 cm$^{-1}$

HRMS (HAPCl+): calc. for C$_{18}$H$_{17}$F$_5$O$_3$S (M+) 408.0819, found 408.0812, 1.7 ppm.

(3,4-dichlorophenyl)(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)sulfane (2.10h):

Following General Procedure B, 0.16 g (0.50 mmol) of compound 2.1 was reacted with 0.13 mL (1.0 mmol) of 3,4-dichlorothiophenol at 70 °C for 0.5 h. After workup, the product was purified by flash chromatography using 0–10% Et$_2$O in PhMe, to furnish 0.17 g (83% yield) of desired product 2.10h as a colorless solid, m.p. 59 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.67 (d, $J = 1.9$ Hz, 1 H), 7.43 (q, $J = 8.4$ Hz, 2 H), 6.49 (s, 2 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.38 (t, $J = 14.5$ Hz, 2 H)
\(^{13}\text{C} \text{NMR (126 MHz, CDCl}\_3\text{):} \delta 153.3, 137.9, 137.5, 135.2, 134.8, 133.1, 130.9, 128.6 (t, J = 281.3 \text{ Hz}), 127.1 (t, J = 3.5 \text{ Hz}), 126.8 (d, J = 2.2 \text{ Hz}), 107.6, 61.1, 56.3, 45.6 (t, J = 23.9 \text{ Hz})

\(^{19}\text{F} \text{NMR (376 MHz, CDCl}\_3\text{):} \delta –78.78 (t, J = 14.5 \text{ Hz, 2 F})

\text{IR (film):} \ 2999, 2937, 2839, 2359, 2341, 1591, 1508, 1456, 1423, 1366, 1346, 1315, 1246, 1225, 1184, 1151, 1126, 1034, 1013, 995, 947, 924, 876, 814, 777, 690, 667 \text{ cm}^{-1}

\text{HRMS (HAPCI\textsuperscript{+}):} \ \text{calc. for C}_{17}\text{H}_{17}\text{Cl}_{2}\text{F}_{2}\text{O}_{3}\text{S (M+H) 409.0244, found 409.0241, 0.7 ppm.}

\textbf{Preparation of Compound 9i}

4-mercaptopbenzonitrile (2.9i):\textsuperscript{20} Compound 2.9i was prepared according to a previous report, with modifications to the first step.\textsuperscript{20} An oven dried 250 mL 3-neck round bottom flask was equipped with a magnetic stirbar and reflux condenser was charged with 3.65 g (20 mmol) of \(\rho\)-bromobenzonitrile, 0.58 g (1.0 mmol) of Xantphos, and 0.46 g (0.5 mmol) of Pd\(_2\)(dba)\(_3\) and evacuated and backfilled 3X with N\(_2\). The reactants were dissolved in anhydrous PhMe (114 mL), and subsequently 2.3 mL (20 mmol) of methyl-3-mercaptopropionate and 8 mL (46 mmol) of Hunig’s base were added. The reaction vessel was submerged in a 120 °C oil bath and stirred overnight. At ambient temperature
the reaction was filtered, the filtrate was concentrated, and the crude product purified by flash chromatography on silica gel by a gradient using 0–10–30–100% EtOAc in hexanes to furnish 2.9i-1 as an orange/pink solid, m.p. 51 °C.

\(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.55 (d, J = 8.5 \text{ Hz}, 2 \text{ H}), 7.33 (d, J = 8.5 \text{ Hz}, 2 \text{ H}), 3.71 (s, 3 \text{ H}), 3.25 (t, J = 7.4 \text{ Hz}, 2 \text{ H}), 2.69 (t, J = 7.4 \text{ Hz}, 2 \text{ H})\)

\(^13C\) NMR (126 MHz, CDCl\(_3\)): \(\delta 171.8, 143.6, 132.5, 127.4, 118.9, 108.9, 52.2, 33.6, 27.2\)

IR (film): 3090, 3007, 2951, 2845, 2226, 1738, 1595, 1489, 1437, 1418, 1404, 1364, 1252, 1194, 1177, 1090, 1061, 1015, 978, 901, 845, 820, 787, 706, 679, 588, 546 cm\(^{-1}\)

HRMS (HAPCl\(^+\)): calc. for C\(_{11}\)H\(_{12}\)NO\(_2\)S (M+H) 222.0589, found 222.0585, 1.8 ppm.

An oven-dried 500 mL round bottom flask equipped with a magnetic stirbar and rubber septum was charged with anhydrous MeOH (200 mL). The reaction flask was submerged in a 0 °C bath. On a clean paper towel 1.38 g (60 mmol) of sodium metal in mineral oil was washed with hexanes and added to the MeOH in portions. Once all of the sodium metal was dissolved the NaOMe solution was poured into a 500 mL round bottom flask containing 2.9i-1 at R.T.. The reaction was stirred overnight and then quenched with aqueous 1 N HCl. The MeOH was removed in vacuo and the resulting aqueous solution was filtered, providing 1.79 g (66% over 2 steps) of desired product 2.9i as an orange-brown solid.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.49 (d, $J = 8.4$ Hz, 2 H), 7.31 (d, $J = 8.4$ Hz, 2 H), 3.67 (s, 1 H).

4-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)thio)benzonitrile (2.10i): Following General Procedure C, 0.12 g (0.50 mmol) of compound 2.1 was reacted with 0.14 g (1.0 mmol) of 2.10i at 100 °C for 20 h. After workup, the product was purified by flash chromatography using 0–10–40% EtOAc in hexanes, to furnish 0.151 g (82% yield) of desired product 10i as a yellow solid, m.p. 130–132 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.67 (d, $J = 8.3$ Hz, 2 H), 7.64 (d, $J = 8.4$ Hz, 2 H), 6.50 (s, 2 H), 3.41 (t, $J = 14.5$ Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.3, 138.0, 135.6, 133.8, 132.5, 128.8 (t, $J = 281.9$ Hz), 126.8 (t, $J = 3.4$ Hz), 118.2, 113.3, 107.7, 61.1, 56.3, 45.8 (t, $J = 23.7$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -70.08 (t, $J = 14.6$ Hz, 2 F)

IR (film): 3001, 2963, 2940, 2839, 2230, 1593, 1508, 1487, 1462, 1424, 1346, 1317, 1246, 1227, 1152, 1128, 1040, 1013, 995, 874, 831, 781, 692, 664, 548 cm$^{-1}$

HRMS (HAPCI⁺): calc. for C$_{18}$H$_{18}$F$_2$NO$_3$S (M+H) 366.0975, found 366.0958, 4.6 ppm.
3-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)thio)phenol (2.10j): Following General Procedure B, 0.16 g (0.50 mmol) of compound 2.1 was reacted with 0.10 mL (1.0 mmol) of 3-hydroxythiophenol at 70 °C for 4 h. After workup, the product was purified by flash chromatography using 0–15–30% EtOAc in hexanes, to furnish 0.15 g (84% yield) of desired product 2.10j in 99% purity (as determined by $^1$H and $^{19}$F NMR) as a colorless solid, m.p. 98–102 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24 (t, $J = 7.9$ Hz, 1 H), 7.15 (d, $J = 7.7$ Hz, 1 H), 7.08 (s, 1 H), 6.89 (dd, $J = 8.2$, 2.5 Hz, 1 H), 6.49 (s, 2 H), 4.95–4.92 (m, 1 H), 3.86 (s, 9 H), 3.36 (t, $J = 14.7$ Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 155.8, 153.2, 137.7, 130.1, 128.8 (t, $J = 280.1$ Hz), 128.4, 128.2 (t, $J = 2.0$ Hz), 127.6 (t, $J = 3.2$ Hz), 122.7, 117.1, 107.7, 61.0, 56.3, 45.5 (t, $J = 24.4$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –71.27 (t, $J = 14.7$ Hz, 2 F)

IR (film): 3404, 2939, 2361, 2341, 1593, 1508, 1458, 1423, 1346, 1315, 1248, 1225, 1150, 1126, 1036, 1018, 993, 887, 781, 689, 667, 405 cm$^{-1}$
HRMS (ESI+): calc for C_{17}H_{18}F_{2}O_{4}SNa (M+Na) 379.0792, found 379.0793, 0.3 ppm.

Scheme 2-12: Coupling of Aryl Thiols over Alkyl Thiols:

Prepared according to General Procedure C, with the following modifications. To an oven-dried 5 mL microwave vial equipped with a magnetic stirbar was added 0.12 g (0.50 mmol) of 2.1, 2 mL of DCE, 0.16 mL (1.5 mmol) of thiophenol, 0.26 mL (1.5 mmol) of 1-octanethiol, and 3.2 µL (0.025 mmol) of TMG. The vial was sealed with a PTFE-lined silicon septa in a crimp-top cap, and then General Procedure C was followed as normal. To assess the selectivity of the coupling reaction for thiophenol, the reaction mixture was assessed by $^{19}$F NMR, GC-MS, and FID-GC. By $^{19}$F NMR no formation of compound 2.11 was observed, while both GC methods showed less than 1% of compound 2.11 formed. Upon isolation 0.155 g (91% yield) of compound 2.2 was recovered, which compares favorably to the yield observed under standard reaction conditions (vida supra).
Preparation and Characterization of Compounds in Scheme 2-13

4-(3-(2,2-difluoro-2-(octylthio)ethyl)phenyl)morpholine (2.12d): Prepared according to General Procedure D, 0.113 g (0.50 mmol) of compound 2.5d was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10 mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of o-xylene at 110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.111 g (60 % yield) of desired compound 2.12d as a pale orange oil.

\[^1^H\text{NMR (500 MHz, CDCl}_3\): \delta 7.30 (t, J = 7.88 Hz, 1 H), 7.03 (dd, J = 7.89, 1.97 Hz, 1 H), 6.99 (d, J = 2.19 Hz, 1 H), 6.96 (d, J = 7.57 Hz, 1 H), 3.94–3.92 (m, 4 H), 3.37 (t, J = 7.65, 6.34 Hz, 2 H), 1.62 (tt, J = 7.65, 6.34 Hz, 2 H), 1.36–1.33 (m, 2 H), 1.29–1.25 (m, 9 H), 0.88 (t, J = 6.95 Hz, 3 H)

\[^1^3^C\text{NMR (126 MHz, CDCl}_3\): \delta 149.3, 133.8 (t, J = 3.82 Hz), 130.1 (t, J = 277.98 Hz), 129.6, 124.7, 119.3, 116.4, 66.4, 50.7, 46.0 (t, J = 24.66 Hz), 31.9, 29.9, 29.3, 29.2, 29.0, 28.1 (t, J = 3.59 Hz), 22.8, 14.2

\[^1^9^F\text{NMR (376 MHz, CDCl}_3\): \delta –73.38 (t, J = 14.53 Hz, 2 F)

\]
(2-(4′-(tert-butyl)-[1,1′-biphenyl]-2-yl)-1,1-difluoroethyl)(octyl)sulfane (2.12g):

Prepared according to General Procedure D, 0.136 g (0.50 mmol) of compound 2.5g was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10 mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of o-xylene at 110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.159 g (76 % yield) of desired compound 2.12d as a pale orange oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.57–7.54 (m, 4 H), 7.49 (d, $J$ = 8.43 Hz, 2 H), 7.41 (t, $J$ = 7.61 Hz, 1 H), 7.28 (d, $J$ = 7.62 Hz, 1 H), 3.47 (t, $J$ = 14.50 Hz, 2 H), 2.83 (t, $J$ = 7.47 Hz, 2 H), 1.64 (p, $J$ = 7.34 Hz, 2 H), 1.39 (s, 9 H), 1.35–1.26 (m, 11 H), 0.88 (t, $J$ = 6.95 Hz, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 150.6, 141.4, 138.2, 132.8 (t, $J$ = 3.45 Hz), 130.3 (t, $J$ = 277.55 Hz), 129.5, 129.3, 128.9, 127.0, 126.5, 125.9, 46.0 (t, $J$ = 24.63 Hz), 34.9, 32.0, 31.8, 31.5, 30.0, 29.2, 29.0, 28.2 (t, $J$ = 3.28 Hz), 22.8, 14.2

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –73.36 (t, $J$ = 14.64. Hz, 2 F)
ethyl (E)-3-(3,2-difluoro-2-(octylthio)ethyl)phenyl)acrylate (2.12j): Prepared according to General Procedure D, 0.119 g (0.50 mmol) of compound 2.5j was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10 mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of o-xylene at 110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.148 g (77 % yield) of desired compound 2.13c as a white semisolid.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.68 (d, \(J = 16.03\) Hz, 1 H), 7.48 (d, \(J = 7.58\) Hz, 1 H), 7.45 (d, \(J = 2.03\) Hz, 1 H), 7.36 (t, \(J = 7.57\) Hz, 1 H), 7.31 (d, \(J = 7.51\) Hz, 1 H), 6.45 (d, \(J = 16.01\) Hz, 1 H), 4.27 (q, \(J = 7.13\) Hz, 2 H), 3.40 (t, \(J = 14.40\) Hz, 2 H), 2.80 (t, \(J = 7.54\) Hz, 2 H), 1.61 (p, \(J = 7.28\) Hz, 2 H), 1.34 (t, \(J = 7.12\) Hz, 6 H), 1.27–1.25 (m, 9 H), 0.88 (t, \(J = 6.93\) Hz, 3 H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ 167.0, 144.3, 134.8, 133.2 (t, \(J = 3.76\) Hz), 132.4, 130.3, 130.0 (t, \(J = 277.09\) Hz), 129.1, 127.4, 118.8, 60.7, 45.6 (t, \(J = 24.98\) Hz), 31.9, 29.9, 28.9, 29.1, 28.9, 28.1 (t, \(J = 3.51\) Hz), 22.8, 14.5, 14.2

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): δ −73.50 (t, \(J = 14.39\) Hz, 2 F)
(2-(3,5-dimethylphenyl)-1,1-difluoroethyl)(octyl)sulfane (2.12p): Prepared according to General Procedure D, 0.084 g (0.50 mmol) of compound 2.5p was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10 mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of o-xylene at 110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.094 g (60 % yield) of desired compound 2.13p as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.95 (s, 1 H), 6.91 (s, 2 H), 3.32 (t, $J = 14.71$ Hz, 2 H), 2.80 (t, $J = 7.50$ Hz, 2 H), 2.32 (s, 6 H), 1.62 (tt, $J = 7.67$, 5.45 Hz, 2 H), 1.41–1.33 (m, 2 H), 1.30–1.26 (m, 9 H), 0.89 (t, $J = 6.96$ Hz, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 138.0, 132.1 (t, $J = 3.92$ Hz), 130.4 (t, $J = 277.16$ Hz), 129.5, 128.5, 45.7 (t, $J = 24.58$ Hz), 39.4, 32.0, 29.9, 29.4, 29.3, 29.2, 29.0, 28.1 (t, $J = 3.69$ Hz), 21.4, 14.3

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –73.36 (t, $J = 14.76$ Hz, 2 F)
(2-(2,6-dimethylphenyl)-1,1-difluoroethyl)(octyl)sulfane (2.12r): Prepared according to General Procedure D, 0.084 g (0.50 mmol) of compound 2.5r was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10 mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of o-xylene at 110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.082 g (52 % yield) of desired compound 2.13r as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.10 (dd, $J = 8.56, 6.30$ Hz, 1 H), 7.05 (d, $J = 7.05$ Hz, 2 H), 3.54 (t, $J = 15.42$ Hz, 2 H), 2.83 (t, $J = 7.52$ Hz, 2 H), 2.38 (s, 6 H), 1.64 (p, $J = 7.49$ Hz, 2 H), 1.37 (t, $J = 7.53$ Hz, 2 H), 1.28 (dt, $J = 9.78, 4.93$ Hz, 9 H), 0.88 (t, $J = 6.72$ Hz, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 138.7, 131.1 (t, $J = 278.94$ Hz), 129.8 (t, $J = 2.24$ Hz), 128.4, 127.6, 127.4, 39.3 (t, $J = 24.69$ Hz), 29.9, 29.3, 29.2, 29.0, 28.3 (t, $J = 3.60$ Hz), 22.8, 20.9, 14.2

$^{19}$F NMR (376 MHz, CDCl$_3$): δ −71.37 (t, $J = 15.47$ Hz, 2 F)

3-(2,2-difluoro-2-(octylthio)ethyl)-1-tosyl-1H-indole (2.13a): Prepared according to General Procedure D, 0.167 g (0.50 mmol) of compound 2.7a was reacted with 0.26 mL
(1.50 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10 mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of \( \alpha \)-xylene at 110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.160 g (66 % yield) of desired compound 2.13a as an orange semisolid.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.96 (d, \( J = 8.26 \) Hz, 1 H), 7.75 (d, \( J = 8.45 \) Hz, 2 H), 7.57 (s, 1 H), 7.53 (d, \( J = 7.80 \) Hz, 1 H), 7.31 (ddd, \( J = 8.34, 7.22, 1.31 \) Hz, 1 H), 7.27–7.24 (m, 1 H), 7.20 (d, \( J = 8.18 \) Hz, 2 H), 3.48 (t, \( J = 14.09 \) Hz, 2 H), 2.80 (t, \( J = 7.46 \) Hz, 2 H), 2.33 (s, 3 H), 1.61 (p, \( J = 7.45 \) Hz, 2 H), 1.34–1.31 (m, 2 H), 1.30–1.23 (m, 9 H), 0.88 (t, \( J = 6.92 \) Hz)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 145.1, 135.3, 135.1, 130.9, 130.2 (t, \( J = 277.62 \) Hz), 130.1, 130.0, 127.0, 126.4, 125.0, 123.5, 119.9 (t, \( J = 2.05 \) Hz), 113.8, 35.7 (t, \( J = 26.76 \) Hz), 31.9, 29.9, 29.3, 29.2, 28.9, 29.2 (t, \( J = 3.48 \) Hz), 22.8, 21.7, 14.2

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –72.66 (t, \( J = 14.26 \) Hz, 2 F)

4-(2,2-difluoro-2-(octylthio)ethyl)-1-phenyl-1H-pyrazole (2.13c): Prepared according to General Procedure D, 0.103 g (0.50 mmol) of compound 2.7c was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10
mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of o-xylene at 110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.104 g (59 % yield) of desired compound 2.13c as a white solid (MP = ~25 °C).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.88 (s, 1 H), 7.68 (dd, \(J = 8.59, 1.21 \) Hz, 2 H), 7.66 (s, 1 H), 7.45 (dd, \(J = 8.57, 7.41 \) Hz, 2 H), 7.29 (t, \(J = 7.43 \) Hz, 1 H), 3.35 (t, \(J = 14.33 \) Hz, 2 H), 2.84 (t, \(J = 7.43 \) Hz, 2 H), 1.64 (tt, \(J = 7.60, 6.36 \) Hz, 2 H), 1.37 (dd, \(J = 9.88, 5.19 \) Hz, 2 H), 1.27 (q, \(J = 5.42, 4.65 \) Hz, 9 H), 0.88 (t, \(J = 6.93 \) Hz, 3 H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ 142.1, 140.2, 130.1 (t, \(J = 276.32 \) Hz), 127.1 (d, \(J = 2.61 \) Hz), 126.7, 119.2, 113.9, 35.3 (t, \(J = 26.75 \) Hz), 31.9, 29.7, 29.3, 29.2, 29.0, 28.2 (t, \(J = 3.59 \) Hz), 22.8, 14.2

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): δ –74.33 (t, \(J = 14.42 \) Hz, 2 F)

\(\text{4-(2,2-difluoro-2-(octylthio)ethyl)dibenzo[b,d]thiophene (2.13d): Prepared according to General Procedure D, 0.123 g (0.50 mmol) of compound 2.7d was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10 mmol) of pyridine, and 0.08 mL (1.0 mmol) of 2-methoxyethanol in 1.5 mL of o-xylene at}

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110 °C for 15 h. After workup, the product was purified by flash chromatography using 0–100% DCM in hexanes to furnish 0.150 g (77 % yield) of desired compound 2.13d as a clear solid (MP = ~25 °C).

^1H NMR (500 MHz, CDCl3): δ 8.14 (ddd, J = 11.47, 6.19, 2.29 Hz, 2 H), 7.87 (dd, J = 6.18, 2.94 Hz, 1 H), 7.48–7.46 (m, 4 H), 3.71 (t, J = 14.33 Hz, 2 H), 2.84 (t, J = 7.50 Hz, 2 H), 1.63 (p, J = 7.49 Hz, 2 H), 1.35 (t, J = 7.49 Hz, 2 H), 1.27 (dd, J = 14.01, 5.23 Hz, 9 H), 0.88 (t, J = 6.71 Hz, 3 H)

^13C NMR (126 MHz, CDCl3): δ 141.2, 139.1, 136.2, 136.0, 130.5 (t, J = 278.31 Hz), 129.2, 127.1 (t, J = 3.57 Hz), 127.0, 124.9, 124.6, 122.9, 121.9, 121.2, 44.9 (t, J = 25.59 Hz), 31.9, 29.9, 29.2, 29.2, 29.0, 28.3 (t, J = 3.62 Hz), 22.8, 14.2

^19F NMR (376 MHz, CDCl3): δ –71.76 (t, J = 14.41 Hz, 2 F)
References for Chapter 2 Appendix:


3.1. Metal-Free Reactions of Alcohols with gem-Difluoroalkenes

Gem-difluoroalkenes are synthetically accessible\(^1\) and useful starting materials for generating biologically active fluorinated compounds; thus, much effort has been expended to further functionalize them.\(^{1h,1x}\) Due to the \(\sigma\)-withdrawing effect of the fluorine atoms, gem-difluoroalkenes are activated towards nucleophilic attack at the difluorinated carbon.\(^{1x}\). \(^2\) This allows heteroatom nucleophiles to react directly with gem-difluoroalkenes, resulting in \(\alpha\)-fluorination of the heteroatom, perturbing normal biological properties. Fluorination \(\alpha\)- to ethereal oxygens can provide many benefits,\(^3\) including reduced metabolic lability, modulation of logP to improve permeability, and imparting conformational bias (Figure 3-1).\(^4\) These perturbations arise from the \(\sigma\)-withdrawing property of fluorine that reduces the electron density of the ethereal oxygen, making the lone pair electrons of the oxygen weaker hydrogen-bond acceptors or participants in resonance.\(^{4b}\)

Figure 3-1: Fluorinated Ethers in Medicinal Chemistry\(^{3c}\)
Based on the potential benefits from α-fluorination of ethers in bioactive compounds, the patent literature contains many fluorinated ethers. Both difluoro and trifluoromethyl ethers are well represented, with several trifluoromethyl arylethers present in marketed therapeutics (Figure 3-1a).\textsuperscript{3c, 5} However, fluorinated dialkyl ethers are less common, due to the synthetic difficulty in accessing this moiety. Gem-difluorinated dialkyl ethers are\textsuperscript{6} only synthesized via deoxyfluorination\textsuperscript{7} or through reactions with gaseous difluoroethylene.\textsuperscript{8} The most common method to synthesize gem-difluorinated dialkyl ethers involves deoxyfluorination.\textsuperscript{7} However, major limitations of deoxyfluorination include the use of expensive deoxyfluorinating reagents and poor functional group compatibility with oxygen or sulfur containing substrates. Additionally, the use of deoxyfluorinating reagents on large scale represents a safety hazard, due to the release of HF as a byproduct,\textsuperscript{9} which is hazardous to human and environmental health and destroys many materials commonly used in synthetic chemistry labware.

Despite these synthetic issues, the patent literature contains thousands of fluorinated dialkyl ethers. Considering difficulty in synthesizing these substructures, many of these patented compounds are prophetic, and the full utility of the gem-difluorinated dialkyl ether substructure in medicinal chemistry remains under explored. Based on the interactions of biological nucleophiles with gem-difluoroalkenes as mechanistic inhibitors,\textsuperscript{10} and on the specific case of a gem-difluoroalkene containing Herpes simplex virus replication inhibitor reacting with alcohol solvents to provide gem-difluoro dialkyl ethers (Figure 3-2),\textsuperscript{10f, 11} we envisioned that alcohols might react with gem-difluoroalkenes to provide the desired gem-difluoro dialkyl ethers under mild conditions.
Of the existing reactions of gem-difluoroalkenes with alcohols, the vast majority result in a net C–F functionalization reaction to provide mono-fluoroalkenes. For instance, intramolecular nucleophilic cyclizations of gem-difluoroalkenes with alcohols generate 2-fluoro benzo[b]furans (Scheme 3-1a), or other heterocycles, such as furans.\textsuperscript{12a, 13} However, β-fluorination stabilizes difluoroalkenes, and in these systems controlled base addition can enable fluorine retentive protonation upon intramolecular cyclization with alcohols (Scheme 3-1b).\textsuperscript{14} Furthermore, many base-catalyzed intermolecular additions of alcohol nucleophiles to gem-difluoroalkenes defluorinated the substrate.\textsuperscript{15}

Under acidic conditions, solvolysis reactions with alcohols generate non-fluorinated products, due to rapid fluoride elimination generating a free alcohol that tautomerizes to an acyl fluoride and delivers acid or amide derived products.\textsuperscript{16} This same defluorination occurs when hydroxide is added to gem-difluoroalkenes.\textsuperscript{16} Similarly, intermolecular 3+2
cycloadditions of gem-difluoroalkenes with N–O oxides generate non-fluorinated products (Scheme 3-1c). ¹⁷ Similarly, when bi-dentate nucleophiles, such as catechols or glycols, ¹⁸ react with gem-difluoroalkenes, the substrate undergoes two sequential C–F functionalizations, providing non-fluorinated products (Scheme 3-1d). ¹⁸⁻¹⁹ Further, with excess pre-activated alcohol nucleophiles, ²⁰ or with alcohol nucleophiles under high temperature and excess base, ¹⁵d, ²¹ two sequential C–F functionalizations occur.
Scheme 3-1: Representative Reactions of *gem*-Difluoroalkenes with O-Based Nucleophiles

*a) 2–F Benzo[b]furan Synthesis via Intramolecular C–F Cyclization*\(^{12}\)

\[
\begin{align*}
\text{PhOH} & \quad \text{OH} \\
\text{Ph} & \quad \text{F} \\
\text{F} & \quad \text{MeCN, 20 °C} \\
\text{F} & \quad \text{Bn} \\
\text{Me} & \quad \text{MeOH, THF, 70 °C} \\
\text{F} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

*b) Controlled Base Addition Controls Fluoride Elimination*\(^{14}\)

\[
\begin{align*}
\text{PhO} & \quad \text{OH} \\
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{F} \\
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

*c) O-Based Nucleophiles Generate Acyl Fluorides*\(^{17}\)

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\begin{align*}
\text{Bn} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

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\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

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\begin{align*}
\text{F} & \quad \text{H} \\
\text{F} & \quad \text{H} \\
\text{F} & \quad \text{H} \\
\text{F} & \quad \text{H} \\
\text{F} & \quad \text{H}
\end{align*}
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\begin{align*}
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\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F}
\end{align*}
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\begin{align*}
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\text{Me} & \quad \text{Me}
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\end{align*}
\]

The loss of fluoride in nucleophilic functionalization reactions of *gem*-difluoroalkenes is expected, as *gem*-difluoroalkenes typically undergo an addition / elimination process.
to provide the C–F functionalization product.\textsuperscript{1h, 1x} This arises from the unique reactivity of fluorinated alkenes relative to non-fluorinated alkenes. The $\sigma$-withdrawing effects of fluorine activate the difluorinated position for regioselective nucleophilic attack, as the resulting carbanion is stabilized by the gem-difluoro group, lowering the activation energy of nucleophilic attack (\textbf{Figure 3-3}).\textsuperscript{1h, 1x} Unfortunately, the carbanion is less thermodynamically stable than a fluoride anion. Thus, the anionic intermediate undergoes $\beta$-fluoride elimination to deliver monofluorinated products (\textbf{Figure 3-3}).\textsuperscript{1h, 1x, 22}

\textbf{Figure 3-3}: Physicochemistry of \textit{gem}-Difluoroalkenes

As highlighted by the addition of alcohols to \textit{gem}-difluoroalkene containing uracil derivatives, O-based nucleophiles can react with \textit{gem}-difluoroalkenes without undergoing fluoride elimination, demonstrating the possibility of a general fluorine-retentive hydrofunctionalization reaction of alcohols with \textit{gem}-difluoroalkenes. Under base-catalyzed solvolysis conditions, intermolecular reactions of alcohols with \textit{gem}-difluoroalkenes proceed without $\beta$-fluoride elimination (\textbf{Scheme 3-2a}).\textsuperscript{10f, 11, 23} This strategy exhibits an addition / protonation mechanism, but lacks selectivity for the difluorinated product, unless controlled by a combination of Pd and a perfluoroalkyl electrophile.\textsuperscript{23b} Unfortunately, the use of the nucleophile as a solvent dramatically limits the range of usable nucleophiles, as many nucleophiles are themselves synthetic intermediates, are expensive, or are solid reagents. However, in one case a 3-
hydroxypyridine nucleophile added into gem-difluoroalkenes and selectively retained both fluorine atoms, without using the hydroxypyridine as the solvent (Scheme 3-2b).  

**Scheme 3-2:** Rare Fluorine-Retentive Reactions of gem-Difluoroalkenes with Nucleophiles

---

**a) Representative Fluorine Retentive Reactions of gem-Difluoroalkenes with Alcohols**

\[
\begin{align*}
\text{MeO} & \quad \text{NaBH}_4 \\
\text{N} & \quad \text{EtOH} \\
\text{MeO} & \quad \text{OEt}
\end{align*}
\]

**b) Fluorine-Retentive Nucleophilic Addition of 3-Hydroxypyridine to gem-Difluoroalkenes**

\[
\begin{align*}
\text{F} & \quad \text{Li}_2\text{CO}_3 \\
\text{F} & \quad \text{DMF, R.T.} \\
\text{F} & \quad \text{86\%} \\
\text{F} & \quad 14\%
\end{align*}
\]

**c) Rare Fluorine-Retentive Cyclization Reactions of gem-Difluoroalkenes**

\[
\begin{align*}
\text{NC} & \quad \text{I}_2 \\
\text{CO}_2\text{H} & \quad \text{MeCN, 52 °C} \\
\text{O} & \quad \text{86\%}
\end{align*}
\]

**d) \(\beta\)-Anion Propogation Prevents Fluoride Elimination**

\[
\begin{align*}
\text{Ph} & \quad \text{MsOH} \\
\text{Me} & \quad \text{CH}_2\text{Cl}_2 \\
\text{Ph} & \quad \text{HO}
\end{align*}
\]

**e) Intramolecular Trapping of \(\beta\)-Anion with Aldehyde Preventing Fluoride Elimination**

\[
\begin{align*}
\text{O}_2\text{N} \quad \text{DBU} \\
\text{HO} \quad \text{DMF} \\
\text{O}_2\text{N}
\end{align*}
\]
Other rare examples of fluorine-retentive nucleophilic addition of alcohols to difluoroalkenes exploit difunctionalization with strong oxidants or unique reagents. Cyclizations of *gem*-difluoroalkenes with O-based nucleophiles in the presence of either iodine\textsuperscript{14,25} or mercury and a tin-hydride\textsuperscript{25b} proceed without the loss of fluoride (Scheme 3-2c). Two examples utilize elegant reagent design to enable fluorine-retentive intermolecular O-based nucleophilic addition to *gem*-difluoroalkenes. In the first, electrophiles were designed with the strategic incorporation of a \(\gamma\)-epoxide. The \(\beta\)-anion preferentially opens the epoxide instead of eliminating fluoride, enabling fluorine retentive nucleophilic addition (Scheme 3-2d).\textsuperscript{26} In the second example, specially designed nucleophiles position an aldehyde proximal to the \(\beta\)-anion, rapidly trapping the \(\beta\)-anionic intermediate via intramolecular cyclization after nucleophilic addition, retaining both fluorine atoms (Scheme 3-2e).\textsuperscript{27} However, general examples of such “fluorine-retentive” nucleophilic hydro-functionalization reactions of *gem*-difluoroalkenes remain elusive.

3.2. Organocatalytic Strategy for Hydrophenolation of *gem*-Difluoroalkenes

After the successful hydrofunctionalization of *gem*-difluoroalkenes with thiol-based nucleophiles,\textsuperscript{28} we envisioned that, due to the similar properties of sulfur and oxygen, *gem*-difluoroalkenes might undergo fluorine-retentive hydrofunctionalization with alcohols under similar conditions. However, alcohol nucleophiles present a greater challenge than thiol nucleophiles, as alcohols possess both lower nucleophilicity\textsuperscript{29} and lower acidity\textsuperscript{30} than the corresponding thiols (Figure 3-4).
**Figure 3-4:** The Physicochemistry of Alcohols Presents a Greater Challenge than Thiols

<table>
<thead>
<tr>
<th></th>
<th>Swain-Scott Nucleophilicity ($s$)</th>
<th>Acidity $pK_a$ (H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Methyl-S]</td>
<td>6.95</td>
<td>![Methyl-SH]</td>
</tr>
<tr>
<td>![Phenol-O]</td>
<td>5.75</td>
<td>![Phenol-OH]</td>
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</tbody>
</table>

Even with these challenges, we envisioned that employing alcohols in a nucleophilic hydrofunctionalization of *gem*-difluoroalkenes would enable access to an underrepresented bioactive fluorinated functional group. Thus, to complement the fluorine-retentive, organocatalytic nucleophilic hydrofunctionalization reactions of *gem*-difluoroalkenes with thiols, we developed a new organocatalytic system to regioselectively add phenols across *gem*-difluoroalkenes that minimizes the loss of fluoride (Scheme 3-3).
Scheme 3-3: Extension of Hydrofunctionalization Reactions of *gem*-Difluoroalkenes to Phenol Nucleophiles

*a) Organocatalytic Hydrothiophenolation*

\[
\text{F}_2\text{C} = \text{CH} + \text{HS} \text{C}_6\text{H}_4\text{R}^2 \xrightarrow{\text{5\% TMG}} \text{F}_2\text{C} = \text{SCH}_2 \text{C}_6\text{H}_4\text{R}^2 \quad \text{vs.} \quad \text{F}_2\text{C} = \text{C} = \text{CH}_2 \text{C}_6\text{H}_4\text{R}^2
\]

\[
70-100 \degree \text{C, 1,2-DCE}
\]

*b) This Work: Organocatalytic Hydrophenolation*

\[
\text{F}_2\text{C} = \text{CH} + \text{HO} \text{C}_6\text{H}_4\text{R}^2 \xrightarrow{\text{Base Cat.}} \text{F}_2\text{C} = \text{C} = \text{CHO} \text{C}_6\text{H}_4\text{R}^2 \quad \text{vs.} \quad \text{F}_2\text{C} = \text{C} = \text{CH}_2 \text{C}_6\text{H}_4\text{R}^2
\]

Standard optimization delivered conditions for adding phenolic nucleophiles across *gem*-difluoroalkenes (Table 3-1). Initially, we explored similar conditions to those used for functionalization with aryl thiols [entry 1: 25% TMG, 1,2-dichloroethane (1,2-DCE), 80 °C]; however, using these conditions, phenolic nucleophiles reacted poorly, giving no yield of the desired β,β-difluorophenethylarylether product 3.3 or the α-monofluorovinylether side product 3.4. Utilizing the same catalyst with a higher boiling solvent and higher temperatures provided low yield and moderate selectivity of 3.3 (entry 2). Considering the intrinsic differences in acidity and nucleophilicity between phenolic and thiophenolic nucleophiles, we explored the use of stronger bases, such as iBuOK (entry 3), 1,8-diazabicyclo[5.4.0]undec-7ene (DBU, entry 4), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, entry 5). Use of the stronger nitrogenous bases improved the yields of product 3.3, but did not greatly increase selectivity, while the inorganic iBuOK selectively delivered
3.4. The use of stronger phosphorazine superbases reduced the selectivity versus α-monofluorovinylether side product 3.4 (entry 6), presumably due to deprotonation and β-fluoride elimination of desired product 3.4. The use of aromatic solvents provided improved selectivity versus other solvents (entries 3, 7–12), while increased temperature improved the yield (entries 14–16). We envisioned that, similar to cation-π catalysis reactions, the judicious selection of solvent might enable anion-π stabilization of the unstable β-anionic intermediate, slowing elimination. As such, we investigated a variety of aromatic solvents with different electronic character. However, these solvents did not alter the selectivity or yield, indicating no anion-π stabilization (entries 2, 9-11). Finally, we settled on the use of 50% TBD in 1,2-dichlorobenzene (DCB) at 140 °C for 24 h as the standard conditions (entry 17). In control reactions, subjecting pure 3.3 to the optimized conditions generated mixtures of 3.3:3.4, indicating that the product is unstable to the reaction conditions. Thus, for any specific substrate, optimization of the time, temperature, and strength of base might improve the reaction outcome.
Table 3-1: Optimization of the Reaction Conditions\textsuperscript{[a]}

\[
\begin{array}{cccccc}
\text{Entry} & \text{Base} & \text{pK}_a^{[b]} & \text{Solv.} & \text{Conv.} & \text{3.3} & \text{3.4} \\
\hline
1^{[c]} & \text{TMG} & 16 & \text{DCE} & 40 & 0 & 0 \\
2 & \text{TMG} & 16 & (\text{NO}_2)\text{C}_6\text{H}_5 & 40 & 22 & 9 \\
3^{[d]} & \text{tBuOK} & \text{N/D} & (\text{NO}_2)\text{C}_6\text{H}_5 & 39 & 7 & 25 \\
4^{[d]} & \text{DBU} & 17 & (\text{NO}_2)\text{C}_6\text{H}_5 & 30 & 15 & 7 \\
5 & \text{TBD} & 21 & (\text{NO}_2)\text{C}_6\text{H}_5 & 83 & 46 & 14 \\
6 & \text{P}_2\text{Et} & 25 & (\text{NO}_2)\text{C}_6\text{H}_5 & 72 & 33 & 19 \\
7 & \text{TMG} & 16 & \text{DMF} & 84 & 18 & 30 \\
8 & \text{TMG} & 16 & \text{DMSO} & 98 & 6 & 64 \\
9 & \text{TMG} & 16 & \text{o-Xylene} & 65 & 16 & 3 \\
10 & \text{TMG} & 16 & \text{Benzonitrile} & 67 & 36 & 18 \\
11 & \text{TMG} & 16 & \text{DCB} & 56 & 18 & 3 \\
12 & \text{TBD} & 21 & \text{DCB} & 90 & 53 & 10 \\
13 & \text{TBD} & 21 & \text{DCB} & 89 & 61 & 11 \\
14^{[e]} & \text{TBD} & 21 & \text{DCB} & 63 & 31 & 5 \\
15^{[d,e]} & \text{TBD} & 21 & \text{DCB} & >99 & 70 & 17 \\
16^{[e,f]} & \text{TBD} & 21 & \text{DCB} & >99 & 60 & 17 \\
17^{[g]} & \text{TBD} & 21 & \text{DCB} & >99 & 60 & 17 \\
\end{array}
\]

\[
\text{Ar} = 3,4,5-(\text{OMe})_3\text{C}_6\text{H}_2
\]

\[
\text{3.1} + \text{3.2} \xrightarrow{\text{Base}} \text{3.3} \quad \text{or} \quad \text{3.4}
\]

\[
\text{19}^\text{F NMR analysis using } \alpha,\alpha,\alpha-\text{trifluorotoluene (TFT) as a standard (10 } \mu\text{L, 0.080 mmol)}.
\]

[a] 3.1 (1.0 equiv., 0.10 mmol), 3.2 (5.0 equiv., 0.50 mmol), base (0.25 equiv., 0.025 mmol), solvent (1 M, 0.10 mL), 120 °C, for 4 h under an N\textsubscript{2} atmosphere. Conversion of 3.1 and yields of 3.3 and 3.4 were determined by 19\textsuperscript{F} NMR analysis using \(\alpha,\alpha,\alpha\)-trifluorotoluene (TFT) as a standard (10 \muL, 0.080 mmol). [b] pK\textsubscript{a} in THF.\textsuperscript{[31]} [c] 80 °C. [d]
100 °C. [e] 0.50 equiv. base. [f] 140 °C. [g] 3.1 (1.0 equiv., 0.50 mmol), 3.2 (5.0 equiv., 2.50 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (1 M, 1.0 mL), 140 °C, for 24 h under an N₂ atmosphere.

Using these conditions, a range of phenols were successfully added across gem-difluoroalkenes (Scheme 3-4). Reactions of various electron-deficient phenols (3.6a–f) gave the desired β,β-difluorophenethyl arylethers (3.6) in good yields (>65%) and high selectivities (>7:1) versus the α-monofluorovinylether side products (3.7). Using the standard reaction conditions, electron-neutral and ortho-substituted phenols (3.3, 3.6g–j) delivered the β,β-difluorophenethyl arylethers in moderate to low yields (30–50%) and selectivities (2:1–4:1). Reactions of electron-rich phenols delivered the anticipated products in low yields and selectivities (3.6k–l), although reoptimization of the base might improve the reactivity of these less acidic substrates. I suggest investigating three pathways. First, the more electron-rich phenols are less acidic, thus slightly stronger amine bases such as Verdake's superbase or some of the weaker phosphorazaine superbases might improve these substrates. Second, exploiting biphasic conditions similar to those for electron-deficient difluoroalkenes might improve the reactions with electron-rich phenols, although many electron-rich or -neutral difluoroalkenes do not demonstrate improved selectivity in biphasic conditions. Third, a full reoptimization to exploit more complex, Lewis acid / base pairs such as the pyridine / LiOTf catalyst used for alkyl thiol nucleophiles in Chapter 2 might improve the reaction. A range of useful functional groups for further functionalization were tolerated, like halides (3.6c–f) and nitrogen based functional groups (3.6a–b), although an aniline-derived phenol (3.6l) was
a poor substrate. Furthermore, heteroaryl and aliphatic alcohols did not exhibit any addition to the gem-difluoroalkene electrophile, providing an avenue for further research.

**Scheme 3-4: Scope of Phenol Nucleophiles**
Standard conditions: 3.1 (1.0 equiv., 0.50 mmol), 3.5a–o (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.5 M, 1.0 mL), 140 °C, for 24 h under an N₂ atmosphere. The selectivity of 3.6:3.7 was determined by ¹⁹F NMR analysis of the crude reaction mixture using TFT (50 µL, 0.40 mmol) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [a] 1.0 equiv. TBD. [b] Contains trifluoroethylbenzene side product.

Many synthetically and biomedically useful functional groups were tolerated on the gem-difluoroalkene substrate (Scheme 3-5). Specifically, the reaction tolerated thioethers and ethers (3.9a–b), morpholine (3.9c), nitrogen-containing functional groups (3.9k–l), halides (3.9m–p) amides (3.9q), and pseudohalides (3.9r). Reactions of electron-rich gem-difluoroalkenes generally afforded products in good yields and high selectivities (3.9a–i), although aniline-based and tBu-based gem-difluoroalkenes reacted in lower yields (3.9e–f). Using electron-deficient substrates, the standard reaction conditions generally delivered products in low yield and <1:1 selectivity (3.9j–r), although substrates bearing 3-α,β-unsaturated carbonyl and 3-NO₂ groups afforded products in sufficient yield and selectivity (3.9j, k). To address this limitation, further optimization revealed that a biphasic reaction mixture (9:1 DCB:H₂O) improved both the selectivities and yields for electron-deficient gem-difluoroalkenes (3.9l–r). However, this modification provided only minor benefits for electron-rich and -neutral difluoroalkenes. Presumably for these electron-deficient substrates, the water in the biphasic system (1) provided additional protons to quench the reactive β-fluoroanion, and/or (2) minimized degradation of the product by sequestering some of the base in the aqueous phase. Ortho-substituted gem-difluoroalkenes reacted inconsistently, with a 2-(4-tBu)-Ph-substituted substrate
giving high yield (3.9d), a 2-Me-substituted substrate reacting in low yield and low conversion (3.9h), and a 2,6-\textsubscript{Me}\textsubscript{2}-substituted substrate not reacting at all (3.9i).
Scheme 3-5: Scope of *gem*-Difluoroalkene Electrophiles

\[ RCH_2\text{F} + HO-Ar \rightarrow RCH(OAr)_2 \]

[a] 50% TBD  
140 °C, DCB  
\( N_2 \), 24 h  

[b] 50% TBD  
140 °C, DCB:H\(_2\)O  
\( N_2 \), 24 h  

\( Ar = 2,4-\text{Cl}_2\text{-C}_6\text{H}_3 \)
[a] Standard conditions: 3.8a–r (1.0 equiv., 0.50 mmol), 3.5c (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.5 M, 1.0 mL), 140 °C, for 24 h under an N₂ atmosphere. The selectivity of 3.9:3.10 was determined by ¹⁹F NMR analysis of the crude reaction mixture using TFT (50 µL, 0.40 mmol) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [b] Standard conditions: 3.8a–r (1.0 equiv., 0.50 mmol), 3.5c (3.0 equiv., 1.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.45 M, 0.90 mL), H₂O (0.05 M, 0.10 mL), 140 °C, for 24 h under an N₂ atmosphere. The selectivity of 3.9:3.10 was determined by ¹⁹F NMR analysis of the crude reaction mixture using TFT (50 µL, 0.40 mmol) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [c] 4-Bromophenol used as the nucleophile. [d] Yield is reported from ¹⁹F analysis of the crude reaction mixture. [e] Second run used 0.40 mmol of 3.9q. [f] Second run used 0.30 mmol of 3.9r.

Heteroaryl-substituted gem-difluoroalkenes reacted similarly to their aryl-derived counterparts (Scheme 3-6). Electron-rich heteroaryl groups, such as indole and pyrazole, gave high selectivity (3.12a, b), although the yield of pyrazole 3.12b was moderate. A 2-substituted dibenzothiophene reacted in moderate yield and selectivity (3.12c). When subjected to the biphasic conditions, a pyridyl substrate gave good yield and selectivity (3.12d). This series of reactions also highlighted the compatibility of sulfonamide (3.12a) and acetal (3.12d) protecting groups. Notably, the reaction did not tolerate Boc protecting groups.
Scheme 3-6: Scope of Heteroaryl gem-Difluoroalkene Electrophiles

![Chemical Structures]

[a] Standard conditions: 3.11a–d (1.0 equiv., 0.50 mmol), 3.5c (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.5 M, 1.0 mL), 140 °C, for 24 h under an N₂ atmosphere. The selectivity of 3.12:3.13 was determined by ¹⁹F NMR analysis of the crude reaction mixture using TFT (50 µL, 0.40 mmol) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs. [b] Standard conditions: 3.11a–d (1.0 equiv., 0.50 mmol), 3.5c (3.0 equiv., 1.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.45 M, 0.90 mL), H₂O (0.05 M, 0.10 mL), 140 °C, for 24 h under an N₂ atmosphere. The selectivity of 3.12:3.13 was determined by ¹⁹F NMR analysis of the crude reaction mixture using TFT (50 µL, 0.40 mmol) as a standard and is reported in parentheses. Yields are reported as the isolated yield of >95% pure material and represent the average of 2 runs.
3.3. Mechanistic Considerations

The present reaction presumably operates through an addition / protonation sequence, in which the base plays key roles as both a promoter and a quencher of the reaction (Figure 3-5). Initially, organic base (B) activates the phenol pronucleophile, and subsequently, the phenoxide nucleophile adds to the electrophilic difluorinated carbon of the gem-difluoroalkene. This addition generates an unstable β-fluoro anionic intermediate (A) that can react via two pathways. First, intermediate (A) can either accept a proton from the phenol pronucleophile or from the protonated organic base (B) to provide the desired product 3.3. Second, fluoride elimination from anionic intermediate (A) can provide the undesired monofluoroalkene 3.4. Alternatively, 3.4 can form via base-mediated elimination of HF from 3.3.

Based on this presumed mechanism, the pK_a of the base catalyst must fall within a narrow range to selectively provide 3.3 over 3.4. The base catalyst must be sufficiently basic to deprotonate the phenol. In THF, a non-coordinating aprotic solvent, phenol’s pK_a of 18 disfavors deprotonation by weaker bases, such as TMG (pK_a = 16), although stronger bases, such as TBD (pK_a = 21), efficiently deprotonate and activate the phenol. However, bases that are too strong will decompose product 3.3 to generate 3.4. Specifically, the strong σ-electron withdrawing effect of the gem-difluoro group and ethereal oxygen activates 3.3 for elimination. Such deprotonation was observed in control experiments involving the base-mediated decomposition of 3.3, particularly with strong “superbases,” such as the phosphorazine base P_2Et (pK_a = 25). Therefore, in the present studies, TBD provided appropriate reactivity, specifically balancing activation of the
phenol with decomposition of product. However, we note that other currently unexplored bases might also work for this reaction. Further, for any specific substrate combination with distinct pKₐs of the phenol and product, an alternate base might prove optimal.

**Figure 3-5: Proposed Mechanism**

3.4. Conclusions

In conclusion, we developed an organocatalytic method to convert *gem*-difluoroalkenes to β,β-difluorophenethyl ethers through the direct nucleophilic addition of phenols. Our convergent method uses easily accessible starting materials, adding phenol nucleophiles across *gem*-difluoroalkenes in the presence of only catalytic quantities of a weak amine base and delivering the desired products in moderate to good yields and selectivities. This contrasts the classical syntheses of such products, that are either non-
convergent, relying on functional group interconversions\textsuperscript{7, 32} to generate the fluorine-based substructure, or require harsh conditions\textsuperscript{33} and/or gaseous reagents\textsuperscript{8}. Notably, this method contrasts the many reactions of gem-difluoroalkenes that selectively generate monofluoroalkene products\textsuperscript{1h}. Moreover, the reaction tolerates many useful functional groups, both for further functionalization and for medicinal chemistry. Ongoing efforts aim to enable the fluorine-retentive addition other nucleophiles to gem-difluoroalkenes, and to expand the hydrophenolation of gem-difluoroalkenes to include aliphatic and secondary gem-difluoroalkenes.
3.5. References for Chapter 3


4. (a) Huchet, Q. A.; Trapp, N.; Kuhn, B.; Wagner, B.; Fischer, H.; Kratochwil, N. A.; Carreira, E. M.; Muller, K., Partially fluorinated alkoxy groups - Conformational adaptors to changing environments. *J. Fluorine Chem.* **2017**, *198*, 34-46; (b) Xing, L.; Blakemore,


Chapter 3 Appendix

Experimental Procedures and Spectra for Compounds in Chapter 3
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**General Considerations:** Unless otherwise noted, reactions were performed under an atmosphere of air using oven-dried glassware. Organocatalytic reactions of phenols and gem-difluoroalkenes were performed in one-dram borosilicate glass scintillation vials sealed with a screw-top cap containing a PTFE-lined septum. Unless otherwise noted all other reactions were performed in round-bottom flasks sealed with rubber septa. PTFE syringes equipped with stainless-steel needles were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by either $^{19}$F NMR with an internal standard of $\alpha,\alpha,\alpha$-trifluorotoluene or by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualized by quenching of fluorescence. Normal phase column chromatography was conducted using an automated separations system utilizing gradient elution with VWR Common Silica Gel 60 Å, 40–60 µm. Reverse phase column chromatography was conducted using an automated flash chromatography system utilizing gradient elution with a Teledyne ISCO C18 Redisep Rf Gold 50 g column. Isolated yields reported in the manuscript represent an average of at least 2 independent runs of final compound deemed to be at least 95% pure by NMR. Yields reported in the supporting information refer to a single experiment. Unless otherwise noted, compounds were isolated in >98% purity as determined by $^1$H and $^{19}$F NMR.

Unless otherwise noted, reagents were purchased from commercial sources and used as received. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was purchased from Sigma Aldrich. Solvents, including dimethylformamide (DMF), toluene (PhMe), dichloromethane (DCM), methanol (MeOH), acetonitrile (MeCN), and tetrahydrofuran (THF) were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon. Chemical abbreviations utilized in this
document include: 1,2-Dichlorobenzene (DCB), N-methylpyrroolidine (NMP), α,α,α-trifluorotoluene (TFT), sodium sulfate (Na₂SO₄), magnesium sulfate (MgSO₄), ethyl acetate (EtOAc), diethyl ether (Et₂O), ammonium chloride (NH₄Cl), n-butyllithium (n-BuLi), sodium hydroxide (NaOH), room temperature (R.T.), t-butyll carbonate anhydride (Boc₂O), potassium carbonate (K₂CO₃), and hydrochloric acid (HCl).

Proton nuclear magnetic resonance (¹H NMR) and fluorine nuclear magnetic resonance (¹⁹F NMR) were taken on a Bruker DRX 500 spectrometer (500 and 376 MHz respectively). Fluorine nuclear magnetic resonance (¹⁹F NMR) was taken on a Bruker AVIII 400 Avance spectrometer (376 MHz). Proton and carbon nuclear magnetic resonance (¹³C NMR) were taken on a Bruker AVIII 500 Avance spectrometer with a CPDUL cryoprobe (500 and 126 MHz respectively). Chemical shifts (δ) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to the proton resonance of residual solvent in the NMR solvent (CHCl₃: δ = 7.26 ppm; DMSO: δ = 2.50 ppm). Chemical shifts (δ) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonance of the solvent residual peak (CDCl₃: δ = 77.2 ppm; DMSO: δ = 39.52 ppm). Chemical shifts for fluorine are reported in ppm upfield from trichlorofluoromethane (0 ppm), and are referenced to added TFT as a standard (δ = −63.77 ppm) unless otherwise specified. NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, 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-hexanes/PhMe) on a Waters Q-Tof Premier™, for which
sample plus near mass internal exact mass standard were dissolved in hexanes, and hexanes or PhMe/hexanes were used as ionization solvent. Infrared spectra were measured on a Perkin Elmer Spectrum Two Fourier Transform Infrared Spectrometer by drying samples on a diamond ATR Sample base plate. Uncorrected melting points were measured on a Thomas Hoover Capillary Melting Point apparatus.

**General Procedure for the Preparation of Gem-Difluoroalkenes (A):** An oven-dried 3-neck round-bottomed flask equipped with a magnetic stir bar was charged with aryl aldehyde (1.0 equiv.) and triphenylphosphine (1.2 or 1.5 equiv.). The system was sealed with three PFTE septa, and subsequently evacuated and backfilled with N₂ three times. Dry NMP was added via syringe transfer (PTFE syringe with oven-dried stainless-steel needle), and the system was immersed in a preheated 100 °C oil bath. Once no solid reagents remained (approximately 2 min of heating), potassium bromodifluoroacetate (1.5 or 1.8 equiv.) was added portion-wise over 0.5 h, with the rate of addition controlling the evolution of CO₂ gas. Once all of the potassium bromodifluoroacetate was added, the solution was allowed to stir for 0.5–1 h. Upon completion, the reaction was cooled to R.T. and then quenched with H₂O. Subsequently, Et₂O was added to the reaction, and the mixture was washed with H₂O (five times), and the aqueous layer was back-extracted with Et₂O (two times). The combined organic layers were dried over Na₂SO₄ and concentrated. The crude material was dry-packed onto silica gel and then eluted through a plug of silica gel with EtOAc:hexanes (1:1) to remove triphenylphosphine oxide. Subsequently, H₂O₂ (30% in H₂O) was added to the mother
liquor and allowed to react for 30 min to oxidize the residual triphenylphosphine. The organic layer was washed with H\textsubscript{2}O (three times), dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated, and subjected to normal phase flash chromatography using EtOAc and hexanes.

**Preparation of Gem-Difluoroalkenes:**

5-(2,2-difluorovinyl)-1,2,3-trimethoxybenzene (3.1): Compound 3.1 corresponds to compound 2.1 in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

1-(2,2-difluorovinyl)-4-methoxybenzene (3.8a): Compound 3.8a corresponds to compound 2.5a in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
(4-(2,2-difluorovinyl)phenyl)(methyl)sulfane (3.8b): Compound 3.8b corresponds to compound 2.5b in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

4-(3-(2,2-difluorovinyl)phenyl)morpholine (3.8c): Compound 3.8c corresponds to compound 2.5d in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
4′-(tert-butyl)-2-(2,2-difluorovinyl)-1,1′-biphenyl (3.8d): Compound 3.8d corresponds to compound 2.5g in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

![Diagram of 3.8e](image)

4-(2,2-difluorovinyl)-N,N-dimethylaniline (3.8e): Compound 3.8e corresponds to compound 2.5e in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

![Diagram of 3.8f](image)

1-(tert-butyl)-4-(2,2-difluorovinyl)benzene (3.8f): Following General Procedure A, 4-tert-butylbenzaldehyde (3.34 mL, 20mmol) was reacted with PPh₃ (6.3 g, 24 mmol) and BrCF₂CO₂K (6.2 g, 30 mmol) in NMP (10 mL, 2 M). Following workup, the product was purified by flash chromatography using a gradient of 0–50% Et₂O in pentane, furnishing 1.16 g of desired product 3.8f (30% yield) as a colorless oil; ¹H NMR matched the previously reported spectrum.¹
1-(2,2-difluorovinyl)-3,5-dimethylbenzene (3.8g): Following General Procedure A, 3,5-dimethylbenzaldehyde (2.10 mL, 15.0 mmol) was reacted with PPh₃ (6.23 g, 22.5 mmol) and BrCF₂CO₂K (6.05 g, 27.0 mmol). Following workup, the product was purified by flash chromatography using a gradient of 0–10% EtOAc in hexanes, furnishing 1.163 g (44% yield) of desired product 3.8g as a clear oil.

**¹H NMR** *(400 MHz, CDCl₃):* δ 6.97 (bs, 2 H), 6.90 (bs, 1 H), 5.21 (dd, *J* = 26.41, 4.03 Hz, 1H), 2.32 (s, 6 H)

**¹³C NMR** *(126 MHz, CDCl₃):* δ 156.3 (dd, *J* = 298.23, 287.44 Hz), 138.3, 130.3 (t, *J* = 6.70 Hz), 128.9 (t, *J* = 2.15 Hz), 125.6 (dd, *J* = 6.56, 3.67 Hz), 82.3 (dd, *J* = 28.88, 13.63 Hz), 21.4

**¹⁹F NMR** *(376 MHz, CDCl₃):* δ −82.39 (dd, *J* = 32.54, 26.54 Hz, 1 F), −84.62 (dd, *J* = 32.49, 3.99 Hz, 1F)

**IR (film):** 3019, 2921, 2868, 1726, 1605, 1448, 1379, 1350, 1297, 1198, 1160, 1038, 965, 892, 851, 814, 765, 750, 715, 690, 583, 539, 515 cm⁻¹

**HRMS (HAPCl⁺):** calc. for C₁₀H₁₀F₂ (M⁺) 168.0751, found 168.0744, 4.2 ppm.
1-(2,2-difluorovinyl)-2,4-dimethylbenzene (3.8h): Following General Procedure A, 2,4-dimethylbenzaldehyde (3.20 mL, 22.0 mmol) was reacted with PPh\(_3\) (8.84 g, 33.0 mmol) and BrCF\(_2\)CO\(_2\)K (8.76 g, 40.0 mmol). Following workup, the product was purified by flash chromatography using a gradient of 0–10% EtOAc in hexanes, furnishing 1.57 g (41% yield) of desired product 3.8h as a clear oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.31\) (dd, \(J = 8.44, 2.00\) Hz, 1 H), \(7.02\) (dd, \(J = 4.24, 2.31\) Hz, 2 H), \(5.34\) (dd, \(J = 25.61, 3.94\) Hz, 1 H), 2.32 (s, 3 H), 2.27 (s, 3 H)

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta 156.2\) (dd, \(J = 295.18, 288.05\) Hz), 137.2, 135.8 (dd, \(J = 4.84, 1.67\) Hz), 131.1, 128.1 (dd, \(J = 7.88, 1.99\) Hz), 127.0, 126.0 (dd, \(J = 6.89, 4.94\) Hz), 79.3 (dd, \(J = 28.66, 14.94\) Hz), 21.2, 20.0

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta -84.76\) (dd, \(J = 33.14, 4.06\) Hz, 1 F), \(-85.53\) (ddd, \(J = 33.09, 25.53, 1.83\) Hz, 1 F)

IR (film): 2923, 1726, 1616, 1569, 1505, 1453, 1379, 1345, 1281, 1250, 1235, 1180, 1111, 1074, 1037, 948, 917, 876, 836, 818, 765, 750, 721, 615, 581, 549, 534 cm\(^{-1}\)

HRMS (HAPCl\(+\)): calc. for C\(_{10}\)H\(_{10}\)F\(_2\) (M\(^+\)) 168.0751, found 168.0745, 3.6 ppm.
2-(2,2-difluorovinyl)-1,3-dimethylbenzene (3.8i): Following General Procedure A, 2,6-dimethylbenzaldehyde (2.2 mL, 15.0 mmol) was reacted with PPh$_3$ (5.91 g, 22.5 mmol) and BrCF$_2$CO$_2$K (6.17 g, 27.0 mmol). Following workup, the product was purified by flash chromatography using a gradient of 0–10% EtOAc in hexanes, furnishing 0.763 g (28% yield) of desired product 3.8i as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.14 (dd, $J = 8.57$, 6.35 Hz, 1 H), 7.07 (d, $J = 7.53$ Hz, 2 H), 5.23 (dd, $J = 27.50$, 2.26 Hz, 1 H), 2.29 (s, 6 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): 155.0 (q, $J = 291.73$, 288.36 Hz), 137.5 (dd, $J = 2.57$, 1.37 Hz), 127.8, 127.6, 78.1 (dd, $J = 27.32$, 20.62 Hz), 20.5 (d, $J = 2.42$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –83.38 (dd, $J = 32.45$, 26.96 Hz, 1 F), –87.16 (dd, $J = 33.11$, 2.37 Hz, 1 F)

IR (film): 3024, 2956, 2923, 2330, 1736, 1586, 1468, 1445, 1380, 1329, 1276, 1254, 1222, 1166, 1096, 1032, 932, 850, 802, 768, 746, 698, 599, 537 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{10}$H$_{10}$F$_2$ (M) 168.0751, found 168.0741, 1.0 mmu.
**ethyl (E)-3-(3-(2,2-difluorovinyl)phenyl)acrylate (3.8j):** Compound 3.8j corresponds to compound 2.5j in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

**1-(2,2-difluorovinyl)-3-nitrobenzene (3.8k):** Compound 3.8k corresponds to compound 2.5n in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

**3-(2,2-difluorovinyl)benzonitrile (3.8l):** Following General Procedure A, 3-cyanobenzaldehyde (6.55 g, 50mmol) was reacted with PPh₃ (15.75 g, 60 mmol) and BrCF₂CO₂K (15.97 g, 75 mmol) in NMP (25 mL, 2 M). Following workup, the product was
purified by flash chromatography using a gradient of 0–50% Et₂O in pentane, furnishing 4.41 g of desired product 3.8l (53% yield) as a colorless oil; ¹H NMR matched the previously reported spectrum.¹

1-bromo-4-(2,2-difluorovinyl)benzene (3.8m): Following General Procedure A, 4-bromobenzaldehyde (3.7 g, 20 mmol) was reacted with PPh₃ (6.3 g, 24 mmol) and BrCF₂CO₂K (6.2 g, 30 mmol) in NMP (10 mL, 2 M). Following workup, the product was purified by flash chromatography using a gradient of 0–50% Et₂O in pentane, furnishing 2.61 g of desired product 3.8m (60% yield) as a colorless oil; ¹H NMR matched the previously reported spectrum.¹

1-(2,2-difluorovinyl)-2-iodobenzene (3.8n): Compound 3.8n corresponds to compound 2.5i in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
1-(2,2-difluorovinyl)-3-(trifluoromethyl)benzene (3.8o): Following General Procedure A, 3-trifluoromethylbenzaldehyde (2.7 mL, 20 mmol) was reacted with PPh₃ (6.3 g, 24 mmol) and BrCF₂CO₂K (6.2 g, 30 mmol) in NMP (10 mL, 2 M). Following workup, the product was purified by flash chromatography using a gradient of 0–50% Et₂O in pentane, furnishing 2.070 g of desired product 3.8o (50% yield) as a colorless oil; ¹H NMR matched the previously reported spectrum.¹

1,3-dichloro-5-(2,2-difluorovinyl)benzene (3.8p): Compound 3.8p corresponds to compound 2.5l in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
4-(2,2-difluorovinyl)-N,N-diisopropylbenzamide (3.8q): Following General Procedure A, compound 3.8q–1 (0.823, 3.60 mmol) was reacted with PPh₃ (1.50 g, 5.30 mmol) and BrCF₂CO₂K (1.42 g, 6.50 mmol) in NMP (2.0 mL, 2 M). Following workup, the product was purified by flash chromatography using a gradient of 0–30% EtOAc in hexanes, furnishing 0.655 g (69% yield) of desired product 3.8q as a colorless solid (MP = 43–44 °C).

**¹H NMR (500 MHz, DMSO-D₆, 25 °C):** δ 7.41 (d, J = 8.09 Hz, 2 H), 7.29 (d, J = 8.21 Hz, 2 H), 5.85 (dd, J = 28.05, 4.06 Hz, 1 H), 3.61 (bs, 2.04, 2 H), 1.38–1.15 (m, 12 H)

**¹H NMR (500 MHz, DMSO-D₆, 60 °C):** δ 7.41 (d, J = 7.92 Hz, 2 H), 7.28 (d, J = 7.89 Hz, 2 H), 5.79 (dd, J = 27.83, 4.01 Hz, 1 H), 3.64 (hept, J = 6.41 Hz, 2 H), 1.28 (bs, 12 H)

**¹³C NMR (126 MHz, DMSO-D₆, 60 °C):** δ 169.8, 156.1 (dd, J = 297.83, 286.17 Hz), 138.2 (t, J = 2.29 Hz), 130.5 (dd, J = 7.75, 5.77 Hz), 128.1 (dd, J = 6.61, 3.79 Hz), 126.3, 82.3 (dd, J = 29.45, 11.75 Hz), 20.9

**¹⁹F NMR (376 MHz, DMSO-D₆, 25 °C):** δ –82.16 (dd, J = 32.14, 28.07 Hz, 1 F), –84.02 (dd, J = 32.19, 4.05 Hz, 1 F)

**IR (film):** 3434, 2252, 2126, 1729, 1660, 1345, 1276, 1052, 1024, 1005, 822, 760, 623 cm⁻¹
HRMS (ESI+): calc. for C\textsubscript{15}H\textsubscript{20}F\textsubscript{2}NO (M+H) 268.1513, found 268.1500, 1.3 mmu.

4-(2,2-difluorovinyl)phenyl trifluoromethanesulfonate (3.8r): Compound 3.8r corresponds to compound 2.5f in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

3-(2,2-difluorovinyl)-1-tosyl-1\textit{H}-indole (3.11a): Compound 3.11a corresponds to compound 2.8a in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
4-(2,2-difluorovinyl)-1-phenyl-1H-pyrazole (3.11b): Compound 3.11b corresponds to compound 2.8c in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

![Image of 3.11c](image)

4-(2,2-difluorovinyl)dibenzo[b,d]thiophene (3.11c): Compound 3.11c corresponds to compound 2.8d in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

![Image of 3.11d](image)

2-(3-(2,2-difluorovinyl)phenyl)-5-(1,3-dioxolan-2-yl)pyridine (3.11d): Compound 3.11d corresponds to compound 2.8b in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
General Procedure for the Organocatalyzed Addition of Phenols to Gem-Difluoroalkenes (B-1): An oven-dried one-dram vial equipped with a magnetic stir bar was charged with 1.0 equivalent of difluoroalkene and 5.0 equivalents of phenol. The system was brought into a glovebox, and 0.50 equivalents of TBD were added. Dry DCB (1.0 mL) was added via syringe transfer (PTFE syringe with oven-dried stainless-steel needle), and the vial was sealed with a screw-top cap containing a PTFE-lined septum. The system was removed from the glovebox, and placed within a heating mantle preheated to 140 °C and stirred for 24 h. The reaction was cooled to R.T., and then standardized by adding 50 µL (0.40 mmol) of TFT. The mixture was diluted with DCM, and then stirred for 5 min. The reaction was analyzed by $^{19}$F NMR, and then washed 3X with 1 N NaOH (aq.). The combined aqueous layer was extracted 2X with DCM, and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was loaded onto celite and then purified by flash reverse phase chromatography with gradient elution from 98% H$_2$O in MeCN to 100% MeCN to provide the desired product in >95% purity.

General Procedure for the Organocatalyzed Addition of Phenols to Gem-Difluoroalkenes (B-2): An oven-dried one-dram vial equipped with a magnetic stir bar was charged with 1.0 equivalent of difluoroalkene and 3.0 equivalents of phenol. The system was brought into a glovebox, and 0.50 equivalents of TBD were added. Dry DCB (0.90 mL) was added via syringe transfer (PTFE syringe with oven-dried stainless-steel needle), and the vial was sealed with a screw-top cap containing a PTFE-lined septum.
The system was removed from the glovebox, and distilled H₂O (0.10 mL, distilled under N₂ to remove dissolved O₂) was added via syringe transfer (PTFE syringe with oven-dried stainless-steel needle) under N₂. The reaction was placed within a heating mantle preheated to 140 °C and stirred for 24 h. The reaction was cooled to R.T., and then standardized by adding 50 µL (0.40 mmol) of TFT. The mixture was diluted with DCM, and then stirred for 5 min. The reaction was analyzed by ¹⁹F NMR, and then washed 3X with 1 N NaOH (aq.). The combined aqueous layer was extracted 2X with DCM, and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was loaded onto celite and then purified by flash reverse phase chromatography with gradient elution from 98% H₂O in MeCN to 100% MeCN to provide the desired product in >95% purity.

Compounds in Table 3-1:

5-(2,2-difluoro-2-phenoxyethyl)-1,2,3-trimethoxybenzene (3.3): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.236 g (2.50 mmol) of phenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.080 g (49% yield) of desired product 3.3 as a colorless solid (MP = 65–66 °C)

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\( ^1H \text{ NMR (500 MHz, CDCl}_3) \): \( \delta \) 7.32 (t, \( J = 7.93 \text{ Hz} \), 2 H), 7.19 (t, \( J = 7.48 \text{ Hz} \), 1 H), 7.14 (d, \( J = 7.95 \text{ Hz} \), 2 H), 6.60 (s, 2 H), 3.87 (s, 9 H), 3.39 (t, \( J = 11.01 \text{ Hz} \), 2 H)

\( ^{13}C \text{ NMR (126 MHz, CDCl}_3) \): \( \delta \) 153.2, 150.5, 137.6 (d, \( J = 1.43 \text{ Hz} \)), 129.4, 127.7 (t, \( J = 3.29 \text{ Hz} \)), 125.6, 123.8, 121.7 (t, \( J = 266.95 \text{ Hz} \)), 107.6, 60.9, 56.2, 42.5 (t, \( J = 30.28 \text{ Hz} \))

\( ^{19}F \text{ NMR (376 MHz, CDCl}_3) \): \( \delta \) –70.44 (t, \( J = 11.05 \text{ Hz} \), 2 F)

IR (film): 2940, 2841, 2252, 1699, 1592, 1509, 1492, 1463, 1423, 1361, 1324, 1262, 1238, 1194, 1156, 1128, 1068, 1051, 1026, 1005, 942, 909, 828, 807, 764, 749, 692, 658, 649 cm\(^{-1}\)

HRMS (HAPCl+): calc. for C\(_{17}\)H\(_{18}\)F\(_2\)O\(_4\) (M+) 324.1173, found 324.1171, 0.6 ppm.

(Z)-5-(2-fluoro-2-phenoxyvinyl)-1,2,3-trimethoxybenzene (3.4): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.236 g (2.50 mmol) of phenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H\(_2\)O, furnishing desired product 0.024 g (16% yield) 3.4 as an orange oil; Characterization represents major isomer.
\( ^1H \text{ NMR (500 MHz, CDCl}_3\):} \ \delta \ 7.37 \ (dd, \ J = 8.66, 7.48 \text{ Hz}, 2 \text{ H}), \ 7.17–7.14 \ (m, 3 \text{ H}), \ 6.66 \ (s, 2 \text{ H}), \ 5.65 \ (d, \ J = 5.63 \text{ Hz}, 1 \text{ H}), \ 3.82 \ (s, 3 \text{ H}), \ 3.76 \ (s, 6 \text{ H})

\( ^{13}C \text{ NMR (126 MHz, CDCl}_3\):} \ \delta \ 154.7, \ 154.0 \ (d, \ J = 3.50 \text{ Hz}), \ 153.3, \ 130.1, \ 127.6 \ (d, \ J = 8.43 \text{ Hz}), \ 124.5, \ 117.5, \ 116.3, \ 105.0 \ (d, \ J = 4.09 \text{ Hz}), \ 92.7 \ (d, \ J = 38.61 \text{ Hz}), \ 61.0, \ 56.1

\( ^{19}F \text{ NMR (376 MHz, CDCl}_3\):} \ \delta \ -83.38 \ (d, \ J = 5.55 \text{ MHz}, 1 \text{ F}).

Compounds in Scheme 3-4:

![Chemical Structure](image)

5-(2,2-difluoro-2-(4-nitrophenoxy)ethyl)-1,2,3-trimethoxybenzene (3.6a): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.348 g (2.50 mmol) of 4-nitrophenol in the presence of 0.066 g (0.5 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H\(_2\)O, furnishing 0.125 g (69% yield, 97% purity) of desired product 3.6a as a dark yellow solid (MP = 117–120 °C)

\( ^1H \text{ NMR (500 MHz, CDCl}_3\):} \ \delta \ 8.22 \ (d, \ J = 9.16 \text{ Hz}, 2 \text{ H}), \ 7.28 \ (d, \ J = 8.93 \text{ Hz}, 2 \text{ H}), \ 6.57 \ (s, 2 \text{ H}), \ 3.88 \ (s, 6 \text{ H}), \ 3.86 \ (s, 3 \text{ H}), \ 3.42 \ (t, \ J = 11.37 \text{ Hz}, 2 \text{ H})
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 155.4, 153.3, 145.0, 138.0, 126.8 (t, $J = 3.36$ Hz), 125.4, 124.0 (t, $J = 269.29$ Hz), 121.4 (t, $J = 1.88$ Hz), 116.6, 107.7, 61.0, 56.3, 42.5 (t, $J = 29.26$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –71.41 (t, $J = 11.41$ Hz, 2 F)

IR (film): 2940, 2841, 1614, 1592, 1522, 1509, 1492, 1461, 1424, 1346, 1325, 1301, 1238, 1209, 1157, 1124, 1060, 1009, 943, 930, 911, 853, 801, 764, 750, 723, 692, 649 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{17}$H$_{18}$F$_2$NO$_6$ (M+H) 370.1102, found 370.1099, 0.8 ppm.

4-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)benzonitrile (3.6b): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.298 g (2.50 mmol) of 4-hydroxybenzonitrile in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.143 g (82% yield, 94% purity) of desired product 3.6b as a yellow oil

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.62 (d, $J = 8.81$ Hz, 2 H), 7.23 (d, $J = 8.37$ Hz, 2 H), 6.56 (s, 2 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.40 (t, $J = 11.28$ Hz, 2 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.9, 153.3, 133.8, 126.9 (t, $J = 3.35$ Hz), 124.0 (t, $J = 269.56$ Hz), 121.8 (d, $J = 1.82$ Hz), 118.3, 117.0, 109.2, 107.7, 61.0, 56.3, 42.5 (t, $J = 29.30$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –71.23 (t, $J = 11.45$ Hz, 2 F)

IR (film): 2940, 2842, 2253, 2231, 1596, 1505, 1464, 1424, 1360, 1325, 1296, 1241, 1210, 1173, 1156, 1129, 1068, 1004, 908, 841, 802, 732, 649 cm$^{-1}$

HRMS (ESI+): calc. for C$_{18}$H$_{17}$F$_2$NO$_4$Na (M+Na): 372.1023, found 372.1026, 0.8 ppm.

![chemical structure](3.6c)

5-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-1,2,3-trimethoxybenzene (3.6c):

Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.145 g (72% yield) of desired product 3.6c as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.40 (d, $J = 2.46$ Hz, 1 H), 7.27–7.25 (m, 1 H), 7.19 (dd, $J = 8.83$, 2.46 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.43 (t, $J = 11.03$ Hz, 2 H)
**$^{13}$C NMR (126 MHz, CDCl$_3$):** $\delta$ 153.2, 145.3 (t, $J = 1.69$ Hz), 137.8, 131.3, 130.3, 128.2, 127.8, 127.0 (t, $J = 3.45$ Hz), 124.07 (t, $J = 269.41$ Hz), 123.93 (t, $J = 2.03$ Hz), 107.9, 61.0, 56.3, 42.4 (t, $J = 29.38$ Hz)

**$^{19}$F NMR (376 MHz, CDCl$_3$):** $\delta$ –70.83 (t, $J = 11.04$ Hz, 2 F)

**IR (film):** 2940, 2839, 1592, 1508, 1476, 1463, 1423, 1360, 1324, 1258, 1238, 1128, 1061, 1008, 942, 867, 808, 764, 700, 666, 528 cm$^{-1}$

**HRMS (HAPCI$^+$):** calc. for C$_{17}$H$_{16}$Cl$_2$F$_2$O$_4$ (M$^+$) 392.0394, found 394.0424, 3.8 ppm.

![Diagram](image.png)

**5-(2,2-difluoro-2-(3-iodophenoxy)ethyl)-1,2,3-trimethoxybenzene (3.6d):** Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.551 g (2.50 mmol) of 3-iodophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.158 g (71% yield, 98% purity) of desired product 3.6d as a brown oil.

**$^1$H NMR (500 MHz, CDCl$_3$):** $\delta$ 7.53–7.50 (m, 2 H), 7.12 (dd, $J = 8.25$, 2.15 Hz, 1 H), 7.03 (t, $J = 8.01$ Hz, 1 H), 6.56 (s, 2 H), 3.86 (s, 9 H), 3.36 (t, $J = 11.08$ Hz, 2 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.1, 150.7 (d, $J = 2.30$ Hz), 137.7 (d, $J = 1.69$ Hz), 134.7, 130.9, 130.7, 127.3 (t, $J = 3.39$ Hz), 123.8 (t, $J = 267.33$ Hz), 121.2, 107.6, 93.5, 60.9, 56.2, 42.4 (t, $J = 29.73$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –70.60 (t, $J = 11.13$ Hz, 2 F)

IR (film): 2938, 2839, 1591, 1583, 1509, 1465, 1422, 1360, 1324, 1260, 1237, 1192, 1156, 1126, 1054, 1008, 945, 910, 865, 832, 765, 750, 735, 686, 665, 649 cm$^{-1}$

MS (EI+): calc. for C$_{17}$H$_{17}$F$_2$IO$_4$ (M+) 450.0, found 449.9.

$\text{5-(2-(3-chloro-2-fluorophenoxy)-2,2-difluoroethyl)-1,2,3-trimethoxybenzene (3.6e):}$

Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.26 mL (2.50 mmol) of 2-fluoro-3-chlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.139 g (74% yield, 95% purity) of desired product 3.6e as a clear solid (MP = 50–51 °C)
\( ^1H \text{ NMR (500 MHz, CDCl}_3 \): } \delta 7.23 (dd, \, J = 8.07, 6.34, 1.56 \, Hz, \, 1 \, H), 7.19 (dd, \, J = 8.32, 6.81, 1.40 \, Hz, \, 1 \, H), 7.01 (td, \, J = 8.26, 1.86 \, Hz, \, 1 \, H), 6.60 (s, \, 2 \, H), 3.87 (s, \, 6 \, H), 3.86 (s, \, 3 \, H), 3.43 (t, \, J = 11.06 \, Hz, \, 2 \, H)

\( ^{13}C \text{ NMR (126 MHz, CDCl}_3 \): } \delta 153.2, 150.4, 137.7 (t, \, J = 1.45 \, Hz), 127.5, 127.0 (t, \, J = 3.51 \, Hz), 123.97, 123.96 (t \, J = 269.84 \, Hz), 123.93, 122.6, 122.3 (d, \, J = 15.84 \, Hz), 107.6, 61.0, 56.2, 42.2 (t, \, J = 29.40 \, Hz)

\( ^{19}F \text{ NMR (376 MHz, CDCl}_3 \): } \delta -71.19 (td, \, J = 11.30, 5.34 \, Hz, \, 2 \, F), -131.17 (p, \, J = 6.19 \, Hz, \, 1 \, F)

\textbf{IR (film): } 2941, 2842, 2253, 1705, 1595, 1509, 1483, 1462, 1424, 1360, 1325, 1275, 1260, 1243, 1181, 1156, 1129, 1069, 1027, 1004, 956, 907, 838, 821, 764, 746, 650 \, \text{cm}^{-1}

\textbf{HRMS (HAPCI\(^+\)): } \text{calc. for } C_{17}H_{16}ClF_3O_4 (M^+) \, 376.0689, \text{ found } 376.0682, \, 1.9 \, \text{ppm.}

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

\textbf{5-(2-(4-bromophenoxy)-2,2-difluoroethyl)-1,2,3-trimethoxybenzene (3.6f): } Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.432 g (2.50 mmol) of 4-bromophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 \, ^\circ \text{C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase}
flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.137 g (68% yield, 97% purity) of desired product 3.6f (or 2) as a clear oil

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\text{):} \delta 7.42 (d, J = 8.83 \text{ Hz}, 2 \text{ H}), 7.01 (d, J = 8.62 \text{ Hz}, 2 \text{ H}), 6.57 (s, 2 \text{ H}), 3.86 (s, 9 \text{ H}), 3.37 (t, J = 11.08 \text{ Hz}, 2 \text{ H}) \]

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3\text{):} \delta 153.2, 149.4, 137.7 (t, J = 1.62 \text{ Hz}), 132.4, 127.4, 123.7 (t, J = 267.88 \text{ Hz}), 123.6, 118.6, 107.6, 60.9, 56.2, 42.4 (t, J = 29.85 \text{ Hz}) \]

\[ ^{19}F \text{ NMR (376 MHz, CDCl}_3\text{):} \delta -70.87 (t, J = 11.24 \text{ Hz}, 2 \text{ F}) \]

\[ \text{IR (film):} 2939, 2842, 2252, 1594, 1509, 1486, 1464, 1424, 1361, 1324, 1275, 1260, 1239, 1199, 1156, 1129, 1068, 1012, 908, 827, 797, 764, 744, 698, 649 \text{ cm}^{-1} \]

\[ \text{HRMS (HAPCI\text{+:})}: \text{calc. for C}_{17}\text{H}_{17}\text{BrF}_2\text{O}_4 (M\text{+}) 402.0278, \text{found 402.0267, 2.7 ppm.} \]

\[ \text{4-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)-1,1'-biphenyl (3.6g): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.426 g (2.50 mmol) of 4-phenylphenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 \text{ °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash normal phase chromatography using a gradient of hexanes to 5% PhMe and 15% EtOAc in} \]

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hexanes, furnishing 0.107 g of pure compound 3.6g as colorless solid (MP = 67–70 °C), and 0.053 g of 80% pure compound 3.6g

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.56–7.54 (m, 4 H), 7.44 (t, $J$ = 7.55 Hz, 2 H), 7.35 (t, $J$ = 7.37 Hz, 1 H), 7.22 (d, $J$ = 8.23 Hz, 2 H), 6.62 (s, 2 H), 3.88 (s, 9 H), 3.42 (t, $J$ = 10.95 Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.2, 149.9 (t, $J$ = 2.09 Hz), 140.4, 138.7, 137.7 (t, $J$ = 1.33 Hz), 128.9, 128.2, 127.7 (t, $J$ = 3.23 Hz), 127.5, 127.2, 123.9 (t, $J$ = 266.44 Hz), 122.0, 107.7, 61.0, 56.3, 42.6 (t, $J$ = 30.29 Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –70.42 (t, $J$ = 10.93 Hz, 2 F)

IR (film): 2253, 1595, 1510, 1486, 1464, 1424, 1325, 1241, 1131, 1009, 905, 729, 650 cm$^{-1}$

HRMS (HAPCI⁺): calc. for C$_{23}$H$_{22}$F$_2$O$_4$ (M⁺) 400.1486, found 400.1478, 2.0 ppm.

5-(2,2-difluoro-2-(o-tolyloxy)ethyl)-1,2,3-trimethoxybenzene (3.6h): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.26 mL (2.50 mmol) of o-cresol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 hours.
h. After workup with 1 N NaOH (aq.), the product was purified by normal-phase flash chromatography using a gradient of 0–10% EtOAc in hexanes with 1% PhMe, followed by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.068 g (40% yield) of desired product 3.6h as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃): δ 7.21 (dd, J = 8.37, 1.74 Hz, 1 H), 7.15 (t, J = 7.00 Hz, 2 H), 7.08 (dt, J = 7.45, 6.99, 1.39 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.41 (t, J = 10.56 Hz, 2 H), 2.05 (s, 3 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.1, 148.9, 137.7 (d, J = 1.32 Hz), 131.22, 131.19, 127.8 (t, J = 3.67 Hz), 126.7, 125.5, 124.1 (t, J = 266.78 Hz), 121.9 (d, J = 1.71 Hz), 107.8, 61.0, 56.3, 42.7 (t, J = 30.67 Hz), 16.4

¹⁹F NMR (376 MHz, CDCl₃): δ –69.81 (t, J = 10.57 Hz, 2 F)

IR (film): 2939, 2840, 1591, 1508, 1494, 1460, 1423, 1360, 1324, 1262, 1238, 1177, 1156, 1126, 1091, 1042, 1009, 944, 892, 862, 832, 749, 704, 658, 618 cm⁻¹

HRMS (HAPCI⁺): calc. for C₁₈H₂₀F₂O₄ (M⁺) 338.1330, found 338.1320, 3.0 ppm.
5-(2,2-difluoro-2-(2-isopropylphenoxy)ethyl)-1,2,3-trimethoxybenzene  (3.6i):

Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.336 mL (2.50 mmol) of 2-isopropylphenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.061 g (34% yield) of desired product 3.6i as a clear oil.

¹H NMR (500 MHz, CDCl₃): δ 7.30–7.26 (m, 2 H), 7.18 (dt, J = 6.21, 2.47 Hz, 2 H), 6.64 (s, 2 H), 3.90 (s, 9 H), 3.45 (t, J = 10.31 Hz, 2 H), 2.90 (p, J = 6.89 Hz, 1 H), 1.08 (d, J = 6.92 Hz, 6 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.2, 147.6 (t, J = 1.78 Hz), 141.3, 127.9 (t, J = 3.83 Hz), 126.6, 126.5, 125.8, 124.0 (t, J = 266.37 Hz), 121.7 (t, J = 1.95 Hz), 107.8, 61.0, 56.2, 42.8 (t, J = 30.60 Hz), 26.5, 23.1

¹⁹F NMR (376 MHz, CDCl₃): δ –69.54 (t, J = 10.36 Hz, 2 F)

IR (film): 2963, 2840, 1592, 1508, 1489, 1459, 1423, 1362, 1323, 1260, 1238, 1179, 1156, 1127, 1086, 1045, 1009, 944, 892, 860, 829, 809, 752, 722, 705, 659, 603, 545, 529, 472, 455 cm⁻¹

HRMS (HAPCI⁺): calc. for C₂₀H₂₄F₂O₄ (M⁺) 366.1643, found 366.1638, 1.4 ppm.
2-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)-1,1’-biphenyl (3.6j): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.426 g (2.50 mmol) of 2-phenylphenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.127 g (40 % yield, 63% purity) of compound 3.6j as a pale oil

**¹H NMR (500 MHz, CDCl₃):** δ 7.42–7.38 (m, 1 H), 7.34–7.29 (m, 7 H), 7.25 (td, J = 7.44, 1.28 Hz, 1 H), 6.35 (s, 2 H), 3.84 (s, 3 H), 3.75 (s, 6 H), 3.19 (t, J = 10.75 Hz, 2 H)

**¹³C NMR (126 MHz, CDCl₃):** δ 153.0, 147.5, 138.1, 135.3, 131.3, 129.6, 129.4, 128.9, 128.4, 128.0, 127.7, 127.4 (d, J = 3.80 Hz), 127.2, 125.7, 123.9 (t, J = 269.20 Hz), 122.1 (d, J = 2.15 Hz), 107.6, 60.9, 56.1, 42.6 (t, J = 30.32 Hz)

**¹⁹F NMR (376 MHz, CDCl₃):** δ –69.38 (t, J = 10.89 Hz, 2 F)

**IR (film):** 2938, 2839, 1754, 1699, 1591, 1507, 1479, 1460, 1422, 1359, 1324, 1275, 1259, 1235, 1188, 1155, 1125, 1045, 1010, 946, 916, 830, 748, 701, 660, 613, 569, 528 cm⁻¹

**HRMS (HAPCI⁺):** calc. for C₂₃H₂₂F₂O₄ (M⁺) 400.1486, found 400.1486, 0.0 ppm.
5-(2,2-difluoro-2-(4-methoxyphenoxy)ethyl)-1,2,3-trimethoxybenzene (3.6k):

Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.310 g (2.50 mmol) of 4-methoxyphenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H2O, furnishing 0.089 g (51% yield, 95% purity) of desired product 3.6k as a colorless solid (MP = 64–66 °C)

\[ \text{H NMR (500 MHz, CDCl}_3\text{:} \delta 7.05 (d, J = 8.58 Hz, 2 H), 6.83 (d, J = 8.99 Hz, 2 H), 6.59 (s, 2 H), 3.86 (s, 9 H), 3.77 (s, 3 H), 3.36 (t, J = 10.92 Hz, 2 H)} \]

\[ \text{C NMR (126 MHz, CDCl}_3\text{:} \delta 157.3, 153.1, 143.7, 137.6 (d, J = 1.39 Hz), 127.8 (d, J = 3.21 Hz), 123.8 (t, J = 266.76 Hz), 123.2, 114.4, 107.6, 60.9, 56.2, 55.6, 42.4 (t, J = 30.37 Hz)} \]

\[ \text{F NMR (376 MHz, CDCl}_3\text{:} \delta -70.65 (t, J = 11.00 Hz, 2 F)} \]

\[ \text{IR (film): 3003, 2939, 2839, 2252, 1702, 1592, 1506, 1463, 1423, 1362, 1324, 1298, 1267, 1241, 1192, 1156, 1128, 1040, 1009, 943, 910, 842, 807, 784, 763, 735, 698, 649 cm}^{-1} \]

\[ \text{HRMS (HAPCl+): calc. for C}_{18}\text{H}_{20}\text{F}_2\text{O}_5 (M+) 354.1279, found 354.1269, 2.8 ppm.} \]
3-(1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethoxy)-N,N-dimethylaniline (3.6l):

Following General Procedure B-1, 0.115 g (0.50 mmol) of compound 3.1 was reacted with 0.343 g (2.50 mmol) of 3-dimethylaminophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by normal-phase flash chromatography using a gradient of 0–30% EtOAc in hexanes to remove 3-dimethylaminophenol, followed by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.051 g (28% yield, 97% purity) of compound 3.6l as a yellow semisolid

¹H NMR (500 MHz, CDCl₃): δ 7.16 (t, J = 8.20 Hz, 1 H), 6.59 (s, 2 H), 6.55 (dd, J = 8.39, 2.50 Hz, 1 H), 6.52 (d, J = 7.52 Hz, 1 H), 6.46 (t, J = 2.39 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.37 (t, J = 11.05 Hz, 2 H), 2.93 (s, 6 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.1, 151.7, 151.6 (t, J = 2.25 Hz), 137.6, 129.6, 127.9 (t, J = 3.21 Hz), 123.9 (t, J = 266.13 Hz), 109.7, 109.5, 107.6, 105.9, 61.0, 56.2, 42.6 (t, J = 30.60 Hz), 40.6

¹⁹F NMR (376 MHz, CDCl₃): δ –69.93 (t, J = 11.10 Hz, 2 F)

IR (film): 2938, 2840, 1699, 1608, 1592, 1505, 1460, 1423, 1358, 1324, 1263, 1236, 1126, 1045, 1003, 941, 876, 838, 812, 765, 750, 687, 668, 612, 528 cm⁻¹
**HRMS (ESI+):** calc. for C\textsubscript{19}H\textsubscript{24}F\textsubscript{2}NO\textsubscript{4} (M+H) 368.1673, found 368.1662, 3.0 ppm.

**Compounds in Scheme 3-5:**

![Compounds in Scheme 3-5](image_url)

(4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)(methyl)sulfane \((3.9a)\):

Following General Procedure B-1, 0.093 g (0.50 mmol) of compound 3.8a was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H\textsubscript{2}O, furnishing 0.112 g (68% yield, 98% purity) of desired product 3.9a as a tan solid (MP = 69–70 °C)

\(\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3\):} δ 7.40 (d, \(J = 2.18\) Hz, 1 H), 7.32 (d, \(J = 8.05\) Hz, 2 H), 7.25 (d, \(J = 8.37\) Hz, 2 H), 7.23 (d, \(J = 8.65\) Hz, 1 H), 7.18 (ddd, \(J = 8.78, 2.49, 0.98\) Hz, 1 H), 3.45 (t, \(J = 11.11\) Hz, 2 H), 2.49 (d, \(J = 1.07\) Hz, 3 H)

\(\text{\textsuperscript{13}C NMR (126 MHz, CDCl}_3\):} δ 145.3, 138.3, 131.3, 131.2, 130.3, 128.4, 128.3 (t, \(J = 3.40\) Hz), 127.7, 126.6, 124.1 (t, \(J = 1.97\) Hz), 124.0 (t, \(J = 269.68\) Hz), 41.7 (t, \(J = 29.35\) Hz), 15.9

\(\text{\textsuperscript{19}F NMR (376 MHz, CDCl}_3\):} δ –71.10 (t, \(J = 11.09\) Hz, 2 F)
IR (film): 2924, 1476, 1433, 1352, 1324, 1283, 1260, 1217, 1174, 1119, 1095, 1061, 1019, 958, 907, 868, 843, 800, 762, 733, 696, 675, 650 cm⁻¹

HRMS (HAPCI⁺): calc. for C₁₅H₁₂Cl₂F₂OS (M⁺) 347.9954, found 347.9944, 2.9 ppm.

1-bromo-4-(1,1-difluoro-2-(4-methoxyphenyl)ethoxy)benzene (3.9b): Following General Procedure B-1, 0.086 g (0.50 mmol) of compound 3.8b was reacted with 0.433 g (2.50 mmol) of 4-bromophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.097 g (56% yield) of desired product 3.9b as a peach solid (MP = 51–52 °C)

¹H NMR (500 MHz, CDCl₃): δ 7.43 (d, J = 8.87 Hz, 2 H), 7.29 (d, J = 8.25 Hz, 2 H), 7.01 (d, J = 8.50 Hz, 2 H), 6.91 (d, J = 8.80 Hz, 2 H), 3.82 (s, 3 H), 3.39 (t, J = 11.12 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 159.3, 149.6, 132.4, 131.6, 123.97 (t, J = 3.27 Hz), 123.91 (t, J = 267.23 Hz), 123.6 (d, J = 1.39 Hz), 118.6, 114.0, 55.3, 41.4 (t, J = 29.79 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ –71.48 (t, J = 11.20 Hz, 2 F)
**IR (film):** 3005, 2937, 2838, 1614, 1515, 1486, 1442, 1352, 1324, 1303, 1248, 1200, 1179, 1116, 1087, 1067, 1036, 1013, 908, 847, 821, 796, 785, 764, 736, 697, 677, 650 cm⁻¹

**HRMS (HAPCI+):** calc. for C₁₅H₁₃BrF₂O₂ (M⁺) 342.0067, found 342.0067, 0.0 ppm.

4-(3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)morpholine (3.9c): Following General Procedure B-1, 0.112 g (0.50 mmol) of compound 3.8c was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.148 g (78% yield, 94% purity) of desired product 3.9c as a yellow solid (MP = 61–64 °C)

**¹H NMR (500 MHz, CDCl₃):** δ 7.45 (d, J = 2.47 Hz, 1 H), 7.32 (d, J = 7.91 Hz, 1 H), 7.30–7.28 (m, 1 H), 7.23 (dd, J = 8.82, 2.49 Hz, 1 H), 7.00 (t, J = 1.92 Hz, 1 H), 6.97 (d, J = 7.50 Hz, 1 H), 6.93 (dd, J = 8.25, 2.42 Hz, 1 H), 3.92–3.90 (m, 4 H), 3.51 (t, J = 11.24 Hz, 2 H), 3.24–3.22 (m, 4 H)
\(^{13}\text{C NMR (126 MHz, CDCl}_3\): \(\delta\) 151.4, 145.3, 132.4 (t, \(J = 3.41\) Hz), 131.2, 130.3, 129.2, 128.3, 127.7, 124.1 (t, \(J = 269.23\) Hz), 124.0 (t, \(J = 1.89\) Hz), 122.4, 118.1, 115.1, 67.0, 49.4, 42.4 (t, \(J = 29.15\) Hz)

\(^{19}\text{F NMR (376 MHz, CDCl}_3\): \(\delta\) –70.77 (t, \(J = 11.30\) Hz, 2 F)

\textbf{IR (film):} 2967, 2860, 2250, 1604, 1495, 1476, 1380, 1353, 1325, 1304, 1274, 1259, 1245, 1218, 1175, 1120, 1097, 1068, 998, 976, 908, 869, 837, 812, 763, 745, 697, 650, 618 cm\(^{-1}\)

\textbf{HRMS (ESI+):} calc. for \(\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{F}_2\text{NO}_2\) (M+H) 388.0683, found 388.0669, 3.6 ppm.

\begin{center}
\includegraphics[width=0.5\textwidth]{3.9d}
\end{center}

\textbf{4’-(tert-butyl)-2-(2,4-dichlorophenoxy)-2,2-difluoroethyl-1,1’-biphenyl (3.9d):}

Following General Procedure B-1, 0.136 g (0.50 mmol) of compound 3.8d was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H\(_2\)O, furnishing 0.153 g (70% yield, 97% purity) of desired product 3.9d as a colorless solid (MP = 76–78 °C).
1H NMR (500 MHz, CDCl₃): δ 7.70 (s, 1 H), 7.64–7.62 (m, 3 H), 7.55 (d, J = 7.86 Hz, 2 H), 7.49 (t, J = 7.68 Hz, 1 H), 7.46 (d, J = 2.10 Hz, 1 H), 7.43 (d, J = 7.62 Hz, 1 H), 7.31 (dd, J = 8.90, 1.31 Hz, 1 H), 7.24 (dt, J = 8.85, 1.77 Hz, 1 H), 3.63 (t, J = 11.07 Hz, 2 H), 1.45 (s, 9H)

13C NMR (126 MHz, CDCl₃): δ 150.6, 145.3, 141.4, 138.1, 132.0 (t, J = 3.36 Hz), 131.3, 130.3, 129.6, 129.4, 128.9, 128.5, 127.7, 127.0, 126.6, 125.9, 124.20 (t, J = 2.05 Hz), 124.15 (t, J = 269.29 Hz), 42.3 (t, J = 29.25 Hz), 34.7, 31.5

19F NMR (376 MHz, CDCl₃): δ –70.80 (t, J = 10.98 Hz, 2 F)

IR (film): 2964, 2250, 1476, 1352, 1324, 1256, 1218, 1174, 1116, 1097, 1062, 1043, 1016, 907, 868, 837, 813, 794, 763, 734, 704, 650, 617 cm⁻¹

HRMS (HAPCI⁺): calc. for C₂₄H₂₂Cl₂F₂O (M⁺) 434.1016, found 434.0999, 3.9 ppm.

1-(2-(4-(tert-butyl)phenyl)-1,1-difluoroethoxy)-2,4-dichlorobenzene (3.9f): Following General Procedure B-1, 0.098 g (0.50 mmol) of compound 3.8f was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase
flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.074 g (41% yield) of desired product 3.9f as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.43–7.40 (m, 3 H), 7.35 (d, $J$ = 8.11 Hz, 2 H), 7.28–7.26 (m, 1 H), 7.20 (ddd, $J$ = 8.83, 2.51, 0.80 Hz, 1 H), 3.50 (t, $J$ = 11.31 Hz, 2 H), 1.36 (9 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 150.8, 145.4, 131.3, 130.4, 130.3, 128.6, 128.4, 127.7, 125.5, 124.2 (t, $J$ = 269.81 Hz), 124.1 (t, $J$ = 2.06 Hz), 41.7 (t, $J$ = 29.18 Hz), 34.7, 31.5

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –71.02 (t, $J$ = 11.35 Hz, 2 F)

IR (film): 2965, 2869, 1477, 1352, 1325, 1274, 1260, 1218, 1175, 1159, 1124, 1097, 1062, 1026, 907, 869, 838, 805, 764, 745, 697, 651 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{18}$H$_{18}$Cl$_2$F$_2$O (M$^+$) 358.0703, found 358.0701, 0.6 ppm.

2,4-dichloro-1-(2-(3,5-dimethylphenyl)-1,1-difluoroethoxy)benzene (3.9g): Following General Procedure B-1, 0.085 g (0.50 mmol) of compound 3.8g was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-
phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.092 g (55% yield) of desired product **3.9g** as a pale-yellow oil

**¹H NMR (500 MHz, CDCl₃):** δ 7.41 (d, J = 2.46 Hz, 1 H), 7.25 (d, J = 8.62 Hz, 1 H), 7.18 (dd, J = 8.81, 2.49 Hz, 1 H), 7.02 (s, 2 H), 6.97 (s, 1 H), 3.42 (t, J = 11.40 Hz, 2 H), 2.33 (s, 6 H)

**¹³C NMR (126 MHz, CDCl₃):** δ 145.5, 138.0, 131.3 (t, J = 3.21 Hz), 131.2, 130.3, 129.5, 128.6, 128.4, 127.7, 124.2 (t, J = 269.47 Hz), 124.1 (d, J = 2.20 Hz), 42.1 (t, J = 29.30 Hz), 21.4

**¹⁹F NMR (376 MHz, CDCl₃):** δ −70.95 (t, J = 11.40 Hz, 2 F)

**IR (film):** 3010, 2920, 1608, 1584, 1476, 1433, 1382, 1353, 1298, 1276, 1251, 1218, 1168, 1096, 1061, 962, 866, 847, 809, 764, 751, 715, 695, 661 cm⁻¹

**HRMS (HAPCI⁺):** calc. for C₁₆H₁₄Cl₂F₂O (M⁺) 330.0390, found 330.0391, 0.3 ppm.

![Structural diagram of 2,4-dichloro-1-(2-(2,4-dimethylphenyl)-1,1-difluoroethoxy)benzene (3.9h)](image)

**2,4-dichloro-1-(2-(2,4-dimethylphenyl)-1,1-difluoroethoxy)benzene (3.9h):** Following General Procedure B-1, 0.084 g (0.50 mmol) of compound **3.8h** was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-
phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.050 g (27% yield, 92% purity) of compound 3.9h as a pale-yellow semisolid.

**¹H NMR (500 MHz, CDCl₃):** δ 7.40 (d, J = 2.45 Hz, 1 H), 7.25–7.22 (m, 2 H), 7.17 (dd, J = 8.81, 2.42 Hz, 1 H), 7.04 (s, 1 H), 7.01 (d, J = 7.91 Hz, 1 H), 3.50 (t, J = 11.33 Hz, 2 H), 2.40 (s, 3 H), 2.31 (s, 3 H)

**¹³C (126 MHz, CDCl₃):** δ 145.4 (t, J = 1.58 Hz), 137.74, 137.68, 131.7, 131.4, 131.3, 130.3, 128.5, 127.7, 127.0 (t, J = 3.05 Hz), 126.8, 124.6 (t, J = 270.97 Hz), 124.2 (t, J = 2.00 Hz), 38.6 (t, J = 29.19 Hz), 21.2, 20.0

**¹⁹F NMR (376 MHz, CDCl₃):** δ –70.43 (t, J = 11.44 Hz, 2 F)

**IR (film):** 2923, 1702, 1618, 1583, 1508, 1476, 1382, 1347, 1311, 1258, 1217, 1126, 1095, 1060, 963, 942, 866, 810, 792, 762, 694, 673, 626, 566, 465, 455 cm⁻¹

**MS (EI⁺):** calc. for C₁₆H₁₄Cl₂F₂O (M⁺) 330.0, found 330.0.

![Chemical Structure](image)

**ethyl (E)-3-(3-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)acrylate (3.9j):**

Following General Procedure B-1, 0.119 g (0.50 mmol) of compound 3.8j was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by
reverse-phase flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.127 g (64% yield) of desired product $3.9j$ as a colorless solid (MP = 70–72°C).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.70 (d, $J = 16.02$ Hz, 1 H), 7.56 (s, 1 H), 7.49 (d, $J = 7.46$ Hz, 1 H), 7.42–7.36 (m, 3 H), 7.23 (d, $J = 8.78$ Hz, 1 H), 7.17 (dd, $J = 8.83$, 2.49 Hz, 1 H), 6.47 (d, $J = 16.04$ Hz, 1 H), 4.27 (q, $J = 7.12$ Hz, 2 H), 3.51 (t, $J = 10.93$ Hz, 2 H), 1.34 (t, $J = 7.13$ Hz, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 167.0, 145.1, 144.2, 134.8, 132.5, 132.3 (t, $J = 3.36$ Hz), 131.4, 130.4, 130.3, 129.1, 128.4, 127.7, 127.5, 124.1 (d, $J = 1.84$ Hz), 123.9 (t, $J = 269.66$ Hz), 118.9, 60.6, 42.0 (t, $J = 29.35$ Hz), 14.4

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –70.81 (t, $J = 10.92$ Hz, 2 F)

IR (film): 2983, 2253, 1709, 1640, 1608, 1585, 1476, 1438, 1385, 1367, 1354, 1322, 1274, 1260, 1228, 1179, 1163, 1119, 1097, 1061, 983, 909, 865, 840, 812, 763, 750, 694 cm$^{-1}$

HRMS (HAPCI+): calc. for C$_{19}$H$_{16}$Cl$_2$F$_2$O$_3$ (M+) 400.0445, found 400.0435, 2.5 ppm.
2,4-dichloro-1-(1,1-difluoro-2-(3-nitrophenyl)ethoxy)benzene (3.9k): Following General Procedure B-1, 0.093 g (0.50 mmol) of compound 3.8k was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.083 g (47% yield, 94% purity) of desired product 3.9k as a clear solid (MP = 96–97 °C).

¹H NMR (500 MHz, CDCl₃): δ 8.30 (d, J = 2.07 Hz, 1 H), 8.22 (dd, J = 8.29, 2.46 Hz, 1 H), 7.75 (d, J = 7.72 Hz, 1 H), 7.55 (t, J = 7.94 Hz, 1 H), 7.39 (d, J = 2.45 Hz, 1 H), 7.24 (d, J = 9.03 Hz, 1 H), 7.20 (dd, J = 8.77, 2.33 Hz, 1 H), 3.61 (t, J = 10.49 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 144.9 (d, J = 1.93 Hz), 136.9, 133.5, 131.7, 130.4, 129.5, 128.4, 127.9, 125.8, 124.1 (t, J = 1.96 Hz), 123.5 (t, J = 269.63 Hz), 123.1, 41.9 (t, J = 30.18 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ –70.75 (t, J = 10.61 Hz, 2 F)

IR (film): 2956, 2923, 2870, 1702, 1532, 1475, 1352, 1324, 1300, 1258, 1216, 1173, 1158, 1125, 1097, 1068, 1061, 1027, 970, 908, 866, 802, 765, 34, 697, 677, 657 cm⁻¹

HRMS (HAPCI⁺): calc. for C₁₄H₉Cl₂F₂NO₃ (M⁺) 346.9928, found 346.9925, 0.9 ppm.
3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)benzonitrile (3.9l): Following General Procedure B-2, 0.083 g (0.50 mmol) of compound 3.8l was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.080 g (49% yield) of desired compound 3.9l as a colorless solid (MP = 81–83 °C).

¹H NMR (500 MHz, CDCl₃): δ 7.71 (d, J = 2.26 Hz, 1 H), 7.65–7.63 (m, 2 H), 7.48 (dt, J = 8.52, 4.29 Hz, 1 H), 7.39 (t, J = 2.03 Hz, 1 H), 7.24–7.18 (m, 2 H), 3.53 (t, J = 10.57 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 145.0, 135.2, 134.3, 133.1, 131.72, 131.66, 130.4, 129.4, 128.4, 127.8, 124.1. 123.5 (t, J = 269.93 Hz), 118.6, 112.9, 41.8 (t, J = 29.94 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ –70.80 (t, J = 10.55 Hz, 2 F)

IR (film): 3082, 2955, 2230, 1704, 1587, 1476, 1434, 1382, 1352, 1303, 1278, 1261, 1242, 1232, 1219, 1179, 1102, 1071, 1056, 1003, 976, 942, 918, 904, 873, 866, 823, 811, 800, 758, 738, 694, 644, 618, 577, 463 cm⁻¹

HRMS (HAPCI⁺): calc. for C₁₅H₉Cl₂F₂NO (M⁺) 327.0029, found 327.0031, 0.6 ppm.
1-(2-(4-bromophenyl)-1,1-difluoroethoxy)-2,4-dichlorobenzene (3.9m): Following General Procedure B-2, 0.110 g (0.50 mmol) of compound 3.8m was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.113 g (59% yield) of desired compound 3.9m as a colorless solid (MP = 52–53 °C).

**¹H NMR (500 MHz, CDCl₃):** \( \delta 7.49 \text{ (dd, } J = 8.28, 1.66 \text{ Hz, 2 H)}, 7.40 \text{ (d, } J = 2.33 \text{ Hz, 1 H)}, 7.28 \text{ (d, } J = 8.66 \text{ Hz, 2 H)}, 7.22 \text{ (dd, } J = 8.82, 1.45 \text{ Hz, 1 H)}, 7.19 \text{ (dd, } J = 8.82, 2.30 \text{ Hz, 1 H}), 3.45 \text{ (t, } J = 10.89 \text{ Hz, 2 H})

**¹³C NMR (126 MHz, CDCl₃):** \( \delta 145.2, 132.4, 131.7, 131.5, 130.6 \text{ (t, } J = 3.23 \text{ Hz}), 130.4, 128.5, 127.8, 124.2, 123.8 \text{ (t, } J = 269.87 \text{ Hz}), 122.2, 41.7 \text{ (t, } J = 29.56 \text{ Hz})

**¹⁹F NMR (376 MHz, CDCl₃):** \( \delta -71.02 \text{ (t, } J = 10.82 \text{ Hz, 2 F})

**IR (film):** 2925, 1701, 1583, 1476, 1433, 1408, 1384, 1350, 1260, 1217, 1099, 1073, 1061, 1014, 897, 868, 843, 799, 762, 672, 623, 565, 489 cm⁻¹

**HRMS (HAPCI⁺):** calc. For C₁₄H₉BrCl₂F₂O (M⁺) 379.9182, found 379.9169, 3.4 ppm.
2,4-dichloro-1-(1,1-difluoro-2-(2-iodophenyl)ethoxy)benzene (3.9n): Following General Procedure B-2, 0.133 g (0.50 mmol) of compound 3.8n was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.105 g (49% yield) of desired compound 3.9n as a colorless solid (MP = 54–55 °C).

\[ ^1H \text{NMR (500 MHz, CDCl}_3\text{):} \delta 7.91 (dd, J = 7.91, 1.30 Hz, 1 H), 7.52 (dd, J = 7.77, 1.56 Hz, 1 H), 7.40 (d, J = 2.48 Hz, 1 H), 7.35 (td, J = 7.56, 1.30 Hz, 1 H), 7.27–7.25 (m, 1 H), 7.19 (dd, J = 8.79, 2.51 Hz, 1 H), 7.01 (td, J = 7.66, 1.71 Hz, 1 H), 3.77 (t, J = 10.94 Hz, 2 H) \]

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3\text{):} \delta 145.3, 140.0, 135.2 (t, J = 2.76 Hz), 131.8, 131.5, 130.4, 129.6, 128.7, 128.4, 127.8, 124.4, 124.1 (t, J = 270.10 Hz), 102.2, 46.1 (t, J = 29.23 Hz) \]

\[ ^{19}F \text{NMR (376 MHz, CDCl}_3\text{):} \delta -69.75 (t, J = 10.84 Hz, 2 F) \]

\textbf{IR (film):} 2924, 1698, 1584, 1565, 1475, 1436, 1384, 1349, 1276, 1258, 1216, 1124, 1096, 1061, 1046, 1014, 868, 811, 765, 748, 694, 671, 652, 626, 613, 566, 488, 473, 459 cm\(^{-1}\) 

\textbf{HRMS (HAPCI\(^+\))}: calc. for C\(_{14}\)H\(_9\)Cl\(_2\)F\(_2\)IO (M\(^+\)) 427.9043, found 427.9029, 3.3 ppm.
2,4-dichloro-(1,1-difluoro-2-(3-(trifluoromethyl)phenyl)ethoxy)benzene (3.9o):
Following General Procedure B-2, 0.104 g (0.50 mmol) of compound 3.8o was reacted
with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of
TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by
reverse-phase flash chromatography using a gradient of 2–100% MeCN in H2O,
furnishing 0.094 g (51% yield) of desired compound 3.9o as a clear oil.

1H NMR (500 MHz, CDCl3): δ 7.69 (s, 1 H), 7.60 (t, J = 7.69 Hz, 2 H), 7.49 (t, J = 7.84 Hz,
1 H), 7.40 (t, J = 2.00 Hz, 1 H), 7.24 (dd, J = 8.82, 1.38 Hz, 1 H), 7.19 (dd, J = 8.83, 2.36
Hz, 1 H), 3.56 (t, J = 10.71 Hz, 2 H)

13C NMR (126 MHz, CDCl3): δ 145.2, 134.2, 132.6 (t, J = 3.33 Hz), 131.6, 130.4, 129.0,
128.5, 127.8, 127.6 (q, J = 3.98 Hz), 125.3, 124.9 (q, J = 3.90 Hz), 124.1, 123.8 (t, J =
269.71 Hz), 123.1, 42.1 (t, J = 29.68 Hz)

19F NMR (376 MHz, CDCl3, β,β,β-trifluoroethanol as standard with ppm = −79.40): δ −
64.86 (s, 3 F), −72.02 (t, J = 10.96 Hz, 2 F)

IR (film): 2949, 1584, 1477, 1454, 1435, 1354, 1329, 1257, 1202, 1166, 1126, 1100,
1076, 1062, 870, 800, 764, 751, 703, 664, 617, 564 cm−1

HRMS (HAPCI+): calc. for C15H9Cl2F5O (M+) 369.9951, found 369.9934, 4.6 ppm.
2,4-dichloro-1-(2-(3,5-dichlorophenyl)-1,1-difluoroethoxy)benzene (3.9p): Following General Procedure B-2, 0.105 g (0.50 mmol) of compound 3.8p was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.078 g (42% yield, 98% purity) of desired compound 3.9p as a pinkish colorless solid (MP = 46–47 °C).

\[ \text{IR (film): } 1592, 1570, 1476, 1436, 1385, 1351, 1258, 1062, 867, 800, 763, 702, 643, 565 \text{ cm}^{-1} \]

\[ \text{HRMS (HAPCI+): calc. for C}_{14}\text{H}_8\text{Cl}_4\text{F}_2\text{O} (M^+) 369.9297, found 369.9300, 0.8 ppm. \]
4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-N,N-diisopropylbenzamide (3.9q):

Following General Procedure B-2, 0.134 g (0.50 mmol) of compound 3.8q was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.126 g (59% yield, 94% purity) of desired compound 3.9q as an orange solid (MP = 81–83 °C).

\[ \text{H NMR (500 MHz, CDCl}_3, 25 ^\circ \text{C):} \delta 7.40 \text{ (d, } J = 7.91 \text{ Hz, 2 H), 7.37 (d, } J = 2.48 \text{ Hz, 1 H), 7.29 (d, } J = 7.88 \text{ Hz, 2 H), 7.23 (d, } J = 8.90 \text{ Hz, 1 H), 7.18 (dd, } J = 8.82, 2.47 \text{ Hz, 1 H), 3.74 (bs, 1 H), 3.49 (t, } J = 10.96 \text{ Hz, 2 H), 1.46 (bs, 6 H), 1.21 (bs, 6 H)} \]

\[ \text{C NMR (126 MHz, CDCl}_3): \delta 170.8, 145.2, 138.6, 132.1 (t, } J = 3.17 \text{ Hz), 131.5, 130.9, 130.3, 128.5, 127.8, 126.2, 125.8, 124.2, 124.0 (t, } J = 270.95 \text{ Hz), 41.99 (t, } J = 29.30 \text{ Hz), 20.9} \]

\[ \text{F NMR (376 MHz, CDCl}_3): \delta -70.73 \text{ (t, } J = 11.26 \text{ Hz, 2 F)} \]
IR (film): 2993, 2969, 2933, 1628, 1440, 1375, 1360, 1339, 1261, 1241, 1226, 1214, 1204, 1112, 1094, 1058, 1028, 902, 876, 856, 842, 811, 800, 771, 753, 676, 578 cm⁻¹

HRMS (ESI+): calc. for C₂₁H₂₃Cl₂F₂NO₂Na (M+Na) 452.0972, found 452.0966, 1.3 ppm.

4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl trifluoromethanesulfonate (3.9r): Following General Procedure B-2, 0.144 g (0.50 mmol) of compound 3.8r was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.110 g (49% yield) of desired compound 3.9r as a light brown oil.

¹H NMR (500 MHz, CDCl₃): δ 7.49 (d, J = 8.59 Hz, 2 H), 7.39 (d, J = 2.38 Hz, 1 H), 7.30–7.27 (m, 2 H) 7.23 (d, J = 8.83 Hz, 1 H), 7.20 (dd, J = 8.81, 2.36 Hz, 1 H), 3.53 (t, J = 10.63 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 149.4, 145.0 (t, J = 1.72 Hz), 132.7, 132.2 (t, J = 3.48 Hz), 131.7, 130.4, 129.7, 127.8, 124.2 (t, J = 2.10 Hz), 123.6 (t, J = 269.31 Hz), 121.5, 118.9 (q, J = 320.68 Hz), 41.6 (t, J = 29.85 Hz)
$^{19}$F NMR (376 MHz, CDCl$_3$, delay time = 5 s): $\delta$ –70.80 (t, $J = 10.64$ Hz, 2 F), –73.85 (s, 3 F)

IR (film): 1704, 1601, 1584, 1504, 1476, 1421, 1353, 1251, 1212, 1183, 1140, 1113, 1100, 1061, 1020, 946, 890, 807, 764, 729, 694, 674, 640, 609, 579, 523, 492 cm$^{-1}$

HRMS (HAPCI+): calc. for C$_{15}$H$_9$Cl$_2$F$_5$O$_4$S (M+) 449.9519, found 449.9516, 0.7 ppm.

Compounds in Scheme 3-6:

3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-1-tosyl-1H-indole (3.12a): Following General Procedure B-1, 0.167 g (0.50 mmol) of compound 3.11a was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.209 g (84% yield, 96% purity) of desired product 3.12a as an orange solid (MP = 90–93 °C).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.01 (d, $J = 8.28$ Hz, 1 H), 7.78 (d, $J = 8.16$ Hz, 2 H), 7.68 (s, 1 H), 7.60 (d, $J = 7.85$ Hz, 1 H), 7.38 (d, $J = 2.34$ Hz, 1 H), 7.35 (t, $J = 7.75$ Hz, 1 H), 7.27 (t, $J = 7.32$ Hz, 1 H), 7.22–7.16 (m, 5 H), 3.61 (t, $J = 10.78$ Hz, 2 H), 2.32 (s, 3 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 145.1, 135.3, 135.0, 131.5, 130.8, 130.3, 130.0, 129.2, 128.5, 128.3, 127.7, 126.9, 126.3, 125.4, 125.0, 124.3 (t, $J = 1.90$ Hz), 123.9 (t, $J = 269.38$ Hz), 123.4, 119.8, 113.7, 112.8 (t, $J = 3.71$ Hz), 32.1 (t, $J = 31.48$ Hz), 21.6

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –70.61 (t, $J = 10.86$, 2 F)

IR (film): 2258, 1598, 1476, 1448, 1369, 1324, 1275, 1259, 1217, 1188, 1175, 1122, 1090, 1061, 1020, 977, 908, 869, 811, 784, 765, 747, 703, 672, 750 cm$^{-1}$

HRMS (ESI+): calc. for C$_{23}$H$_{18}$Cl$_2$F$_2$NO$_3$S (M+H) 496.0353, found 496.0371, 3.6 ppm.

![Chemical Structure](image)

**4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)-1-phenyl-1H-pyrazole (3.12b):**

Following General Procedure B-1, 0.104 g (0.50 mmol) of compound 3.11b was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H$_2$O, furnishing 0.081 g (44% yield) of desired product 3.12b as a yellow solid (MP = 44–46 °C).
\( ^1 \)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.97 (s, 1 H), 7.74 (s, 1 H), 7.70–7.68 (m, 2 H), 7.45 (dd, \( J = 8.56, 7.31 \) Hz, 2 H), 7.42 (d, \( J = 2.45 \) Hz, 1 H), 7.30–7.26 (m, 2 H), 7.20 (dd, \( J = 8.85, 2.52 \) Hz, 1 H), 3.47 (t, \( J = 10.99 \) Hz, 2 H)

\( ^{13} \)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) 145.2, 142.1, 140.1, 131.5, 130.4, 129.6, 128.4, 127.8, 127.3, 126.7, 124.2 (t, \( J = 1.91 \) Hz), 123.9 (t, \( J = 268.72 \) Hz), 119.2, 113.0 (t, \( J = 3.88 \) Hz), 31.9 (t, \( J = 31.29 \) Hz)

\( ^{19} \)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –71.98 (t, \( J = 11.04 \) Hz, 2 F)

IR (film): 3053, 2927, 1601, 1576, 1505, 1476, 1431, 1403, 1385, 1343, 1258, 1215, 1187, 1120, 1097, 1062, 1042, 1017, 955, 905, 867, 838, 808, 756, 711, 691, 674, 656 cm\(^{-1}\)

HRMS (ESI+): calc. for C\(_{17}\)H\(_{13}\)Cl\(_2\)F\(_2\)N\(_2\)O (M+H) 369.0373, found 369.0347, 2.6 mmu.

\begin{figure}
\centering
\includegraphics[width=0.4\textwidth]{structure.png}
\caption{Structure of 3.12c}
\end{figure}

4-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)dibenzo[b,d]thiophene (3.12c): Following General Procedure B-1, 0.123 g (0.50 mmol) of compound 3.11c was reacted with 0.408 g (2.50 mmol) of 2,4-dichlorophenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H\(_2\)O,
furnishing 0.119 g (58% yield, 93% purity) of desired product 3.12c as a colorless solid (MP = 119–121 °C).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.15 (d, $J$ = 7.98 Hz, 2 H), 7.90–7.88 (m, 1 H), 7.57 (d, $J$ = 7.39 Hz, 1 H), 7.52–7.47 (m, 3 H), 7.40 (s, 1 ), 7.25 (d, $J$ = 8.79 Hz, 1 H), 7.18 (d, $J$ = 7.87 Hz, 1 H), 3.82 (t, $J$ = 10.93 Hz, 2 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 145.2 (d, $J$ = 1.74 Hz), 141.3, 139.1, 136.2, 136.0, 131.5, 130.3, 129.3, 128.7, 127.7, 127.0, 126.3 (t, $J$ = 24.55 Hz), 124.8, 124.6, 124.4 (t, $J$ = 1.87 Hz), 124.3 (t, $J$ = 270.61 Hz), 122.9, 121.9, 121.3, 41.3 (t, $J$ = 29.97 Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –69.59 (t, $J$ = 10.99 Hz, 2 F)

IR (film): 1476, 1444, 1405, 1385, 1352, 1325, 1265, 1170, 1122, 1099, 1062, 1022, 907, 842, 817, 797, 733, 706, 650, 618 cm$^{-1}$

HRMS (HAPCI$^+$): calc. for C$_{20}$H$_{12}$Cl$_2$F$_2$OS (M+) 407.9954, found 407.9940, 3.4 ppm.

2-(3-(2-(2,4-dichlorophenoxy)-2,2-difluoroethyl)phenyl)-5-(1,3-dioxolan-2-yl)pyridine (3.12d): Following General Procedure B-2, 0.1446 g (0.50 mmol) of compound 3.11d was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the
presence of 0.033 g (0.25 mmol) of TBD at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H₂O, furnishing 0.137 g (61% yield, 95% purity) of desired compound 3.12d as a yellow solid (MP = 84–86 °C).

¹H NMR (500 MHz, CDCl₃): δ 8.78 (d, J = 2.20 Hz, 1 H), 8.05 (s, 1 H), 7.96 (q, J = 2.71, 1.94 Hz, 1 H), 7.86 (dd, J = 8.14, 2.33 Hz, 1 H), 7.76 (d, J = 8.15 Hz, 1 H), 7.47 (d, J = 4.72 Hz, 2 H), 7.38 (d, J = 2.58 Hz, 1 H), 7.24 (d, J = 8.84 Hz, 1 H), 7.17 (dd, J = 8.89, 2.58 Hz, 1 H), 5.91 (s, 1 H), 4.16–4.11 (m, 2 H), 4.10–4.05 (m, 2 H), 3.59 (t, J = 11.10 Hz, 2 H)

¹³C NMR (126 MHz, CDCl₃): δ 158.0, 148.4, 145.4, 139.4, 135.1, 132.24, 132.17 (t, J = 2.94 Hz), 131.5, 131.4, 130.3, 129.5, 129.0, 128.5, 127.7, 126.6, 124.18, 124.12 (t, J = 269.56 Hz), 120.3, 102.1, 65.6, 42.3 (t, J = 29.16 Hz)

¹⁹F NMR (376 MHz, CDCl₃): δ –70.75 (t, J = 11.02 Hz, 2 F)

IR (film): 2887, 1703, 1601, 1569, 1475, 1354, 1256, 1095, 1062, 1025, 982, 942, 864, 839, 799, 757, 698, 564 cm⁻¹

HRMS (ESI+): calc. for C₂₂H₁₈Cl₂F₂NO₃ (M+H) 452.063, found 452.0627, 1.1 ppm.
References for Chapter 3 Appendix:

Chapter 4 – Metal Catalyzed Dioxygenation Reactions of Difluoroalkenes

4.1. Metal Catalyzed Reactions of gem-Difluoroalkenes

β,β-Difluoroalkenes display unique reactivity relative to typical alkenes, with the termini possessing distinct electronic character, thus enabling differential functionalization of each carbon.¹ Transition metal-free reactions exploit this reactivity through selective nucleophilic addition to the difluorinated position over the non-fluorinated position (Figure 4-1).¹ᵃ,² However, transition-metal-catalyzed reactions of gem-difluoroalkenes undergo defluorination to generate mono-fluorinated products (Figure 4-1a).¹ᵃ ³ Recently developed reactions have provided methods for functionalizing both the fluorinated and non-fluorinated carbon without eliminating fluoride via: 1) protonation of the unstable intermediate²ᵃ,²ᵇ or 2) exploiting a fluorination–metalation sequence (Figure 4-1b, c).⁴
Transition metals catalyze C–F functionalization reactions of gem-difluoroalkenes following distinct reactivity patterns relative to functionalization of other C–halogen bonds. Typically, transition metals perform oxidative addition to the C–X bond to begin catalytic reactions. However, the strong olefinic C–F bonds (120–129 kcal/mol)\(^5\) preclude direct oxidative addition under most conditions. As such, only a few recently reported reactions proceed via direct oxidative additions (Scheme 4-1a). These reactions require Pd-catalyst systems coupled with tetrafluoroethene (Scheme 4-1b),\(^6\) or Ni-based catalyst systems using high temperature (Scheme 4-1c).\(^3q,7\) Alternate direct C–F bond reductions require photocatalysis.\(^8\)
**Scheme 4-1:** Transition-Metal Catalyzed Reactions of *gem*-Difluoroalkenes Exploiting C–F Oxidative Addition

**a) Representative Mechanism of C–F Oxidative Addition**

**b) Oxidative Addition to C–F Bonds Under Pd Catalysis**$^{6a}$

**c) Oxidative Addition to C–F Bonds Under Ni Catalysis$^{7b}$**

Frequently, the metal-catalyzed reactions of *gem*-difluoroalkenes avoid oxidative addition to the C–F bond. Instead, the reactions initiate through two mechanisms, olefin-
metal coordination\textsuperscript{3d, 3p, 9} or C–H oxidative addition (Scheme 4-2a).\textsuperscript{3n, 3o, 3r, 10} These reaction pathways are accessible by a wide variety of metal catalyst systems, including Cu (Scheme 4-2b),\textsuperscript{3d, 3e, 3g, 3p, 9e, 9f, 11} Rh (Scheme 4-2c),\textsuperscript{3l, 3r} Co,\textsuperscript{3o} Fe,\textsuperscript{3c} Mn,\textsuperscript{3f, 3l} Zn,\textsuperscript{3b} Ni,\textsuperscript{3h, 3k} and Pd\textsuperscript{3a, 3n} systems. Following either initiation method, the same series of steps affect the net C–F functionalization. First, the metal undergoes regioselective insertion, adding the metal-bound nucleophile to the difluorinated carbon and the metal to the non-fluorinated carbon. Then the sequence terminates through facile $\beta$-fluoride elimination from the metallated intermediate to provide a M–F and the mono-fluorinated product (Scheme 4-2a).
A second mode of reactivity with transition metals involves fluoride addition to gem-difluoroalkenes to establish an equilibrium between the unstable anionic intermediate and the starting gem-difluoroalkene. Once the equilibrium forms, a transition metal traps the
β-anionic intermediate and performs further bond-forming reactions (Scheme 4-3a). This strategy enables Ag-catalyzed homo-dimerization of the β-anionic intermediate (Scheme 4-3b)\textsuperscript{4b} or Ag-catalyzed cross coupling with olefins\textsuperscript{4a} after fluorination. More recent examples of this strategy exploit Pd-catalysis\textsuperscript{4c-f} or photocatalysis\textsuperscript{12} to effect similar difunctionalization reactions. These metal-catalyzed difunctionalization reactions a) couple the non-fluorinated carbon of the gem-difluoroalkene to alcohols (Scheme 4-3c)\textsuperscript{4c} or allyl functionalities,\textsuperscript{4e, 12} b) enable oxidative cross-coupling with olefins\textsuperscript{4a} or arenes (Scheme 4-3b),\textsuperscript{4d} or c) initiate 3+2 annulations with alkynes.\textsuperscript{4f} However, current difunctionalization reactions currently exclusively involve fluorination followed by metalation, and only provide access to trifluoromethyl-derived products. One unique difunctionalization reaction avoids metal catalysis, but is still restricted to trifluoromethyl-derived products.\textsuperscript{13} Thus, difunctionalization reactions of gem-difluoroalkenes with non-fluoride nucleophiles remain unknown.
Scheme 4-3: Fluorinative Functionalization of *gem*-Difluoroalkenes to Provide Trifluoromethyl Products

- **a) Representative Mechanism:** Fluorinative Difunctionalization of *gem*-Difluoroalkenes

- **b) Ag-Catalyzed Homodimerization of *gem*-Difluoroalkenes**

- **c) Pd-Catalyzed Fluoroarylation of *gem*-Difluoroalkenes**

- **c) Pd-Catalyzed Hydroxylfluorination of *gem*-Difluoroalkenes**
4.2. Dioxygenation Reactions of Alkenes

Alkenes undergo C–C or C–heteroatom bond formation via both nucleophilic and electrophilic strategies, making them a valuable functional handle in synthetic chemistry. Oxidation reactions of alkenes represent a particularly valuable strategy for rapid, late stage functionalization of simple compounds. Several strategies enable the addition of varying amounts of oxygen to alkenes. Mono-oxidation reactions of alkenes exploit classical reactions, such as epoxidation,14 hydroboration-oxidation,15 or Wacker-type reactions.16 Alkenes also serve as a directing group for oxidation via allylic oxidation strategies,17 or as a site for oxidative removal of a carbon through ozonolysis.18

Dioxidation reactions of alkenes provide an opportunity to introduce multiple functional groups en route to complex structures.19 However, current dioxidations of alkenes typically generate either the same oxygen-based functional group on both positions of the alkene (e.g. dihydroxylation and epoxidation-hydroxide addition),20 or a regiochemical mixture of two distinct oxygen-containing groups.21 Classical dioxidation strategies generate two racemic alcohols, such as Co catalyzed acetylation / hydroxylation followed by hydrolysis,21 the use of osmium tetroxide,22 or epoxidation followed by nucleophilic addition of hydroxide.19b,23 Several methods, such as Sharpless dioxidation reactions,19d enable the stereoselective incorporation of two alcohols to an alkene.

Regioselective functionalization of an alkene with two different oxygen-based functional groups typically requires a dihydroxylation step followed by selective protection/deprotection and subsequent functionalization (Figure 4-2a),24 epoxidation
then ring opening via addition of an alcohol (Figure 4-2b),\textsuperscript{25} or non-selective oxidation with two different oxygen containing functional groups (Figure 4-2c).\textsuperscript{21} Although an ideal method would selectively install both O-based functional groups in a single step, such selective unsymmetric dioxygenations of alkenes typically require the use of either strong oxidizing agents (Figure 4-2d),\textsuperscript{26} or N-hydroxy reagents as coupling partners (Figure 4-2e).\textsuperscript{27} These latter reactions proceed through a net anti-Markovnikov addition of functionalized oxygen groups to styrenes, an addition only recently achieved with alcohols.\textsuperscript{28}
In contrast, oxidation reactions of fluoroalkenes are under-developed, as several obstacles prevent such reactions. First, oxidation reactions generally react through the HOMO of alkenes. The high electrophilicity of fluoroalkenes lowers the HOMO and makes any oxidation reaction of fluoroalkenes more difficult. Second, oxidation of fluoroalkenes is restricted to the non-fluorinated carbon, as installing an oxygen functionality at the fluorinated carbon results in defluorination of the substrate.
4.3. Co-Catalyzed Selective Unsymmetric Dioxidation of $\beta,\beta$-Difluorostyrenes

To complement these recently reported difunctionalization reactions of gem-difluoroalkenes and regioselective deoxygenation reactions of alkenes, we present a Co-catalyzed unsymmetrical dioxygenation reaction of difluoroalkenes to generate $\beta$-phenoxy-$\beta,\beta$-difluorobenzyl alcohols. This work exploits a regioselective addition of phenols and molecular oxygen to $\beta,\beta$-difluorostyrenes via one-electron redox chemistry with Co. The reaction avoids $\beta$-fluoride elimination through oxidation of the $\beta$-anionic intermediate to provide the stable $\beta$-phenoxy-$\beta,\beta$-difluorobenzyl alcohol products. Notably, the products bear fluorine within sufficient vicinity to modulate the acidity and basicity of both O-based functional groups,\textsuperscript{30} which influences the solubility,\textsuperscript{31} lipophilicity,\textsuperscript{30a, 32} molecular conformation,\textsuperscript{33} and ligand-protein interactions relative to the non-fluorinated analogs.\textsuperscript{34} Further, the positioning of the F-atoms at the metabolic soft spot can block cytochrome P-450 mediated O-dealkylation processes,\textsuperscript{35} thus likely increasing stability of the substructure relative to the parent non-fluorinated analogs. Thus, we speculate that this substructure, although underrepresented in the literature, should be beneficial for chemical biologists and medicinal chemists.

Following our previous work on the base-catalyzed hydrofunctionalization of difluoroalkenes with thiols\textsuperscript{2a} and phenols,\textsuperscript{2c} we initially aimed to explore the nucleophilic addition of phenols to gem-difluoroalkenes. In the presence of dissolved oxygen, we observed two intriguing products bearing alcohol and ketone groups at the benzylic position (Table 4-1, entry 1). This unsymmetric dioxygenation product formed $\beta$-phenoxy-
β,β-difluorobenzyl alcohols and ketones with exclusive regioselectivity. In contrast to O₂, external oxidants, including MnO₂, K₂S₂O₈, NMO, and oxone, mainly reduced the overall yield and minimally altered selectivity (Table 4-1, entry 2–5). Most oxidizing metals, such as Fe(III) or Ag(I), failed to increase the selectivity between the alcohol and ketone products (Table 4-1, entry 6–11). However, the use of a cobalt catalyst selectively provided the alcohol product in moderate to high yield (Table 4-1, entry 12). Further exploration revealed that an oxygen atmosphere increased the rate of reaction even without TBD as an activating base, and that Co(II) and (III) were competent catalysts, while Co(0), (I), and (IV) precatalysts decreased the reactivity and selectivity (Table 4-1, entry 13–16). After thorough optimization, a simple, unligated system of Co(acac)₂, 1,2-dichlorobenzene, O₂, and 90–140 °C proved most effective (Table 4-1, entry 17).
Table 4-1: Optimization of Selective Dioxygenation of Difluoroalkenes

![Chemical structure diagram]

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</tbody>
</table>

[a] Standard conditions: 4.1 (1.0 equiv., 0.10 mmol), 4.2 (3.0 equiv., 0.30 mmol), DCB (0.25 M, 0.40 mL), 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD, 10%, 0.010 mmol), 100 °C, 18 h. [b] As determined by ¹⁹F NMR analysis of the reaction mixture using α,α,α-trifluorotoluene (TFT) as a standard (10 µL). [c] In the absence of 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD). [d] 110 °C, 24 hours. [e] isolated yield.

Under these conditions, a broad range of gem-difluoroalkenes were competent in the reaction, with most substrates providing >10:1 selectivity for the alcohol product over the
ketone product (Scheme 4-4). Highly-reactive electron-rich substrates required lower reaction temperature and/or shorter reaction times, to give the products in moderate to good yields (4.5a–f). More forcing conditions decomposed the starting materials, but did not provide the desired products by ¹⁹F NMR analysis. In contrast, electron-deficient substrates required more forcing conditions, and yields were slightly reduced (4.5g–l). At extreme temperatures (>140 °C) the substrate decomposed. Mono-ortho-substituted substrates reacted sluggishly, and despite elevated time and temperature did not reach full conversion. However, the products were isolated in moderate yield, with the unreacted starting material recovered (4.5e, m). Bis-ortho-substituted substrates did not react (4.5n). Unfortunately, amine-containing substrates were not competent in this reaction (4.5d).
Scheme 4-4: Scope of β,β-Difluorostyrenes

\[
\text{R} \quad + \quad \text{4.2} \quad \xrightarrow{10-20\% \text{Co(acac)}_2} \quad \text{4.5a-n}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO</td>
<td>4.5a</td>
<td>74% (16:1)</td>
<td>90</td>
</tr>
<tr>
<td>O2N</td>
<td>4.5f</td>
<td>54% (21:1)</td>
<td>100</td>
</tr>
<tr>
<td>MeO</td>
<td>4.5b</td>
<td>48% (25:1)</td>
<td>90</td>
</tr>
<tr>
<td>MeO</td>
<td>4.5c</td>
<td>67% (14:1)</td>
<td>100</td>
</tr>
<tr>
<td>BnO</td>
<td>4.5d</td>
<td>21% (9:1)</td>
<td>90</td>
</tr>
<tr>
<td>(iPr)2N</td>
<td>4.5e</td>
<td>49% (16:1)</td>
<td>90</td>
</tr>
<tr>
<td>Me</td>
<td>4.5g</td>
<td>50% (9:1)</td>
<td>120</td>
</tr>
<tr>
<td>O2N</td>
<td>4.5h</td>
<td>39% (3:1)</td>
<td>130</td>
</tr>
<tr>
<td>Cl</td>
<td>4.5i</td>
<td>57% (&gt;25:1)</td>
<td>100</td>
</tr>
<tr>
<td>F3C</td>
<td>4.5j</td>
<td>43% (9:1)</td>
<td>140</td>
</tr>
<tr>
<td>O2N</td>
<td>4.5k</td>
<td>41% (12.5:1)</td>
<td>140</td>
</tr>
<tr>
<td>OAr</td>
<td>4.5l</td>
<td>44% (15:1)</td>
<td>140</td>
</tr>
</tbody>
</table>

10–20% Co(acac)_2, 90–140 °C, DCB, 24–48 h, O_2
[a] Standard conditions: 4.4a–n (1.0 equiv., 0.50 mmol), 4.2 (3.0 equiv., 1.5 mmol), DCB (0.25 M, 2.0 mL), Co(acac)$_2$ (10 mol%, 0.050 mmol), temperature as indicated, for 24 h under an O$_2$ atmosphere. The selectivity of alcohol:ketone was determined by $^{19}$F NMR analysis of the reaction mixture and is reported in parentheses. Yields represent the average of 2 runs. [b] Co(acac)$_2$ (20 mol%, 0.10 mmol). [c] 48 h.

Many heterocycles were compatible with the reaction. These substrates followed a similar reactivity pattern (Scheme 4-5), in which electron-rich heterocycles performed better than electron deficient heterocycles under more mild conditions (4.7a–c vs. 4.7d). Heterocycles with and aliphatic amine (4.7c) or steric bulk at the ortho position (4.7e) reacted poorly. Unexpectedly, an ethylene-glycol acetal-protected aldehyde partially deprotected under the reaction conditions (4.7d), requiring reprotection on workup.
Scheme 4-5: Scope of Heteroaryl \( \beta,\beta \)-Difluorostyrenes

Scheme 4-5: Scope of Heteroaryl \( \beta,\beta \)-Difluorostyrenes

[a] Standard conditions: 4.6a–e (1.0 equiv., 0.50 mmol), 4.2 (3.0 equiv., 1.5 mmol), DCB (0.25 M, 2.0 mL), Co(acac)\(_2\) (10 mol\%, 0.050 mmol), temperature as indicated, for 24 h under an \( \text{O}_2 \) atmosphere. The selectivity of alcohol:ketone was determined by \(^{19}\text{F}\) NMR analysis of the reaction mixture and is reported in parentheses. Yields represent the average of 2 runs. [b] Co(acac)\(_2\) (20 mol\%, 0.10 mmol). [c] 36 h. [d] 48 h, worked up with 4 N HCl/1,4-dioxane and ethylene glycol.

Phenolic nucleophiles displayed distinct reactivity (Scheme 4-6). Electron-deficient phenols reacted favorably (4.9a–f, 4.3), although the electronic character of the phenol nucleophile did not greatly affect the overall yields of product. Similar to difluoroalkene
substrates, phenolic nucleophiles bearing an ortho-substituent reacted sluggishly (4.9j–l), but still gave product in synthetically useful yields, with the remaining difluoroalkene recovered unreacted. At present, heterocyclic phenols are not competent substrates, leaving the difluoroalkene fully unreacted (4.9m). However, we remain optimistic that these substrates might become compatible with further adjustments to the catalyst system.
Scheme 4-6: Scope of Phenol Nucleophiles$^[[a]]$

\[
\text{MeO-} \quad \text{OH} \quad \text{R} \quad \text{Ar} \\
\begin{array}{c}
\text{F} \\
\text{O} \\
\text{F} \\
\text{OH}
\end{array}
\]

\[
\text{10–20% Co(acac)$_2$} \\
90–140 °C, DCB \\
24–48 h, O$_2$
\]

\[
\text{4.1} \quad \text{4.8a–j} \quad \text{4.9a–j}
\]

\[
\begin{array}{c}
\text{MeO-} \\
\text{F} \\
\text{O} \\
\text{OH}
\end{array}
\]

\[
\begin{array}{c}
\text{MeO} \\
\text{OMe} \\
\text{OMe}
\end{array}
\]

\[
\begin{array}{c}
\text{NO$_2$} \\
\text{CN} \\
\text{Cl}
\end{array}
\]

\[
\text{Br} \\
\text{I}
\]

\[
\text{NHTs} \\
\text{Ph} \\
\text{Me}
\]

\[
\begin{array}{c}
\text{4.9a} \\
\text{4.9b} \\
\text{4.9c}
\end{array}
\]

\[
\text{52% (8.6:1)} \\
\text{71% (8:1)} \\
\text{51% (4:1)}
\]

\[
\text{100 °C} \\
\text{100 °C} \\
\text{110 °C}
\]

\[
\begin{array}{c}
\text{4.9d} \\
\text{4.9e} \\
\text{4.9f}
\end{array}
\]

\[
\text{72% (6:1)} \\
\text{67% (13:1)} \\
\text{69% (18:1)$^[[b,d]$}}
\]

\[
\text{100 °C} \\
\text{110 °C} \\
\text{100 °C}
\]

\[
\begin{array}{c}
\text{4.9g} \\
\text{4.9h} \\
\text{4.9i}
\end{array}
\]

\[
\text{49% (3.6:1)$^[[b]$}} \\
\text{74% (16:1)} \\
\text{63% (15:1)$^[[c]$}}
\]

\[
\text{120 °C} \\
\text{110 °C} \\
\text{110 °C}
\]

\[
\begin{array}{c}
\text{4.9j} \\
\text{4.9k} \\
\text{4.9l}
\end{array}
\]

\[
\text{49% (19:1)$^[[b,d]$}} \\
\text{40% (18:1)$^[[b,d]$}} \\
\text{59% (14:1)$^[[b,d]$}}
\]

\[
\text{110 °C} \\
\text{110 °C} \\
\text{110 °C}
\]
[a] Standard conditions: 4.1 (1.0 equiv., 0.50 mmol), 4.8a–j (3.0 equiv., 1.5 mmol), DCB (0.25 M, 2.0 mL), Co(acac)$_2$ (10%, 0.050 mmol), temperature as indicated, for 24 h under an O$_2$ atmosphere. The selectivity of alcohol:ketone was determined by $^{19}$F NMR analysis of the reaction mixture and is reported in parentheses. Yields represent the average of 2 runs. [b] Co(acac)$_2$ (20 mol%, 0.10 mmol). [c] 36 h. [d] 48 h.

4.4. Mechanistic Considerations

Based on mechanistic studies and an analysis of previous work we propose two mechanisms involving Co/O$_2$-mediated generation of phenoxy radical prior to engagement of the difluoroalkene.

In the first proposed mechanism, Co plays two key roles, as both an initiator and quencher of the catalytic sequence (Figure 4-3). In the first step, Co reacts with O$_2$ to generate superoxide radical (O$_2^{•-}$), which subsequently abstracts H$^•$ from phenol to generate PhO$^•$ (B) and a peroxide anion (HO$_2^{–}$). Reaction of PhO$^•$ (B) with the difluoroalkene generates stabilized benzyl radical C. This C–O bond-forming event occurs at the electron-deficient difluorinated position, consistent with other known radical addition reactions to gem-difluoroalkenes. The anticipated oxidation of C by O$_2$ or Cobalt-bound peroxide anion might generate benzylperoxide D, and subsequent single electron reduction of D by the Co(III) intermediate eventually generates benzyl alcohol product 4.5 by bond homolysis and regenerates Co(II). These final steps (C→4.5) are consistent with reaction of styrenes and N–oxides using a Co(II) catalyst system in the presence of tert-butylhydroperoxide (TBHP).
In the second proposed mechanism, Co initiates a radical chain reaction with oxygen and phenol (Figure 4-4). Co initiates the reaction by reducing \( \text{O}_2 \) to generate superoxide radical \( (\text{O}_2^\cdot) \),\(^{36}\) which subsequently abstracts \( \text{H}^\cdot \) from phenol to generate \( \text{PhO}^\cdot \) (B) to initiate the radical chain reaction, and a peroxide anion \( (\text{HO}_2^-) \).\(^{37}\) Reaction of \( \text{PhO}^\cdot \) (B) with the difluoroalkene generates stabilized benzyl radical C. Here the mechanisms
diverge, as C oxidizes with O₂ to generate benzylperoxide anion D. In what is likely an electron transfer reaction, Co(III) abstracts an electron from benzylperoxide intermediate D, which likely undergoes bond homolysis to generate a benzyl alcohol radical, which abstracts a hydrogen radical from a molecule of phenol to regenerate PhO• (B) and propagate the reaction, while oxygen oxidizes Co(II) to Co(III). This mechanism explains both the source of the phenone side product and the influence of Co on selectivity, as the benzylperoxide intermediate D can undergo rapid elimination of hydroxide to generate phenone side product E, whereas bond homolysis to generate the benzyl alcohol radical is faster in the presence of Co.
**Figure 4-4:** Proposed Co-Initiated Radical Chain Reaction

This figure illustrates the proposed mechanism for a Co-initiated radical chain reaction. The reaction is initiated by Co(II) (acac)$_2$ with the addition of PhOH, leading to the formation of intermediate A. Oxygen (O$_2$) and PhOH then react with Co(II) to form Co(III)-O$_2$H, which then reacts with the intermediate A to form intermediate D. D then reacts with Co(III) to form intermediate E, which then reacts with PhOH to form intermediate F. The cycle continues with the formation of intermediate G and H, which then react to form intermediate I. The final product of the reaction is the formation of another Co(II) (acac)$_2$.
Evidence for early-stage generation of PhO• ($\text{A} \to \text{B}$) derives from a series of electron paramagnetic resonance (EPR) experiments using spin trapping reagents. Specifically, the reaction of Co(II), phenol, $O_2$ and 5-tert-butoxycarbonyl-5-methyl-1-pyrroline-$N$-oxide (BMPO) or 5,5-dimethyl-1-pyrroline-$N$-oxide (DMPO) generated spin-trapped adducts with EPR spectra (Figure 4-5A)\textsuperscript{41} consistent with previous reports of Co(II) generating O-based radicals.\textsuperscript{42,43} The EPR spectrum of the phenoxy radical–BMPO adduct possessed a $^{14}$N hyperfine coupling constant (1.4 mT) and $^1$H hyperfine coupling constant (2.3 mT) consistent with the 2,4-dichlorophenoxyacetic acid C-based radical trapped by DMPO ($^{14}$N hyperfine coupling constant = 1.53 mT, $^1$H hyperfine coupling constant = 2.27 mT).\textsuperscript{44} Further experimental support for radical intermediates includes the decreased yields of product using known radical traps (butylated hydroxytoluene [BHT] and 1,4-benzoquinone) (Table 4-2). Specifically, BHT and 1,4-benzoquinone inhibited the formation of desired product 4.5 without forming fluorinated adducts, which suggests that (1) radicals exist, and (2) the initial radical does not form on the difluoroalkene (Table 4-2). Additional support for the early-stage involvement of phenol comes from kinetic studies demonstrating a saturable first order rate dependence with respect to phenol (Table 4-3).
Figure 4-5: Room Temperature EPR Analysis of Radicals by Spin Trapping with BMPO

Reaction Conditions: Co(acac)$_2$ (1.0 equiv., 0.10 mmol), 4.2 (3.0 equiv., 0.30 mmol) in 0.80 mL DCB 90 °C, for 15 min under an Ar atmosphere, followed by the gas exchange of Ar for O$_2$, 90 °C, for 15 min followed by quenching with BMPO solution.
**Table 4-2: Radical Trap Analysis**[^a]

<table>
<thead>
<tr>
<th>Radical Trap</th>
<th>Conv.</th>
<th>4.5a</th>
<th>4.6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBu OH tBu</td>
<td>68%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>O O</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NO₂ NO₂</td>
<td>92%</td>
<td>54%</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

[^a] Standard conditions: 4.4a (1.0 equiv., 0.50 mmol), 4.2 (3.0 equiv., 1.5 mmol), DCB (0.25 M, 2.0 mL), Co(acac)₂ (0.10 equiv., 0.050 mmol), radical trap (3.0 equiv. 1.5 mmol), 90 °C, for 24 h under an O₂ atmosphere. The conversion of 4.3a and the yield of 4.5a and 4.6a was determined by ¹⁹F NMR analysis of the reaction mixture in the presence of 50 µL (0.40 mmol) of TFT.
Table 4-3: Kinetic Analysis of the Reaction Order in Phenol by GC-FID

<table>
<thead>
<tr>
<th>4.2 Equiv.</th>
<th>$k_{obs}$ (GC-FID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.0040</td>
</tr>
<tr>
<td>1.33</td>
<td>0.0050</td>
</tr>
<tr>
<td>1.67</td>
<td>0.0070</td>
</tr>
<tr>
<td>2.0</td>
<td>0.0080</td>
</tr>
<tr>
<td>2.5</td>
<td>0.0090</td>
</tr>
<tr>
<td>3.0</td>
<td>0.0100</td>
</tr>
<tr>
<td>5.0</td>
<td>0.0120</td>
</tr>
</tbody>
</table>

[a] Standard conditions: 4.4a (1.0 equiv., 0.25 mmol), 4.2 (1.0–5.0 equiv., 0.25–1.25 mmol), DCB (0.25 M, 1.0 mL), Co(acac)$_2$ (0.10 equiv., 0.025 mmol), 90 °C, for 30 min under an O$_2$ atmosphere. The formation of 4.5a was determined by GC-FID analysis standardized with 57 µL (0.25 mmol) of dodecane.

Proposed mechanisms initiating by reacting the difluoroalkene with either Co or O$_2$ were discounted by a series of EPR experiments. Specifically, in stoichiometric experiments monitored by EPR at 10 K, the difluoroalkene did not react with Co(II) or Co(III) by ligation or oxidation (Figure 4-6). Further, zero-order kinetics with respect to the difluoroalkene indicate non-involvement of difluoroalkene early in the catalytic cycle (Table 4-4), ruling out mechanisms involving epoxidation of the difluoroalkene or an electron transfer between Co(III) and a difluoroalkene benzyl radical.$^{21}$
**Table 4-4:** Kinetic Analysis of the Reaction Order in Difluoroalkene by GC-FID\[a\]

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>4.4a Equiv.</th>
<th>(k_{obs}^{\text{GC-FID}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.010</td>
</tr>
<tr>
<td>3.0</td>
<td>0.011</td>
</tr>
<tr>
<td>5.0</td>
<td>0.0060</td>
</tr>
</tbody>
</table>

[a] Standard conditions: 4.4a (1.0–5.0 equiv., 0.25–1.25 mmol), 4.2 (3.0 equiv. 0.75 mmol), DCB (0.25 M, 1.0 mL), Co(acac)\(_2\) (0.10 equiv., 0.025 mmol), 90 °C, for 30 min under an O\(_2\) atmosphere. The formation of 4.5a was determined by GC-FID analysis standardized with 57 \(\mu\)L (0.25 mmol) of dodecane.
Reaction Conditions: [A] 0.017 g (1.0 equiv., 0.10 mmol) of 4.4a was reacted with 0.026 g (1.0 equiv., 0.10 mmol) of Co(acac)$_2$ in 0.40 mL of DCB at 90 °C in Ar for 15 min. A 100 µL sample was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. Then Ar was exchanged for O$_2$, and reacted at 90 °C for 2 h. A 100 µL sample was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. [B] 0.026 g (1.0 equiv., 0.10 mmol) of Co(acac)$_2$ was stirred in 0.40 mL of DCB at 90 °C in Ar for 15 min. A 100 µL sample was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. Then Ar was exchanged for O$_2$, and reacted at 90 °C for 2 h. A 100 µL sample was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. [C] 0.017 g (1.0 equiv., 0.10 mmol) of 4.4a was reacted with 0.0519 g (3.0 equiv., 0.30 mmol) of 4-bromophenol in the presence of 0.0026 g (0.10 equiv., 0.010 mmol) of Co(acac)$_2$ in 0.40 mL of DCB at 90 °C in Ar for 15 min. A 100 µL sample
was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. Then Ar was exchanged for O$_2$, and reacted at 90 °C for 2 h. A 100 μL sample was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. [D] 0.052 g (3.0 equiv., 0.30 mmol) of 4-bromophenol was stirred in the presence of 0.026 g (1.0 equiv., 0.10 mmol) of Co(acac)$_2$ in 0.40 mL of DCB at 90 °C in Ar for 15 min. A 100 μL sample was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. Then Ar was exchanged for O$_2$, and reacted at 90 °C for 2 h. A 100 μL sample was quenched in N$_2$ (liq.), and analyzed by EPR spectroscopy. [E] Calculated spectra using the EasySpin toolbox from Matlab\textsuperscript{45} for Co(acac)$_2$(EtOH)$_2$.\textsuperscript{42}

Several pieces of evidence support Co(II) and O$_2$ playing key roles in initiating the catalytic cycle. First, EPR studies under stoichiometric conditions (Co(II)/O$_2$/PhOH) suggest the formation of initial Co(II) complex (A) bearing two phenolic ligands and two acetylacetonate ligands in an octahedral complex\textsuperscript{42} prior to oxygen activation. This structural assignment was made based on the similarity of the measurements of the g tensor values (Figure 4-6C/D g tensor = 5.8, 3.8, 2.5) of the EPR spectrum in comparison to a known Co(acac)$_2$(EtOH)$_2$ complex assigned through correlation between Density Functional Theory and EPR spectra (Figure 4-6E, g tensor = 5.8, 2.0).\textsuperscript{42} Notably, this same complex is observed as an early intermediate in catalytic reactions quenched by N$_2$ (liq.) and studied by EPR at 10 K, suggesting that (A) forms prior to O$_2$ activation (Figure 4-6C).

Second, following formation of complex A, O$_2$ oxidizes Co(II) to Co(III).\textsuperscript{36} This precatalytic oxidation of Co(II) was observed by 10 K EPR with or without either phenol or difluoroalkene (Figure 4-6), and qualitatively by a color change from red [Co(II)] to green.
[Co(III)]. This step concurrently generates a superoxide radical that we propose serves as the oxidant for the phenol. Supporting this theory, in the absence of O₂, no reaction of difluoroalkene 4.4a occurs (other than thermal degradation, Scheme 4-7), while zero-order kinetics in Co indicate the non-involvement of Co in the rate-determining step (Table 4-5).

Third, data suggesting that Co(II)/O₂/PhOH play key roles early in the catalytic cycle involves the stoichiometric reactions of Co(II) or Co(III) and phenol, which were monitored by EPR at 10 K under Ar. In these reactions, no changes to the Co center were observed (Figure 4-6D) suggesting that O₂ also participates in activating the phenol to generate phenoxy radical (B) prior to reaction with the gem-difluoroalkene to generate benzyl radical (C).

Scheme 4-7: Reaction in the Absence of O₂[^a]

<table>
<thead>
<tr>
<th>Co</th>
<th>4.4a Conv</th>
<th>4.5a Yield</th>
<th>4.6a Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co(acac)₂</td>
<td>40%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Co(acac)₃</td>
<td>40%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

[^a] Standard conditions: 0.017g of 4.4a (1.0 equiv., 0.1 mmol), 0.052 g of 4.2 (3.0 equiv., 0.3 mmol), DCB (0.25 M, 0.40 mL), Co(acac)_n (0.10 equiv., 0.010 mmol), 90 °C,
for 24 h under an Ar atmosphere. The conversion of 4.4 and formation of 4.5a or 4.6a was determined by $^{19}$F NMR analysis standardized with 10 µL (0.080 mmol) of TFT.

**Table 4-5**: Kinetic Analysis of the Reaction Order in Co(acac)$_2$ by GC-FID$^[[a]]$

<table>
<thead>
<tr>
<th>% Co(acac)$_2$</th>
<th>$k_{\text{obs}}$ (GC–FID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.050</td>
<td>0.010</td>
</tr>
<tr>
<td>0.10</td>
<td>0.0090</td>
</tr>
<tr>
<td>0.20</td>
<td>0.010</td>
</tr>
<tr>
<td>0.30</td>
<td>0.0080</td>
</tr>
<tr>
<td>0.40</td>
<td>0.0080</td>
</tr>
<tr>
<td>0.50</td>
<td>0.0060</td>
</tr>
</tbody>
</table>

$^[[a]]$ Standard conditions: 4.4a (1.0 equiv., 0.25 mmol), 4.2 (3.0 equiv., 0.75 mmol), DCB (0.25 M, 1.0 mL), Co(acac)$_2$ (0.050–0.50 equiv., 0.013–0.13 mmol), 90 °C, for 30 min under an O$_2$ atmosphere. The formation of 4.5a was determined by GC-FID analysis standardized with 57 µL (0.25 mmol) of dodecane.

4.5. Conclusions

In conclusion, the use of a Co-based catalyst system in an oxygen-rich environment enables the selective dioxygenation of difluoroalkenes in a process that avoids β-fluoride elimination. The reaction selectively generates a difunctionalized product containing a benzylic alcohol and a difluoroether, versatile functional groups for further exploitation.
Many useful functional groups are tolerated, while the reaction’s simple and mild conditions provide the opportunity for wider application. Mechanistic investigation implicates a radical mechanism, where Co(II) generates a superoxide radical from O₂, which abstracts a hydrogen radical from phenol to form a phenoxy radical. This phenoxy radical attacks the difluorinated position of the difluoroalkene to generate a benzyl radical, which quenches with peroxide anion. Then, electron transfer from the Co catalyst controls the selectivity for reduction of the benzyl peroxide. When viewed in combination with the many direct and facile preparations of difluoroalkenes,¹a the current reaction provides a method for rapid diversification of compounds containing functional groups frequently observed in bioactive compounds.
4.6. References for Chapter 4


29. (a) Hayashi, S.-i.; Nakai, T.; Ishikawa, N., DEFLUORINATIVE COUPLING REACTIONS OFgem-DIFLUOROOLEFINS WITH ORGANOLITHIUM REAGENTS. NOVEL, FACILE METHODS FOR CHAIN ELONGATIONS OF ALDEHYDES LEADING TO AMIDES, ACETYLENES, AND KETONES. *Chem. Lett.* 1980, 9 (8), 935-938; (b)


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References: ..................................................................................................................................425
**General Considerations:**

Unless otherwise noted, reactions were performed under an atmosphere of air using oven-dried glassware. Selective dioxygenation reactions of phenols and difluorostyrenes were performed in 20 mL borosilicate glass scintillation vials sealed with a PTFE-lined screw-top cap. All other reactions were performed in round-bottom flasks sealed with rubber septa. Stainless-steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by either $^{19}$F NMR with an internal standard of $\alpha,\alpha,\alpha$-trifluorotoluene or by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualized by quenching of fluorescence. Column chromatography was conducted using a Teledyne Isco CombiFlash Rf 200 system utilizing gradient elution. Isolated yields reported in the manuscript represent an average of at least 2 independent runs of final compound 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. Cobalt(II) 2,4-pentanedionate [Co(acac)$_2$] was purchased from Alfa Aesar. 1,2–Dichlorobenzene (DCB, anhydrous, 99+%) and $N$-methylpyrrolidine (NMP, anhydrous) were purchased from Sigma Aldrich. Solvents, including dimethylformamide (DMF), toluene (PhMe), dichloromethane (DCM), methanol (MeOH), acetonitrile (MeCN), and tetrahydrofuran (THF) were used directly from a solvent purification system, in which solvent was dried by passage through two columns of activated alumina under argon.
Other chemical abbreviations utilized in this document include: \(\alpha,\alpha,\alpha\)-trifluorotoluene (TFT), sodium sulfate (\(\text{Na}_2\text{SO}_4\)), magnesium sulfate (\(\text{MgSO}_4\)), ethyl acetate (\(\text{EtOAc}\)), diethyl ether (\(\text{Et}_2\text{O}\)), ammonium chloride (\(\text{NH}_4\text{Cl}\)), \(\text{n}^\text{th}\)butyl lithium (\(\text{n}^\text{BuLi}\)), sodium hydroxide (\(\text{NaOH}\)), room temperature (R.T.), \(\text{t}^\text{th}\)butyl carbonate anhydride (\(\text{Boc}_2\text{O}\)), potassium carbonate (\(\text{K}_2\text{CO}_3\)), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and hydrochloric acid (\(\text{HCl}\)).

Proton nuclear magnetic resonance (\(^1\text{H NMR}\)) and fluorine nuclear magnetic resonance (\(^{19}\text{F NMR}\)) were taken on a Bruker AVIIIHD 400 AVANCE spectrometer (400 and 376 MHz respectively). Proton and carbon nuclear magnetic resonance (\(^{13}\text{C NMR}\)) were taken on a Bruker AVIII 500 Avance spectrometer with a CPDUL cryoprobe (500 and 126 MHz respectively). Chemical shifts (\(\delta\)) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to the proton resonance of residual solvent in the NMR solvent (\(\text{CHCl}_3\): \(\delta = 7.26\) ppm; DMSO: \(\delta = 2.50\) ppm). Chemical shifts (\(\delta\)) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonance of the solvent residual peak (\(\text{CDCl}_3\): \(\delta = 77.2\) ppm; DMSO: \(\delta = 39.52\) ppm). Chemical shifts for fluorine are reported uncorrected in ppm upfield from trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (\text{s} = singlet, \text{d} = doublet, \text{t} = triplet, \text{q} = quartet, \text{p} = pentet, \text{m} = multiplet), coupling constant in Hertz (Hz), integration. Electron paramagnetic resonance (EPR) were taken on a Bruker EMXplus EPR spectrometer with an Oxford cryostat. 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 on a Perkin Elmer Spectrum Two Fourier Transform Infrared Spectrometer by drying samples on a diamond ATR Sample base plate. Uncorrected melting points were measured on a Thomas Hoover Capillary Melting Point apparatus.

**Preparation and Characterization of Gem-Difluoroalkenes**

![Molecule Image](image.png)

5-(2,2-difluorovinyl)-1,2,3-trimethoxybenzene (4.1): Compound 4.1 corresponds to compound 2.1 in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
1-(2,2-difluorovinyl)-4-methoxybenzene (4.4a): Compound 4.4a corresponds to compound 2.5a in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

(4-(2,2-difluorovinyl)phenyl)(methyl)sulfane (4.4b): Compound 4.4b corresponds to compound 2.5b in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

1-(benzyloxy)-4-(2,2-difluorovinyl)-2-methoxybenzene (4.4c): Compound 4.4c corresponds to compound 2.5h in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
4-(3-(2,2-difluorovinyl)phenyl)morpholine (4.4d): Compound 4.4d corresponds to compound 2.5d in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

1-(2,2-difluorovinyl)-2,4-dimethylbenzene (4.4e): Compound 4.4e corresponds to compound 3.8h in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.
1-(2,2-difluorovinyl)-3,5-dimethylbenzene (4.4f): Compound 4.4f corresponds to compound 3.8g in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.

![4.4g]

ethyl (E)-3-(3-(2,2-difluorovinyl)phenyl)acrylate (4.4g): Compound 4.4g corresponds to compound 2.5j in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

4-(2,2-difluorovinyl)-N,N-diisopropylbenzamide (4.4h): Compound 4.4h corresponds to compound 3.8q in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.
1-(2,2-difluorovinyl)-3-(trifluoromethyl)benzene (4.4i): Compound 4.4i corresponds to compound 3.8o in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.

1-(2,2-difluorovinyl)-3-nitrobenzene (4.4j): Compound 4.4j corresponds to compound 2.5n in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
4-(2,2-difluorovinyl)benzonitrile (4.4k): Compound 4.4k corresponds to compound 2.5m in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

![Diagram of 4.4l](image)

1,3-dichloro-5-(2,2-difluorovinyl)benzene (4.4l): Compound 4.4l corresponds to compound 2.5l in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

![Diagram of 4.4m](image)

4'-(tert-butyl)-2-(2,2-difluorovinyl)-1,1'-biphenyl (4.4m): Compound 4.4m corresponds to compound 2.5g in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
2-(2,2-difluorovinyl)-1,3-dimethylbenzene (4.4n): Compound 4.4n corresponds to compound 3.8i in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.

3-(2,2-difluorovinyl)-1-tosyl-1H-indole (4.6a): Compound 4.6a corresponds to compound 2.7a in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
4-(2,2-difluorovinyl)-1-phenyl-1H-pyrazole (4.6b): Compound 4.6b corresponds to compound 2.7c in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

\[
\text{Boc-N} \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{S} \\
\text{N}
\end{array}
\]

\textbf{4.6c}

\textit{tert}-butyl 4-(4-(2,2-difluorovinyl)thiazol-2-yl)piperazine-1-carboxylate (4.6c): Compound 4.6c corresponds to compound 2.7f in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{N} \\
\text{O}
\end{array}
\]

\textbf{4.6d}

2-(3-(2,2-difluorovinyl)phenyl)-5-(1,3-dioxolan-2-yl)pyridine (4.6d): Compound 4.6d corresponds to compound 2.7b in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
4-(2,2-difluorovinyl)dibenzo[b,d]thiophene (4.6e): Compound 4.6e corresponds to compound 2.7d in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

General Procedure for the Selective Unsymmetric Dioxygenation of Difluoroalkenes with Phenols (A):

An oven-dried 20 mL scintillation vial, equipped with a magnetic stirbar, was charged with difluoroalkene (0.50 mmol), phenol (1.50 mmol), and Co(acac)$_2$ (0.050–0.20 mmol). The system was purged with O$_2$ gas for 1 min before anhydrous DCB (2.0 mL) was added to the system under a stream of O$_2$ gas. The system was sealed with a PTFE-lined screw-top cap and stirred for 1 min at R.T. Subsequently, the vial was placed into a pre-heated reaction block and stirred vigorously at 90–140 °C for 24–48 h. The vial was cooled to R.T., and 50 µL (0.40 mmol) of TFT was added via microsyringe. The solution was diluted with approximately 1 mL of DCM and then stirred at R.T. for 10 min to allow adequate mixing. After mixing, an aliquot was removed from the vial and passed through a pad of silica gel into an NMR tube using acetone as eluent to remove Co(acac)$_2$, after which the reaction was analyzed by $^{19}$F NMR for completion and selectivity. After $^{19}$F NMR analysis,
the aliquot was sampled for TLC analysis (visualized with 10% phosphomolybdic acid in EtOH) then returned to the vial. Aqueous base (sat. NaOH or Na₂CO₃) was added to the solution and stirred for 30 min, and then extracted with DCM (four times). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo, and then purified by flash chromatography using EtOAc and hexanes.

**Preparation and Characterization of Compounds in Table 4-1**

![Chemical Structure](image)

**2-(4-bromophenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.3):** Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)₂ at 110 ℃ for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.148 g (71% yield) of desired product 4.3 as a yellow solid (MP = 93–95 ℃).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45–7.41 (m, 2 H), 7.03–6.99 (m, 2 H), 6.74 (s, 2 H), 5.00 (td, $J = 7.24$, 3.49 Hz, 1 H), 3.86 (s, 6H), 3.85 (s, 3 H), 3.14 (d, $J = 3.74$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.1, 149.1 (t, $J = 2.05$ Hz), 138.4 (d, $J = 2.06$ Hz), 132.6, 131.0, 123.6, 122.4 (t, $J = 273.70$ Hz), 119.0, 105.0, 74.2 (t, $J = 31.70$ Hz), 61.0, 56.3

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.65 (dd, $J = 141.05$, 6.98 Hz, 1 F), –82.16 (dd, $J = 140.99$, 7.23 Hz, 1 F)

IR (film): 3450, 2939, 1595, 1508, 1485, 1464, 1422, 1326, 1253, 1129, 1068, 1011, 829, 750, 710 cm$^{-1}$

HRMS (ESI+): calc. for C$_{17}$H$_{17}$BrF$_2$O$_5$ (M+) 418.0227, found 418.0212, 3.6 ppm.

**Optimization of Reaction Conditions:**

**Table SI-4-1: Reactions with Oxidants:**
Following General Procedure A, 0.023 g (0.10 mmol) of compound 4.1 was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.0014 g (0.010 mmol) of TBD, and 0.10 mmol of oxidant in 0.40 mL of DCB at 100 °C for 18 h. Reactions were analyzed by $^{19}$F NMR with a 0.010 mL (0.080 mmol) TFT standard.

**Table SI-4-2: Reactions with Oxidizing Metals:**
Following General Procedure A, 0.023 g (0.10 mmol) of compound 4.1 was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.0014 g (0.010 mmol) of TBD, and 0.010 mmol of metal in 0.40 mL of DCB at 100 °C for 18 h. Reactions were analyzed by $^{19}$F NMR with a 0.010 mL (0.080 mmol) TFT standard.
Table SI-4-3: Solvent Screening:

```
\begin{align*}
\text{Solvent} & \quad 4.1 & \quad 4.3 & \quad 4.4 \\
DCB & 7 & 63 & 5 \\
H_2O & 35 & 32 & 1 \\
IPA & 64 & 7 & 0.5 \\
1,4-Dioxane & 61 & 5 & 0 \\
MeCN & 45 & 20 & 2 \\
DMF & 55 & 15 & 5 \\
PhMe & 28 & 55 & 2 \\
DMSO & 49 & 9 & 5 \\
\end{align*}
```

Following General Procedure A, 0.023 g (0.10 mmol) of compound 4.1 was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.003 g (0.010 mmol) of Co(acac)_2 in 0.40 mL of solvent at 100 °C for 18 h. Reactions were analyzed by ^{19}F NMR with a 0.010 mL (0.080 mmol) TFT standard.

Experimental Procedures for Mechanistic Determination:

Table SI-4-4: Control Experiments: Following General Procedure A, 0.085 g (0.50 mmol) of compound 4.4a was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)_2 at 90 °C.
Table SI-4-5: Radical Trap Experiments:

![Chemical structures and reactions]

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<th>4.6a</th>
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<tr>
<td>NO2-NO2</td>
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</table>

**Reaction with Butylated Hydroxy-Toluene (BHT):** Following General Procedure A, 0.085 g (0.50 mmol) of compound 4.4a was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.331 g (1.50 mmol) of BHT and 0.013 g (0.050 mmol) of Co(acac)$_2$ at 110 °C for 15 h. Reactions were analyzed by $^{19}$F NMR with a 0.050 mL (0.40 mmol) TFT standard.
**Reaction with 1,4-Benzoquinone:** Following General Procedure A, 0.085 g (0.50 mmol) of compound 4.4a was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.162 g (1.50 mmol) of 1,4-benzoquinone and 0.013 g (0.050 mmol) of Co(acac)$_2$ at 110 °C for 15 h. Reactions were analyzed by $^{19}$F NMR with a 0.050 mL (0.40 mmol) TFT standard.

**Reaction with 1,4-Dinitrobenzene:** Following General Procedure A, 0.085 g (0.50 mmol) of compound 4.4a was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.252 g (1.50 mmol) of 1,4-dinitrobenzene and 0.013 g (0.050 mmol) of Co(acac)$_2$ at 110 °C for 15 h. Reactions were analyzed by $^{19}$F NMR with a 0.050 mL (0.40 mmol) TFT standard.
Kinetic Experiments by GC-FID: Following General Procedure A, varying quantities of compound 4.4a were reacted with varying amounts of 4-bromophenol in the presence of 0.057 mL (0.25 mmol) of dodecane and varying amounts of Co(acac)_2 at 90 °C. At set timepoints, 0.050 mL samples were removed from the reaction mixture and filtered through a pad of silica with acetone to provide a volume of 1.5 mL. From this solution, a 0.30 mL sample was removed and diluted with EtOAc to provide a final volume of 1.8 mL. The sample was mixed thoroughly and analyzed by GC-FID.

Varying Difluoroalkene Concentration: Following General Procedure A, compound 4.4a (0.0425 g, 0.250 mmol; 0.128 g, 0.075 mmol; or 0.213 g, 1.25 mmol) was reacted with 4-bromophenol (0.130 g, 0.75 mmol) in 1.0 mL of DCB in the presence of dodecane (0.057 mL, 0.25 mmol) and Co(acac)_2 (0.0060 g, 0.025 mmol) at 90 °C. At T = 0, 3, 6, 9, 12, and 15 min a 0.050 mL sample was removed from the reaction mixture and filtered through a pad of silica with acetone to provide a volume of 1.5 mL. From this solution, a 0.30 mL sample was removed and diluted with EtOAc to provide a final volume of 1.8 mL. The sample was mixed thoroughly and analyzed by GC-FID.

Varying Phenol Concentration: Following General Procedure A, compound 4.4a (0.0425 g, 0.250 mmol) was reacted with 4-bromophenol (0.043 g, 0.25 mmol; 0.058 g, 0.033 mmol; 0.072 g, 0.42 mmol; 0.087 g, 0.50 mmol; 0.108 g, 0.63 mmol; 0.130 g, 0.75 mmol; 0.173 g, 1.00 mmol; 0.216 g, 1.25 mmol) in 1.0 mL of DCB in the presence of
dodecane (0.057 mL, 0.25 mmol) and Co(acac)$_2$ (0.0060 g, 0.025 mmol) at 90 °C. At T = 0, 3, 6, 9, 12, and 15 min a 0.050 mL sample was removed from the reaction mixture and filtered through a pad of silica with acetone to provide a volume of 1.5 mL. From this solution, a 0.30 mL sample was removed and diluted with EtOAc to provide a final volume of 1.8 mL. The sample was mixed thoroughly and analyzed by GC-FID.

**Varying Cobalt Concentration:** Following General Procedure A, compound 4.4a (0.0425 g, 0.250 mmol) was reacted with 4-bromophenol (0.13 g, 0.75 mmol) in 1.0 mL of DCB in the presence of dodecane (0.057 mL, 0.25 mmol) and Co(acac)$_2$ (0.0030 g, 0.013 mmol; 0.0060 g, 0.0250 mmol; 0.013 g, 0.050 mmol; 0.019 g, 0.075 mmol; 0.026 g, 0.10 mmol; 0.032 g, 0.125 mmol) at 90 °C. At T = 0, 2, 5, 10, 15, 30, 60, 120 and 240 min a 0.050 mL sample was removed from the reaction mixture and filtered through a pad of silica with acetone to provide a volume of 1.5 mL. From this solution, a 0.30 mL sample was removed and diluted with EtOAc to provide a final volume of 1.8 mL. The sample was mixed thoroughly and analyzed by GC-FID.

**Figure SI-4-1: Difluoroalkene Kinetics**
Figure SI-4-2: Phenol Kinetics:

- Linear ("5" equiv CF2)
- Linear ("3" equiv CF2)
- Linear ("1" equiv CF2)

Equations:
- $y = 0.0062x + 0.1881$
- $y = 0.0114x + 0.1439$
- $y = 0.0099x + 0.0076$
Figure SI-4-3: Cobalt Kinetics
EPR Experimentation:

Electron Paramagnetic Resonance (EPR) spectroscopy was used to test the proposed reaction mechanism. EPR is highly sensitive to the oxidation state and ligand sphere of molecules with unpaired electrons, such as transition metals and stable radicals.\(^1\)

**Reacting Co(acac)\(_2\) and O\(_2\):** Co(acac)\(_2\) (0.021 g, 0.082 mmol) was added to an oven dried one dram vial. The vial was sealed with a screw-top cap containing a PTFE-lined silicon septum, and the reaction was evacuated and backfilled three times with N\(_2\). DCB

![Graph showing [Co]/time, Varying Cobalt](image-url)
(1.0 mL) was added, and a 100 µL aliquot of the reaction mixture was transferred to an EPR tube, frozen in liquid N\textsubscript{2}, and then subjected to EPR analysis at 10 K. The reaction was then put under an O\textsubscript{2} balloon, and stirred at 90 °C for 30 min. A 100 µL aliquot of the reaction mixture was transferred into an EPR tube, frozen in liquid N\textsubscript{2}, and then subjected to EPR analysis at 10 K.

**Reacting Co(acac)*\textsubscript{2} and 4.4a under O\textsubscript{2}:** Following General Procedure A, in an oven-dried one dram vial compound 4.4a (0.043 g, 0.25 mmol) was reacted with Co(acac)*\textsubscript{2} (0.064 g, 0.25 mmol) in DCB (1.0 mL). An O\textsubscript{2} balloon was added, and a 100 µL aliquot of the reaction mixture was transferred to an EPR tube, frozen in liquid N\textsubscript{2}, and then subjected to EPR analysis at 10 K. The reaction was then put under an O\textsubscript{2} balloon, and stirred at 90 °C for 30 min. A 100 µL aliquot of the reaction mixture was transferred into an EPR tube, frozen in liquid N\textsubscript{2}, and then subjected to EPR analysis at 10 K.

**Reacting Co(acac)*\textsubscript{2} and 4-bromophenol under O\textsubscript{2}:** Following General Procedure A, in an oven-dried one dram vial of 4-bromophenol (0.13 g, 0.75 mmol) was reacted with Co(acac)*\textsubscript{2} (0.064 g, 0.25 mmol) in DCB (1.0 mL). An O\textsubscript{2} balloon was added, and a 100 µL aliquot of the reaction mixture was transferred to an EPR tube, frozen in liquid N\textsubscript{2}, and then subjected to EPR analysis at 10 K. The reaction was then put under an O\textsubscript{2} balloon, and stirred at 90 °C for 30 min. A 100 µL aliquot of the reaction mixture was transferred into an EPR tube, frozen in liquid N\textsubscript{2}, and then subjected to EPR analysis at 10 K.
**Following Full Reaction Course:** Following General Procedure A, in an oven-dried one dram vial of compound 4.4a (0.043 g, 0.25 mmol) was reacted with 4-bromophenol (0.13 g, 0.75 mmol) in the presence of Co(acac)$_2$ (0.006 g, 0.03 mmol) in DCB (1.0 mL). An O$_2$ balloon was added, and a 100 µL aliquot of the reaction mixture was transferred to an EPR tube, frozen in liquid N$_2$, and then subjected to EPR analysis at 10 K. The reaction was then put under an O$_2$ balloon, and stirred at 90 °C for 30 min. A 100 µL aliquot of the reaction mixture was transferred into an EPR tube, frozen in liquid N$_2$, and then subjected to EPR analysis at 10 K.

**EPR Parameters:** Full reaction course and Co(acac)$_2$ with phenol under Ar:

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**Figure 4-4:** EPR Spin Trapping with BMPO or DMPO:
**Pathway A:** Following General Procedure A, in an oven-dried one dram vial of compound 4.4a (0.017 g, 0.10 mmol) was reacted with 4-bromophenol (0.052 g, 0.30 mmol) in the presence of Co(acac)$_2$ (0.003 g, 0.01 mmol) in DCB (0.40 mL). An O$_2$ balloon was added, and the reaction was stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T.. Represents spectrum 1 in Figure SI-4-1.

**Pathway B:** Co(acac)$_2$ (0.026 g, 0.10 mmol) was added to an oven dried one dram vial. The vial was sealed with a screw-top cap containing a PTFE-lined silicon septum, and the reaction was evacuated and backfilled three times with N$_2$. DCB (0.40 mL) was added, then put under an O$_2$ balloon and stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 3). Then 4-bromophenol (0.052 g, 0.30 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 4). Then 4.4a (0.017 g, 0.10 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample
of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 6).

**Pathway C:** Co(acac)$_2$ (0.026 g, 0.10 mmol) was added to an oven dried one dram vial. The vial was sealed with a screw-top cap containing a PTFE-lined silicon septum, and the reaction was evacuated and backfilled three times with N$_2$. DCB (0.40 mL) was added, then put under an O$_2$ balloon and stirred at 90 °C for 15 min. Then 4.4a (0.017 g, 0.10 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 5). Then 4-bromophenol (0.052 g, 0.30 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 7).

**Pathway D:** Co(acac)$_2$ (0.026 g, 0.10 mmol) and 4-bromophenol (0.052 g, 0.30 mmol) was added to an oven dried one dram vial. The vial was sealed with a screw-top cap containing a PTFE-lined silicon septum, and the reaction was evacuated and backfilled three times with N$_2$. DCB (0.40 mL) was added, then put under an Ar balloon and stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an
Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 8). Then Ar was exchanged for O₂, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 9). Then 4.4a (0.017 g, 0.10 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 11).

**Pathway E:** Co(acac)₂ (0.026 g, 0.10 mmol) and 4-bromophenol (0.052 g, 0.30 mmol) was added to an oven dried one dram vial. The vial was sealed with a screw-top cap containing a PTFE-lined silicon septum, and the reaction was evacuated and backfilled three times with N₂. DCB (0.40 mL) was added, then put under an Ar balloon and stirred at 90 °C for 15 min. Then 4.4a (0.017 g, 0.10 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 10). Then Ar was exchanged for O₂, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was
transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 12).

**Pathway F:** Co(acac)$_2$ (0.026 g, 0.10 mmol) and 4.4a (0.017 g, 0.10 mmol) was added to an oven dried one dram vial. The vial was sealed with a screw-top cap containing a PTFE-lined silicon septum, and the reaction was evacuated and backfilled three times with N$_2$. DCB (0.40 mL) was added, then put under an Ar balloon and stirred at 90 ºC for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 13). Then Ar was exchanged for O$_2$, and the reaction stirred at 90 ºC for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 14). Then 4-bromophenol (0.052 g, 0.30 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 ºC for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 16).
**Pathway G:** Co(acac)$_2$ (0.026 g, 0.10 mmol) and **4.4a** (0.017 g, 0.10 mmol) was added to an oven dried one dram vial. The vial was sealed with a screw-top cap containing a PTFE-lined silicon septum, and the reaction was evacuated and backfilled three times with N$_2$. DCB (0.40 mL) was added, then put under an Ar balloon and stirred at 90 °C for 15 min. Then 4-bromophenol (0.052 g, 0.30 mmol) in 0.40 mL DCB was added, and the reaction stirred at 90 °C for 15 min. A 100 µL aliquot of the reaction mixture was transferred into an Eppendorf tube containing 10 µL of a 20 mg/200 µL DCB sample of BMPO or DMPO, mixed on a Vortex mixer, and then a capillary tube sample removed for EPR analysis at R.T. (Figure SI-4-1, Spectrum 15).

**Figure SI-4-4: EPR Spectrum from Spin Trapping Experimentation**
Table SI-4-8: Spectral Simulation Parameters for Spectrum 5

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**Table SI-4-9**: Spectral Simulation Parameters for Spectrum 8

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Experimental Procedures and Characterization of Compounds in Scheme 4-4:

2-(4-bromophenoxy)-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-ol (4.5a): Following General Procedure A, 0.085 g (0.50 mmol) of compound 4.4a was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 90 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.109 g (77% yield) of desired product 4.5a as a pale yellow solid (MP = 51–53 °C).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.47 (d, $J$ = 8.64 Hz, 2 H), 7.44–7.41 (m, 2 H), 7.01 (d, $J$ = 8.91 Hz, 2 H), 6.96–6.92 (m, 2H), 5.04 (td, $J$ = 7.18, 4.29 Hz, 1 H), 3.83 (s, 3 H), 2.57 (d, $J$ = 4.27 Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 160.3, 149.2 (t, $J$ = 2.40 Hz), 132.6, 129.1, 127.4, 123.6, 122.6 (t, $J$ = 272.76 Hz), 119.0, 113.9, 74.1 (t, $J$ = 31.82 Hz), 55.4

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –82.39 (d, $J$ = 7.21 Hz, 2 F)
IR (film): 3424, 2957, 2911, 2838, 1891, 1613, 1586, 1515, 1485, 1465, 1442, 1399, 1346, 1246, 1197, 1177, 1144, 1117, 1065, 1032, 1012, 939, 827, 800, 756, 745, 716, 691, 636, 593, 535, 493 cm$^{-1}$

HRMS (ESI–): calc. for C$_{15}$H$_{13}$BrF$_2$O$_3$Cl (M+Cl) 392.9705, found 392.9709, 1.0 ppm.

2-(4-bromophenoxy)-2,2-difluoro-1-(4-(methylthio)phenyl)ethan-1-ol (4.5b):

Following General Procedure A, 0.093 g (0.50 mmol) of compound 4.4b was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.026 g (0.100 mmol) of Co(acac)$_2$ at 90 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.099 g (53% yield) of desired product 4.5b as a yellow solid (MP = 70–72 °C)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (t, $J = 8.70$ Hz, 4 H), 7.28 (d, $J = 8.49$ Hz, 2 H), 7.01 (d, $J = 8.40$ Hz, 2 H), 5.04 (t, $J = 7.06$ Hz, 1 H), 2.83 (bs, 1 H), 2.50 (s, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.0, 139.9, 132.6, 131.9, 128.3, 126.2, 123.6, 122.4 (t, $J = 272.73$ Hz), 119.0, 74.1 (t, $J = 32.16$ Hz), 15.6
\textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}): \( \delta \approx 82.27 \) (dd, \( J = 19.13, 7.12 \) Hz, 2 F)

\textbf{IR (film):} 3397, 2921, 2051, 1892, 1728, 1601, 1484, 1436, 1405, 1346, 1251, 1210, 1195, 1146, 1092, 1066, 1012, 968, 941, 846, 818, 796, 758, 744, 685, 644, 539, 493 cm\textsuperscript{-1}

\textbf{HRMS (ESI–):} calc. for C\textsubscript{15}H\textsubscript{13}BrF\textsubscript{2}O\textsubscript{2}Cl (M+Cl) 408.9476, found 408.9482, 1.5 ppm.

![Structural diagram]

\textbf{1-(4-(benzyloxy)-3-methoxyphenyl)-2-(4-bromophenoxy)-2,2-difluoroethan-1-ol (4.5c):} Following General Procedure A, 0.131 g (0.500 mmol) of compound \textbf{4.4c} was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)\textsubscript{2} at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.150 g (68% yield) of desired product \textbf{4.5c} as a light orange solid (MP = 87–88 °C)
$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 (td, $J = 7.21$, 6.81, 1.94 Hz, 4 H), 7.41–7.34 (m, 2 H), 7.34–7.28 (m, 1 H), 7.11 (d, $J = 1.93$ Hz, 1 H), 7.06–6.96 (m, 3 H), 6.89 (d, $J = 8.29$ Hz, 1 H), 5.17 (s, 2 H), 5.00 (t, $J = 7.12$ Hz, 1 H), 3.90 (s, 3H), 2.83 (bs, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.6, 149.1 (d, $J = 2.75$ Hz), 148.8, 137.0, 132.5, 128.7, 128.3, 128.0, 127.4, 123.6, 122.5 (t, $J = 272.85$ Hz), 120.6, 119.0, 113.4 (d, $J = 1.62$ Hz), 111.3, 74.1 (t, $J = 31.44$ Hz), 71.0, 56.2

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.89 (dd, $J = 141.33$, 7.27 Hz, 1 F), –82.28 (dd, $J = 141.33$, 7.27 Hz, 1 F)

IR (film): 3458, 3033, 2917, 2849, 1735, 1607, 1594, 1514, 1484, 1464, 1454, 1421, 1382, 1337, 1252, 1202, 1138, 1065, 1033, 1012, 914, 844, 827, 800, 738, 696, 648, 551, 494 cm$^{-1}$

HRMS (ESI+): calc. for $\text{C}_{22}\text{H}_{19}\text{BrF}_2\text{O}_4\text{K}$ (M+K) 503.0072, found 503.0078, 1.2 ppm.
2-(4-bromophenoxy)-2,2-difluoro-1-(3-morpholinophenyl)ethan-1-ol (4.5d):

Following General Procedure A, 0.113 g (0.500 mmol) of compound 4.4d was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 90 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–50% EtOAc in hexanes, furnishing 0.044 g (21% yield) of desired product 4.5d as an orange oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43 (d, $J = 8.86$ Hz, 2 H), 7.31 (t, $J = 7.92$ Hz, 1 H), 7.10 (t, $J = 2.00$ Hz, 1 H), 7.04 (d, $J = 7.93$ Hz, 1 H), 7.01 (d, $J = 8.62$ Hz, 2 H), 6.94 (ddd, $J = 8.26, 2.55, 0.96, 1$ H), 5.04 (t, $J = 7.24$ Hz, 1 H), 3.88–3.85 (m, 4 H), 3.20–3.17 (m, 4 H), 2.72 (d, $J = 3.57$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 151.5, 149.1 (d, $J = 2.26$ Hz), 136.3, 132.6, 129.3, 123.6, 122.5 (t, $J = 272.72$ Hz), 119.5, 119.0, 116.4, 115.1, 74.7 (t, $J = 31.27$ Hz), 67.0, 49.4

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.94 (t, $J = 8.00$ Hz, 2 F)

IR (film): 3377, 2965, 2857, 1727, 1604, 1584, 1485, 1448, 1380, 1343, 1304, 1243, 1202, 1145, 1115, 1067, 1012, 997, 978, 962, 933, 888, 827, 785, 756, 737, 698, 644, 529, 494 cm$^{-1}$

HRMS (ESI+): calc. for C$_{18}$H$_{19}$BrF$_2$NO$_3$ (M+H) 414.0516, found 414.0521, 1.2 ppm.
2-(4-bromophenoxy)-1-(2,4-dimethylphenyl)-2,2-difluoroethan-1-ol (4.5e): Following General Procedure A, 0.084 g (0.50 mmol) of compound 4.4e was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 90 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–20% EtOAc in hexanes, furnishing 0.089 g (50% yield) of desired product 4.5e as a pale oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.58 (d, $J = 7.96$ Hz, 1 H), 7.43 (d, $J = 8.90$ Hz, 2 H), 7.11 (d, $J = 8.24$ Hz, 1 H), 7.04 (d, $J = 2.23$ Hz, 2 H), 7.02 (s, 1 H), 5.35 (td, $J = 7.18$, 3.79 Hz, 1 H), 2.85 (d, $J = 4.35$ Hz, 1 H), 2.40 (s, 3 H), 2.35 (s, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.1 (t, $J = 2.25$ Hz), 138.7, 136.7, 132.5, 131.3, 130.9, 127.3 (t, $J = 1.73$ Hz), 127.1, 123.5, 123.0 (t, $J = 273.10$ Hz), 118.8, 70.3 (t, $J = 31.67$ Hz), 21.2, 19.6

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.41 (dd, $J = 140.67$, 7.53 Hz, 1 F), –81.85 (dd, $J = 140.45$, 7.12 Hz, 1 F)
IR (film): 3381, 2923, 1616, 1583, 1484, 1249, 1196, 1142, 1065, 1012, 826, 809, 760, 748, 720, 691, 494 cm$^{-1}$

HRMS (ESI+): calc. for C$_{16}$H$_{15}$BrF$_2$O$_2$Cl (M+Cl) 390.9912, found 390.9920, 2.0 ppm.

$\text{2-}(4\text{-bromophenoxy})\text{-1-(3,5-dimethylphenyl)}\text{-2,2-difluoroethan-1-ol (4.5f)}$: Following General Procedure A, 0.084 g (0.50 mmol) of compound 4.4f was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–15% EtOAc in hexanes, furnishing 0.099 g (44% yield) of desired product 4.5f as a tan solid (MP = 79–81 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 (d, $J = 8.88$ Hz, 2 H), 7.16 (bs, 2 H), 7.04 (bs, 2 H), 7.02 (bs, 1 H), 5.00 (t, $J = 7.25$ Hz, 1 H), 2.74 (bs, 1 H), 2.36 (s, 6 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.2, 138.1, 135.2, 132.5, 130.9, 125.6 (d, $J = 1.49$ Hz), 123.6, 122.5 (t, $J = 272.07$ Hz), 118.9, 74.6 (t, $J = 31.54$ Hz), 21.5
\(^{19}\text{F NMR (376 MHz, CDCl}_3\text{):} \delta \sim 81.59 \text{ (dd, } J = 140.92, 7.09 \text{ Hz, } 1 \text{ F}), \sim 82.16 \text{ (dd, } J = 140.89, 7.38 \text{ Hz, } 1 \text{ F})

\textbf{IR (film):} 3395, 3011, 2919, 2051, 1891, 1760, 1609, 1583, 1484, 1399, 1379, 1345, 1251, 1199, 1143, 1114, 1066, 1012, 953, 938, 905, 886, 828, 803, 786, 762, 744, 716, 699, 686, 645, 561, 536, 493 \text{ cm}^{-1}

\textbf{HRMS (ESI–):} \text{ calc. for C}_{16}\text{H}_{15}\text{BrF}_2\text{O}_2\text{Cl (M+Cl) 390.9912, found 390.9921, 2.3 ppm.}

![Chemical Structure](image)

**ethyl \((E)-3-(3-(2-(4-bromophenoxy)-2,2-difluoro-1-hydroxyethyl)phenyl)acrylate (4.5g):** Following General Procedure A, 0.119 g (0.500 mmol) of compound 4.4g was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)\(_2\) at 120 °C for 48 h. After workup with sat. Na\(_2\)CO\(_3\) (aq.), the product was purified by flash chromatography using a gradient of 5–35% EtOAc in hexanes, furnishing 0.109 g (51% yield) of desired product 4.5g as an orange oil.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.68 (d, $J = 16.16$ Hz, 2 H), 7.56 (d, $J = 7.42$ Hz, 1 H), 7.52 (dt, $J = 7.88$, 1.47 Hz, 1 H), 7.42–7.38 (m, 3 H), 6.98 (m, 2 H), 6.45 (d, $J = 16.02$ Hz, 1 H), 5.10 (t $J = 7.05$ Hz, 1 H), 4.25 (q, $J = 7.11$ Hz, 2 H), 3.53 (bs, 1 H), 1.32 (t, $J = 7.13$ Hz, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 167.2, 148.9 (t, $J = 2.32$ Hz), 144.4, 136.3, 134.5, 132.5, 129.7, 128.9, 128.6, 127.5, 122.3 (t, $J = 273.04$ Hz), 119.0, 118.7, 73.8 (t, $J = 31.46$ Hz), 60.8, 14.4

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.74 (dd, $J = 140.69$, 6.93 Hz, 1 F), –82.25 (dd, $J = 140.78$, 7.25 Hz, 1 F)

IR (film): 3418, 2982, 2051, 1891, 1693, 1584, 1484, 1438, 1397, 1368, 1308, 1252, 1225, 1188, 1148, 1113, 1098, 1066, 1012, 983, 863, 843, 825, 794, 757, 734, 696, 651, 581, 558, 493, 465 cm$^{-1}$

HRMS (ESI–): calc. for C$_{19}$H$_{17}$BrF$_2$O$_4$Cl (M+Cl) 460.9967, found 460.9999, 6.9 ppm.
4-(2-(4-bromophenoxy)-2,2-difluoro-1-hydroxyethyl)-N,N-diisopropylbenzamide (4.5h): Following General Procedure A, 0.134 g (0.500 mmol) of compound 4.4h was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–50% EtOAc in hexanes, furnishing 0.094 g (41% yield) of desired product 4.5h as a white solid (MP = 182–183 °C)

$^1$H NMR (500 MHz, DMSO-D$_6$, 60 °C): $\delta$ 7.57 (dd, $J = 8.45$, 3.06 Hz, 4 H), 7.29 (d, $J = 7.74$ Hz, 2 H), 7.08 (d, $J = 8.34$ Hz, 2 H), 6.51 (d, $J = 5.64$ Hz, 1 H), 5.10 (q, $J = 7.08$ Hz, 1 H), 3.66–3.63 (m, 2 H), 1.28 (bs, 12 H)

$^{13}$C NMR (126 MHz, DMSO-D$_6$, 60 °C): $\delta$ 169.3, 148.8 (d, $J = 2.31$ Hz), 138.7, 137.2, 132.3, 127.7, 124.7, 123.2, 122.6 (t, $J = 272.21$ Hz), 117.7, 72.0 (t, $J = 31.34$ Hz), 54.5, 20.2

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ −81.80 (dd, $J = 140.26$, 7.03 Hz, 1 F), −82.22 (dd, $J = 140.26$, 6.48 Hz, 1 F)

IR (film): 3250, 2974, 2935, 1602, 1515, 1483, 1457, 1407, 1381, 1372, 1349, 1275, 1252, 1209, 1195, 1161, 1141, 1082, 1064, 1038, 1012, 919, 883, 854, 808, 765, 750, 681, 631, 610, 577, 548, 527, 497 cm$^{-1}$

HRMS (ESI+): calc. for C$_{21}$H$_{24}$BrF$_2$NO$_3$Na (M+Na) 478.0805, found 478.0813, 1.7 ppm.
2-(4-bromophenoxy)-2,2-difluoro-1-(3-(trifluoromethyl)phenyl)ethan-1-ol  (4.5i):

Following General Procedure A, 0.104 g (0.500 mmol) of compound 4.4i was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–50% EtOAc in hexanes, furnishing 0.057 g (28% yield) of desired product 4.5i as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.82 (s, 1 H), 7.73 (d, $J = 7.8$ Hz, 1 H), 7.65 (d, $J = 7.8$ Hz, 1 H), 7.52 (t, $J = 7.8$ Hz, 1 H), 7.45 – 7.37 (m, 2 H), 7.06 – 6.91 (m, 2 H), 5.15 (td, $J = 7.0$, 3.6 Hz, 1 H), 2.81 (d, $J = 4.0$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 148.72, 135.96, 132.55, 131.08, 131.36 – 130.33 (q, $J = 32.49$ Hz), 128.82, 125.89 (q, $J = 4.0$ Hz), 124.63 (q, $J = 4.2$ Hz), 123.97 (d, $J = 272.9$ Hz), 123.36, 124.32 – 119.63 (t, $J = 273.01$ Hz), 119.13, 74.39 – 72.98 (t, $J = 31.2$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –82.05 (dd, $J = 140.9$, 6.7 Hz, 1 F), –82.53 (dd, $J = 141.3$, 7.0 Hz, 1 F)
IR (film): 3414, 1584, 1485, 1327, 1250, 1161, 1122, 1064, 1012, 828, 794, 751, 737, 701, 669, 491 cm⁻¹

HRMS (ESI⁻): calc. for C₁₅H₁₀BrF₅O₂Cl (M+Cl) 430.9478, found 430.9504, 2.6 ppm.

2-(4-bromophenoxy)-2,2-difluoro-1-(3-nitrophenyl)ethan-1-ol (4.5j): Following General Procedure A, 0.093 g (0.50 mmol) of compound 4.4j was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)₂ at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.084 g (45% yield) of desired product 4.5j as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.46 (t, J = 1.89 Hz, 1 H), 8.27 (ddd, J = 6.22, 2.30, 1.09 Hz, 1 H), 7.91 (d, J = 7.82 Hz, 1 H), 7.61 (t, J = 7.99 Hz, 1 H), 7.45 (d, J = 8.88 Hz, 2 H), 7.00 (d, J = 9.03 Hz, 2 H), 5.23 (td, J = 6.90, 3.91 Hz, 1 H), 2.91 (d, J = 3.95 Hz, 1 H)

¹³C NMR (126 MHz, CDCl₃): δ 148.7 (t, J = 2.07 Hz), 148.4, 137.1, 133.9, 132.7, 129.5, 124.1, 123.5, 123.0, 122.0 (t, J = 273.01 Hz), 119.4, 73.5 (t, J = 31.89 Hz)
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –82.02 (dd, $J = 140.93$, 6.87 Hz, 1 F), –82.56 (dd, $J = 140.85$, 6.99 Hz, 1 F)

IR (film): 3469, 3094, 2919, 2052, 1890, 1619, 1584, 1529, 1484, 1444, 1400, 1351, 1276, 1251, 1195, 1151, 1115, 1066, 1012, 935, 909, 883, 843, 827, 808, 764, 750, 728, 699, 688, 647, 546, 492 cm$^{-1}$

HRMS (ESI–): calc. for C$_{14}$H$_{10}$BrF$_2$NO$_4$Cl (M+Cl) 407.9450, found 407.9453, 0.7 ppm.

![Chemical Structure](image)

**4-(2-(4-bromophenoxy)-2,2-difluoro-1-hydroxyethyl)benzonitrile (4.5k):** Following General Procedure A, 0.083 g (0.50 mmol) of compound 4.4k was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 140 °C for 24 h. After workup with sat. Na$_2$CO$_3$ (aq.), the product was purified by flash chromatography using a gradient of 0–50% EtOAc in hexanes, furnishing 0.073 g (41% yield) of desired product 4.5k as a white solid (MP = 128–130 °C).
$^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.69 – 7.57 (m, 4 H), 7.41 – 7.32 (m, 2 H), 6.91 (d, $J$ = 9.0 Hz, 1 H), 5.10 (td, $J$ = 6.9, 3.5 Hz, 2 H), 2.91 (d, $J$ = 4.0 Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 148.6, 140.1, 132.6, 132.1, 128.5, 123.4, 121.9 (t, $J$ = 237.2 Hz) 119.3, 118.5, 112.9, 73.6 (t, $J$ = 31.9 Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.75 (dd, $J$ = 140.7, 6.9 Hz, 1 F), –82.32 (dd, $J$ = 140.7, 7.0 Hz, 1 F)

IR (film): 3399, 2908, 2239, 1611, 1580, 1485, 1251, 1152, 1065, 1011, 848, 825, 804, 763, 578, 551, 494 cm$^{-1}$

HRMS (ESI–): calc. for C$_{15}$H$_{10}$BrF$_2$NO$_2$Cl (M+Cl) 387.9557, found 387.9583, 2.6 ppm.

![Chemical Structure](image)

2-(4-bromophenoxy)-1-(3,5-dichlorophenyl)-2,2-difluoroethan-1-ol (4.5l): Following General Procedure A, 0.104 g (0.500 mmol) of compound 4.4l was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at
140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–50% EtOAc in hexanes, furnishing 0.087 g (44% yield) of desired product **4.5l** as a colorless oil.

**H NMR (400 MHz, CDCl₃):** δ 7.48 (dd, J = 5.4, 3.5 Hz, 4 H), 7.42 (t, J = 1.9 Hz, 1 H), 7.12 – 6.96 (m, 2 H), 5.07 (td, J = 6.8, 3.7 Hz, 1 H), 2.85 (d, J = 4.0 Hz, 1 H)

**C NMR (126 MHz, CDCl₃):** δ 148.6, 138.2, 135.0, 132.6, 129.2, 126.3, 123.4, 121.8 (t, J = 272.7), 119.3, 74.2 (t, J = 32.4 Hz)

**F NMR (376 MHz, CDCl₃):** δ –81.76 (dd, J = 140.8, 6.8 Hz, 1 F), –82.32 (dd, J = 140.9, 6.9 Hz, 1 F)

**IR (film):** 3400, 3083, 1592, 1572, 1484, 1435, 1206, 1150, 1065, 1011, 795, 739, 674, 491 cm⁻¹

**HRMS (ESI–):** calc. for C₁₄H₉BrCl₃F₂O₂ (M+Cl) 430.8825, found 430.8837, 1.2 ppm.
2-(4-bromophenoxy)-1-(4’-(tert-butyl)-[1,1’-biphenyl]-2-yl)-2,2-difluoroethan-1-ol (4.5m): Following General Procedure A, 0.136 g (0.500 mmol) of compound 4.4m was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.026 g (0.100 mmol) of Co(acac)₂ at 100 °C for 48 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–25% EtOAc in hexanes, furnishing 0.139 g (60% yield) of desired product 4.5m as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 7.81 (t, J = 1.66 Hz, 1 H), 7.66 (dt, J = 7.39, 1.71 Hz, 1 H), 7.60 (d, J = 8.45 Hz, 2 H), 7.52 (d, J = 2.18 Hz, 2 H), 7.52–7.49 (m, 2 H), 7.45 (d, J = 8.86 Hz, 2 H), 7.04 (d, J = 8.77 Hz, 2 H), 5.16 (t, J = 7.11 Hz, 1 H), 3.00 (bs, 1 H), 1.40 (s, 9 H)

¹³C NMR (126 MHz, CDCl₃): δ 150.7, 149.1, 141.3, 137.9, 135.8, 132.5, 128.8, 127.8, 126.9, 126.5, 125.9, 123.6, 122.5 (t, J = 272.36 Hz), 119.0, 74.5 (t, J = 31.35 Hz), 34.7, 31.5

¹⁹F NMR (376 MHz, CDCl₃): δ −81.63 (dd, J = 140.63, 7.08 Hz, 1 F), −82.03 (dd, J = 140.63, 7.16 Hz, 1 H)

IR (film): 3401, 3065, 2962, 2904, 2867, 1580, 1483, 1399, 1363, 1252, 1209, 1140, 1115, 1067, 1012, 954, 906, 881, 839, 825, 766, 739, 705, 675, 645, 632, 585, 545, 522, 492 cm⁻¹

HRMS (ESI+): calc. for C₂₄H₂₄BrF₂O₂ (M+H) 461.0928, found 461.1971, 2.0 ppm.
Experimental Procedures and Characterization of Compounds in Scheme 4-5:

2-(4-bromophenoxy)-2,2-difluoro-1-(1-tosyl-1H-indol-3-yl)ethan-1-ol (4.7a):

Following General Procedure A, 0.167 g (0.500 mmol) of compound 4.6a was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of \( \text{Co(acac)}_2 \) at 100 °C for 36 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.162 g (62% yield) of desired product 4.7a as an orange solid (MP = 53–55 °C).

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \ \delta \ 7.99 \ (dt, \ J = 8.49, 0.88 \text{ Hz}, 1 \text{ H}), \ 7.77 \ (d, \ J = 8.53 \text{ Hz}, 3 \text{ H}), \ 7.73 \ (d, \ J = 7.75 \text{ Hz}, 1 \text{ H}), \ 7.45–7.41 \ (m, 2 \text{ H}), \ 7.34 \ (ddd, \ J = 8.38, 7.16, 1.28 \text{ Hz}, 1 \text{ H}), \ 7.28–7.24 \ (m, 1 \text{ H}), \ 7.21 \ (d, \ J = 7.65 \text{ Hz}, 2 \text{ H}), \ 6.98 \ (dd, \ J = 8.76, 1.07 \text{ Hz}, 2 \text{ H}), \ 5.35 \ (td, \ J = 6.73, 4.53 \text{ Hz}, 1 \text{ H}), \ 2.68 \ (d, \ J = 4.95 \text{ Hz}, 1 \text{ H}), \ 2.34 \ (s, 3 \text{ H})
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.0 (d, $J = 1.96$ Hz), 145.4, 135.2, 132.6, 130.1, 129.1, 127.0, 125.8 (d, $J = 2.00$ Hz), 125.2, 123.6, 123.5, 122.5 (t, $J = 272.36$ Hz), 120.9 (d, $J = 1.82$ Hz), 119.2, 117.0 (d, $J = 1.66$ Hz), 113.8, 69.1 (t, $J = 33.67$ Hz), 21.7

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.47 (dd, $J = 140.26$, 6.78 Hz, 1 F), –82.05 (dd, $J = 140.24$, 7.22 Hz, 1 F)

IR (film): 3509, 3113, 2924, 2052, 1913, 1596, 1566, 1485, 1447, 1340, 1366, 1278, 1255, 1189, 1172, 1122, 1084, 1066, 1012, 972, 907, 834, 811, 764, 744, 733, 703, 678, 657, 599, 571, 537, 492 cm$^{-1}$

HRMS (ESI–): calc. for C$_{23}$H$_{18}$F$_2$NO$_4$S (M–) 520.0030, found 520.0041, 2.1 ppm.

2-(4-bromophenoxy)-2,2-difluoro-1-(1-phenyl-1H-pyrazol-4-yl)ethan-1-ol (4.7b):

Following General Procedure A, 0.103 g (0.500 mmol) of compound 4.6b was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 110 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified.
by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.140 g (71% yield) of desired product 4.7b as a yellow solid (MP = 70–72 °C)

**1H NMR (400 MHz, CDCl₃):** δ 8.04 (s, 1 H), 7.82 (s, 1 H), 7.65 (d, J = 7.51 Hz, 2 H), 7.43 (dd, J = 8.90, 7.22 Hz, 4 H), 7.29 (t, J = 7.45 Hz, 1 H), 7.04 (d, J = 8.57 Hz, 2 H), 5.16 (td, J = 6.91, 3.91 Hz, 1 H), 3.59 (d, J = 5.46 Hz, 1 H)

**13C NMR (126 MHz, CDCl₃):** δ 149.0, 140.1 (d, J = 1.95 Hz), 139.8, 132.6, 129.6, 127.0, 126.6 (d, J = 1.86 Hz), 123.6, 122.5 (t, J = 271.91 Hz), 119.4, 119.1, 118.9 (d, J = 1.87 Hz), 67.7 (t, J = 33.26 Hz)

**19F NMR (376 MHz, CDCl₃):** δ –82.60 (dd, J = 140.85, 6.21 Hz, 1 F), –83.07 (dd, J = 141.08, 6.84 Hz, 1 F)

**IR (film):** 3279, 2923, 1680, 1600, 1572, 1504, 1485, 1405, 1257, 1209, 1148, 1114, 1067, 1043, 1012, 955, 904, 826, 804, 756, 690, 492 cm⁻¹

**HRMS (ESI+):** calc. for C₁₇H₁₄BrF₂N₂O₂ (M+H) 395.0207, found 395.0220, 3.3 ppm.
tert-butyl 4-(5-(2-(4-bromophenoxy)-2,2-difluoro-1-hydroxyethyl)thiazol-2-yl)piperazine-1-carboxylate (4.7c): Following General Procedure A, 0.166 g (0.500 mmol) of compound 4.6c was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 90 °C for 24 h. After workup with sat. Na$_2$CO$_3$ (aq.), the product was purified by flash chromatography using a gradient of 15–60% EtOAc in hexanes, furnishing 0.095 g (36% yield) of desired product 4.7c as a brown solid (MP = 60–61 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.46 (d, $J = 8.69$ Hz, 2 H), 7.23 (d, $J = 0.68$ Hz, 1 H), 7.06 (d, $J = 8.62$ Hz, 2 H), 5.19 (t, $J = 6.29$ Hz, 1 H), 3.54 (dd, $J = 6.43$, 3.50 Hz, 4 H), 3.47 (td, $J = 5.10$, 1.76 Hz, 4 H), 1.47 (s, 9 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 173.0, 154.7, 148.9, 140.2, 132.7, 123.6, 122.0 (t, $J = 271.72$ Hz), 120.5, 119.2, 80.5, 69.8 (t, $J = 34.07$ Hz), 48.2, 28.5

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.66 (dd, $J = 140.43$, 5.78 Hz, 1 F), –82.45 (dd, $J = 140.58$, 6.84 Hz, 1 F)

IR (film): 3333, 2977, 2928, 2862, 2249, 2103, 1690, 1584, 1514, 1484, 1454, 1420, 1366, 1285, 1250, 1234, 1202, 1162, 1134, 1065, 1012, 997, 970, 905, 860, 843, 829, 805, 771, 757, 731, 692, 646, 632, 552, 493, 463 cm$^{-1}$

HRMS (ESI+): calc. for C$_{20}$H$_{25}$BrF$_2$N$_3$O$_4$S (M+H) 520.0717, found 520.0735, 3.5 ppm.
1-(3-(5-(1,3-dioxolan-2-yl)pyridin-2-yl)phenyl)-2-(4-bromophenoxy)-2,2-difluoroethan-1-ol (4.7d): Following General Procedure A, 0.145 g (0.500 mmol) of compound 4.6d was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 90 °C for 24 h. The reaction was cooled to R.T. and a solution of 4 N HCl in 1,4- dioxane (2.0 mL) and ethylene glycol (1.0 mL) were added. The solution was stirred for 2 h at 130 °C. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.095 g (40% yield) of desired product 4.7d as a brown solid (MP = 85–87 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.76 (d, $J = 2.14$ Hz, 1 H), 8.09 (t, $J = 1.72$ Hz, 1 H), 7.92 (dt, $J = 7.85$, 1.47 Hz, 1 H), 7.86 (dd, $J = 8.19$, 2.21 Hz, 1 H), 7.72 (dd, $J = 8.05$, 0.85 Hz, 1 H), 7.59 (d, $J = 7.70$ Hz, 1 H), 7.46 (t, $J = 7.74$ Hz, 1 H), 7.39 (d, $J = 8.69$ Hz, 2 H), 6.98 (d, $J = 8.71$ Hz, 2 H), 5.89 (s, 1 H), 5.09 (t, $J = 7.10$ Hz, 1 H), 4.36 (bs, 1 H), 4.15–4.04 (m, 4 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 158.0, 149.2, 148.2, 139.0, 136.5, 135.5, 132.5, 132.4, 128.9, 128.6, 127.8, 126.8, 123.6, 122.6 (t, $J = 273.01$ Hz), 120.8, 118.9, 102.0, 74.1 (t, $J = 31.69$ Hz), 65.6

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.75 (t, $J = 5.71$ Hz, 2 F)

IR (film): 3054, 2890, 1726, 1602, 1570, 1485, 1413, 1357, 1264, 1252, 1202, 1145, 1067, 1027, 1012, 983, 942, 908, 841, 796, 735, 703, 650, 579, 494 cm$^{-1}$

HRMS (ESI+): calc. for C$_{22}$H$_{15}$BrF$_2$NO$_4$ (M+H) 478.0466, found 478.0448, 3.8 ppm.

2-(4-bromophenoxy)-1-(dibenzo[b,d]thiophen-4-yl)-2,2-difluoroethan-1-ol (4.7e):

Following General Procedure A, 0.123 g (0.500 mmol) of compound 4.6e was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.026 g (0.100 mmol) of Co(acac)$_2$ at 110 °C for 48 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–20% EtOAc in hexanes, furnishing 0.125 g (57% yield) of desired product 4.7e as a pale yellow oil.
$^1$H NMR (400 MHz, CDCl$_3$): δ 8.16 (ddd, $J = 7.05, 3.87, 1.88$ Hz, 2 H), 7.86–7.84 (m, 1 H), 7.72 (d, $J = 7.45$ Hz, 1 H), 7.53–7.46 (m, 3 H), 7.40–7.38 (m, 2 H), 7.00 (d, $J = 8.59$ Hz, 2 H), 5.45 (td, $J = 7.07, 2.82$ Hz, 1 H), 3.20 (d, $J = 3.92$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 149.0 (d, $J = 3.01$ Hz), 139.5, 139.2, 136.4, 135.3, 132.5, 129.9, 127.1, 126.2, 124.7, 124.6, 123.4, 122.7, 122.3, 121.7, 118.9, 73.7 (t, $J = 32.23$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): δ $-81.01$ (dd, $J = 139.12, 6.75$ Hz, 1 F), $-81.76$ (dd, $J = 139.29, 7.33$ Hz, 1 F)

IR (film): 3412, 3064, 2922, 1888, 1762, 1583, 1550, 1525, 1484, 1444, 1401, 1342, 1276, 1250, 1196, 1147, 1111, 1099, 1066, 1038, 1021, 1012, 938, 904, 827, 793, 750, 706, 688, 646, 627, 577, 556, 492 cm$^{-1}$

HRMS (ESI–): calc. for $C_{20}H_{13}BrF_2O_2Cl$ (M+Cl) 468.9476, found 468.9471, 1.1 ppm.
Experimental Procedures and Characterization of Compounds in Scheme 4-6:

2,2-difluoro-2-(4-nitrophenox)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9a):
Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.209 g (1.50 mmol) of 4-nitrophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)₂ at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.107 g (56% yield) of desired product 4.9a as a yellow oil (MP = 133–135 °C).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\]:} \delta 8.23 (d, \text{J} = 9.19 \text{ Hz, 2 H}), 7.30 (d, \text{J} = 9.27 \text{ Hz, 2 H}), 6.77 (s, 2 H), 5.07 (td, \text{J} = 7.19, 4.02 \text{ Hz, 1 H}), 3.89 (s, 6 H), 3.87 (s, 3 H), 2.73 (d, \text{J} = 4.03 \text{ Hz})

\[ ^13C \text{ NMR (126 MHz, CDCl}_3\]:} \delta 155.0 (d, \text{J} = 1.57 \text{ Hz}), 153.4, 145.2, 138.9 (d, \text{J} = 1.59 \text{ Hz}), 130.3, 125.5, 122.6 (t, \text{J} = 275.02 \text{ Hz}), 121.5 (d, \text{J} = 1.64 \text{ Hz}), 105.0, 74.4 (t, \text{J} = 31.34 \text{ Hz}), 61.0, 56.4
\[ ^{19} \text{F NMR (376 MHz, CDCl}_3\text{):} \delta -82.02 \text{ (dd, } J = 139.86, 7.08 \text{ Hz, 1 F}), -82.44 \text{ (dd, } J = 139.86, 7.43 \text{ Hz, 1 F)} \]

**IR (film):** 3460, 2925, 1594, 1524, 1492, 1463, 1423, 1348, 1326, 1254, 1129, 1004, 856, 749, 707 cm\(^{-1}\)

**HRMS (ESI–):** calc. for C\(_{17}\)H\(_{17}\)F\(_2\)NO\(_7\)Na (M+Na) 408.0871, found 408.0874, 0.7 ppm.

\[ 4-(1,1\text{-difluoro-2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethoxy})benzonitrile \ (4.9b): \]
Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.179 g (1.50 mmol) of 4-hydroxybenzonitrile in the presence of 0.013 g (0.050 mmol) of Co(acac\(_2\)) at 100 °C for 24 h. After workup with sat. Na\(_2\)CO\(_3\) (aq.), the product was purified by flash chromatography using a gradient of 10–40% EtOAc in hexanes, furnishing 0.138 g (82% yield) of desired product 4.9b as a pale yellow solid (MP = 39–42 °C).

\[ ^{1} \text{H NMR (400 MHz, CDCl}_3\text{):} \delta 7.65 \text{ (d, } J = 8.77 \text{ Hz, 2 H}), 7.26 \text{ (d, } J = 8.80 \text{ Hz, 2 H}), 6.77 \text{ (s, 2 H)}, 5.06 \text{ (td, } J = 7.22, 4.04 \text{ Hz, 1 H}), 3.89 \text{ (s, 6 H)}, 3.87 \text{ (s, 3 H)}, 2.67 \text{ (d, } J = 4.05 \text{ Hz)} \]
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 153.5, 153.3, 138.8, 133.9, 130.4, 122.6 (t, \(J = 274.84\) Hz), 122.0, 118.2, 109.6, 105.0, 74.5 (t, \(J = 31.07\) Hz), 61.0, 56.4

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) –82.13 (d, \(J = 3.66\) Hz, 1 F), –82.15 (d, \(J = 3.53\) Hz, 1 F)

IR (film): 3456, 2938, 2841, 2231, 1594, 1503, 1462, 1422, 1326, 1298, 1252, 1236, 1126, 1074, 1004, 922, 843, 809, 790, 768, 733, 702, 661, 640, 548, 465 cm\(^{-1}\)

HRMS (ESI+): calc. for C\(_{18}\)H\(_{18}\)BrF\(_2\)NO\(_3\)K (M+K) 404.0712, found 404.0717, 1.2 ppm.

2-(2,4-dichlorophenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9c):
Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)\(_2\) at 110 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–40% EtOAc in hexanes, furnishing 0.095 g (47% yield) of desired product 4.9c as a yellow oil.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42 (d, $J = 2.43$ Hz, 1 H), 7.28–7.25 (m, 1 H), 7.21 (dd, $J = 8.81$, 2.42 Hz, 1 H), 6.79 (s, 2 H), 5.09 (t, $J = 7.27$ Hz, 1 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.89 (bs, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.1, 144.7 (d, $J = 1.88$ Hz), 138.6, 131.6, 130.3, 130.2, 128.1, 127.8, 123.8 (t, $J = 1.84$ Hz), 122.6 (t, $J = 275.45$ Hz), 105.0, 74.4 (t, $J = 30.98$ Hz), 60.9, 56.2

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.59 (dd, $J = 138.37$, 6.85 Hz, 1 F), –82.67 (dd, $J = 138.48$, 7.65 Hz, 1 F)

IR (film): 3444, 3081, 2940, 2839, 2251, 1594, 1508, 1475, 1463, 1422, 1384, 1325, 1261, 1235, 1185, 1125, 1096, 1075, 1002, 910, 868, 841, 812, 791, 770, 734, 687, 663, 632, 568, 530 cm$^{-1}$

HRMS (ESI+): calc. for C$_{17}$H$_{16}$Cl$_2$F$_2$O$_5$K (M+K) 446.9980, found 446.9998, 4.0 ppm.
2-(3-chloro-2-fluorophenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9d): Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.156 mL (0.220 g, 1.50 mmol) of 3-chloro-4-fluorophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–40% EtOAc in hexanes, furnishing 0.132 g (67% yield) of desired product 4.9d as a pale solid (MP = 115–117 °C).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.23 (ddd, $J = 8.08, 6.36, 1.61$ Hz, 1 H), 7.18 (ddd, $J = 8.52, 6.62, 1.30$ Hz, 1 H), 7.01 (td, $J = 8.26, 1.86$ Hz, 1 H), 6.77 (s, 2 H), 5.07 (t, $J = 7.23$ Hz, 1 H), 3.85 (s, 6 H), 3.84 (s, 3 H), 3.42 (bs, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 153.1, 138.3, 130.8, 127.7, 124.0 (d, $J = 5.69$ Hz), 122.6 (t, $J = 276.48$ Hz), 122.5, 122.4 (d, $J = 15.56$ Hz), 105.0, 74.2 (t, $J = 31.07$ Hz), 60.9, 56.2

$^{19}$F NMR (376 MHz, CDCl$_3$): δ −81.90 (dt, $J = 138.37, 6.47$ Hz, 1 F), −82.46 (dt, $J = 138.62, 6.16$ Hz, 1 F), −130.23 (q, $J = 5.94$ Hz, 1 F)

IR (film): 3461, 2942, 2841, 2105, 1596, 1510, 1481, 1460, 1421, 1326, 1273, 1230, 1186, 1124, 1098, 1074, 1002, 941, 912, 850, 819, 793, 762, 748, 737, 719, 698, 663, 623, 591, 573, 528, 467 cm$^{-1}$

HRMS (ESI+): calc. for C$_{17}$H$_{17}$ClF$_3$O$_5$ (M+H) 393.0717, found 393.0734, 1.7 mmu.
2,2-difluoro-2-(3-iodophenoxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9e):

Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted in the dark with 0.330 g (1.50 mmol) of 3-iodophenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 110 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.156 g (67% yield) of desired product 4.9e as a pale solid (MP = 123–126 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.56 (dt, $J = 7.82, 1.28$ Hz, 1 H), 7.51 (t, $J = 1.90$ Hz, 1 H), 7.13 (ddd, $J = 8.34, 2.23, 1.03$ Hz, 1 H), 7.06 (t, $J = 8.00$ Hz, 1 H), 6.77 (s, 2 H), 5.02 (td, $J = 7.14, 3.90$ Hz, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 2.67 (d, $J = 3.26$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.3, 150.3 (t, $J = 2.14$ Hz), 135.1, 131.0, 130.9, 130.6, 122.5 (t, $J = 272.99$ Hz), 121.2, 105.0, 93.7, 74.4 (t, $J = 31.16$ Hz), 61.0, 56.4

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.89 (ddd, $J = 141.02, 7.26, 7.02$ Hz, 2 F)

IR (film): 3448, 2936, 1580, 1508, 1500, 1466, 1422, 1336, 1326, 1238, 1129, 997, 845, 758, 706 cm$^{-1}$
HRMS (ESI–): calc. for C\textsubscript{17}H\textsubscript{17}F\textsubscript{2}IO\textsubscript{5}Cl (M+Cl) 500.9777, found 500.9782, 1.0 ppm.

2-(4-(2-bromoethyl)phenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9f): Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.302 g (1.50 mmol) of 4(2-bromoethyl)phenol in the presence of 0.026 g (0.10 mmol) of Co(acac)\textsubscript{2} at 100 °C for 48 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–45% EtOAc in hexanes, furnishing 0.162 g (69% yield) of desired product 4.9f as a red oil.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 7.16 (d, J = 8.56 Hz, 2 H), 7.08 (d, J = 8.21 Hz, 2 H), 6.77 (s, 2 H), 5.02 (td, J = 7.24, 3.11 Hz, 1 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.54 (t, J = 7.49 Hz, 2 H), 3.12 (t, J = 7.47 Hz, 2 H)

\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): \delta 153.2, 148.9 (t, J = 2.37 Hz), 138.5 (d, J = 1.63 Hz), 136.6, 130.9, 129.8, 122.5 (t, J = 271.38 Hz), 121.9, 105.0, 74.4 (t, J = 31.77 Hz), 61.0, 56.3, 38.7, 32.9
$^{19}$F NMR (376 MHz, CDCl$_3$): δ $\sim$ 81.56 (dd, $J = 141.41$, 7.45 Hz, 1 F), $\sim$ 81.99 (dd, $J = 141.40$, 7.81 Hz, 1 F)

IR (film): 3446, 2939, 2839, 2250, 1758, 1593, 1507, 1462, 1421, 1325, 1235, 1200, 1125, 1064, 1019, 1002, 910, 831, 809, 764, 751, 731, 697, 646, 551, 531 cm$^{-1}$

HRMS (ESI–): calc. for C$_{19}$H$_{21}$BrF$_2$O$_5$Cl (M+Cl) 481.0229, found 481.0247, 3.7 ppm.

\[ \text{N-(4-hydroxyphenyl)-4-methylbenzenesulfonamide (4.8g):}^{2} \]

Prepared according to reference 2. 4-Aminophenol (1.50 g, 14.0 mmol) was dissolved in 50 mL DCM, and the resulting solution cooled to 0 °C under vigorous stirring. Pyridine (5.1 mL, 63 mmol) was added dropwise, and the resulting solution was stirred for 15 min. A solution of tosyl chloride (2.94 g, 15.4 mmol) in DCM (0.010 L) was added dropwise at 0 °C. The solution was warmed to R.T. and stirred overnight. 3 N HCl (50 mL) was added to quench the reaction, and the mixture was extracted DCM (three times, 15 mL each time). The organic layers were combined and washed with 3 N HCl (20 mL). The combined organic layers were dried over Na$_2$SO$_4$, dried \textit{in vacuo}, and purified by flash chromatography (30–50% EtOAc in Hexanes) to provide 3.05 g (83% yield) of desired product \textbf{4.8g} as a pale yellow solid; $^1$H NMR matched the previously reported spectrum.$^{2}$

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N-(4-(1,1-difluoro-2-hydroxy-2-(3,4,5-trimethoxyphenyl)ethoxy)phenyl)-4-methylbenzenesulfonamide (4.9g): Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.395 g (1.50 mmol) of N-(4-hydroxyphenyl)-4-methylbenzenesulfonamide in the presence of 0.026 g (0.10 mmol) of Co(acac)$_2$ at 120 °C for 24 h. The product was purified without workup by flash chromatography using a gradient of 20–60% EtOAc in hexanes, furnishing 0.134 g (53% yield) of desired product 4.9g as an orange solid (MP = 72–75 °C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.61 (d, $J = 8.27$ Hz, 2 H), 7.19 (d, $J = 7.78$ Hz, 2 H), 7.16 (bs, 1 H), 7.02–6.96 (m, 4 H), 6.74 (s, 2 H), 4.98 (t, $J = 6.94$ Hz, 1 H), 3.84 (s, 9 H), 3.10 (bs, 1 H), 2.35 (s, 3 H)

$^{13}$C (126 MHz, CDCl$_3$): $\delta$ 153.1, 147.4 (d, $J = 1.85$ Hz), 144.2, 138.4, 135.9, 134.2, 131.0, 129.8, 127.3, 123.0, 122.6, 122.4 (t, $J = 271.93$ Hz), 105.0, 74.4 (t, $J = 31.91$ Hz), 61.0, 56.3, 21.6
19F NMR (376 MHz, CDCl3): δ −84.19 (dd, J = 141.15, 5.92 Hz, 1 F), −84.73 (dd, J = 141.11, 7.18 Hz, 1 F)

IR (film): 3468, 3247, 2941, 2840, 2253, 1595, 1505, 1462, 1423, 1398, 1326, 1299, 1275, 1253, 1234, 1201, 1186, 1153, 1126, 1090, 1068, 1018, 1001, 909, 845, 814, 798, 765, 729, 706, 694, 663, 582, 565, 547, 511 cm⁻¹

HRMS (ESI+): calc. for C24H25F2NO7SNa (M+Na) 532.1218, found 532.1227, 1.7 ppm.

2-([1,1'-biphenyl]-4-yloxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9h):
Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.255 g (1.50 mmol) of 4-phenylphenol in the presence of 0.013 g (0.050 mmol) of Co(acac)2 at 110 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–40% EtOAc in hexanes, furnishing 0.157 g (75% yield) of desired product 4.9h as a pale yellow solid MP = 54–56 °C.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.55 (d, $J = 8.54$ Hz, 4 H), 7.43 (t, $J = 7.50$ Hz, 2 H), 7.37–7.33 (m, 1 H), 7.22 (dd, $J = 8.65$, 0.91 Hz, 2 H), 6.81 (s, 2 H), 5.06 (td, $J = 7.09$, 3.94 Hz, 1 H), 3.90 (s, 6 H), 3.88 (s, 3 H), 2.90 (d, $J = 4.01$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.2, 149.4, 140.3, 139.1, 138.5, 131.0, 129.0, 128.2, 127.5, 127.2, 122.6 (t, $J = 272.36$ Hz), 122.0, 105.1, 74.6 (t, $J = 31.88$ Hz), 61.0, 56.3

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.48 (dd, $J = 141.06$, 6.88 Hz, 1 F), –81.99 (dd, $J = 141.05$, 7.20 Hz, 1 F)

IR (film): 3443, 2939, 2838, 2251, 1903, 1594, 1509, 1486, 1462, 1421, 1325, 1289, 1235, 1184, 1125, 1064, 1008, 909, 842, 807, 758, 730, 698, 651, 551, 531, 500 cm$^{-1}$

HRMS (ESI+): calc. for C$_{23}$H$_{22}$F$_2$O$_5$Na (M+Na) 439.1333, found 439.1344, 2.5 ppm.

2,2-difluoro-2-phenoxy-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9i): Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.141 g (1.50 mmol) of phenol in the presence of 0.013 g (0.050 mmol) of Co(acac)$_2$ at 100 °C for
36 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.106 g (62% yield) of desired product 4.9i as an off-white solid (MP = 100–101 °C).

^1H NMR (400 MHz, CDCl₃): δ 7.32 (dd, J = 8.53, 7.23 Hz, 2 H), 7.20 (t, J = 7.42 Hz, 1 H), 7.14 (d, J = 7.18 Hz, 2 H), 6.78 (s, 2 H), 5.03 (ddd, J = 9.10, 6.73, 2.85 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.07 (d, J = 3.91 Hz, 1 H)

^13C NMR (126 MHz, CDCl₃): δ 153.1, 150.0, 138.4, 131.1, 129.5, 125.8, 122.5 (t, J = 271.92 Hz), 121.7, 105.0, 74.5 (t, J = 31.90 Hz), 61.0, 58.2

^19F NMR (376 MHz, CDCl₃): δ -81.49 (dd, J = 141.10, 6.77 Hz, 1 F), -81.97 (dd, J = 141.10, 7.31 Hz, 1 F)

IR (film): 3442, 2940, 2839, 1771, 1592, 1508, 1491, 1462, 1422, 1325, 1291, 1235, 1194, 1125, 1078, 1062, 1026, 1003, 921, 898, 839, 787, 754, 732, 702, 690, 660, 558, 530, 485 cm⁻¹

HRMS (ESI+): calc. for C₁₇H₁₉F₂O₅ (M+H) 341.1201, found 341.1195, 1.8 ppm.
2,2-difluoro-2-(o-tolyloxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9j): Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.16 mL (1.50 mmol) of o-cresol in the presence of 0.026 g (0.100 mmol) of Co(acac)₂ at 110 °C for 48 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–25% EtOAc in hexanes, furnishing 0.089 g (50% yield) of desired product 4.9j as an orange oil.

\[ ^1H \text{NMR (400 MHz, CDCl}_3\] \]: \( \delta 7.21–7.07 \text{ (m, 4 H)}, 6.80 \text{ (s, 2 H)}, 5.07 \text{ (dd, } J = 7.79, 5.83 \text{ Hz, 1 H)}, 3.88 \text{ (s, 6 H)}, 3.86 \text{ (s, 3 H)}, 2.93 \text{ (bs, 1 H)}, 2.05 \text{ (s, 3 H)}

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3\] \]: \( \delta 153.2, 148.4 \text{ (d, } J = 2.00 \text{ Hz)}, 138.6, 131.30, 131.25, 131.18, 126.8, 125.9, 122.7 \text{ (t, } J = 271.11 \text{ Hz)}, 122.0 \text{ (d, } J = 1.66 \text{ Hz)}, 105.1, 74.7 \text{ (t, } J = 31.83 \text{ Hz)}, 61.0, 56.3, 16.3

\[ ^{19}F \text{NMR (376 MHz, CDCl}_3\] \]: \( \delta -80.33 \text{ (dd, } J = 141.28, 5.87 \text{ Hz, 1 F)}, -82.40 \text{ (dd, } J = 141.25, 7.82 \text{ Hz, 1 F)}

\[ \text{IR (film): } 3445, 2939, 2839, 1594, 1507, 1492, 1461, 1421, 1325, 1251, 1234, 1178, 1125, 1062, 1003, 922, 844, 819, 787, 745, 712, 694, 660, 559, 527 \text{ cm}^{-1} \)
HRMS (ESI+): calc. for C_{18}H_{20}F_{2}O_{5}Na (M+Na) 377.1177, found 377.1179, 0.5 ppm.

2,2-difluoro-2-(2-isopropylphenoxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9k):
Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.21 mL (0.204 g, 1.50 mmol) of 2-isopropylphenol in the presence of 0.026 g (0.10 mmol) of Co(acac)$_2$ at 110 °C for 48 h. After workup 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–35% EtOAc in hexanes, furnishing 0.080 g (42% yield) of desired product 4.9k as a black oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24 (dt, $J = 7.74$, 2.51 Hz, 2 H), 7.15 (ddd, $J = 8.03$, 5.34, 2.08 Hz, 2 H), 6.81 (s, 2 H), 5.09 (dt, $J = 8.66$, 4.45 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 2.82 (p, $J = 6.92$ Hz, 1 H), 2.74 (d, $J = 3.95$ Hz, 1 H), 1.03 (dd, $J = 6.92$, 1.01 Hz, 6 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.3, 147.1 (d, $J = 2.01$ Hz), 141.5, 138.6, 131.2 (d, $J = 1.87$ Hz), 126.7, 126.6, 126.2, 122.7 (dd, $J = 271.38$, 2.53 Hz), 121.8, 105.1, 74.9 (dd, $J = 32.84$, 30.16 Hz), 61.0, 56.3, 26.4, 23.1 (d, $J = 16.51$ Hz)
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –79.34 (dd, $J = 140.88, 4.75$ Hz, 1 F), –83.16 (dd, $J = 140.73, 8.56$ Hz, 1 F)

IR (film): 3452, 2964, 2840, 1595, 1508, 1488, 1461, 1422, 1385, 1363, 1325, 1275, 1250, 1234, 1179, 1126, 1084, 1060, 1033, 1004, 910, 836, 812, 785, 754, 732, 698, 661, 573, 530, 473 cm$^{-1}$

HRMS (ESI–): calc. for C$_{20}$H$_{24}$F$_2$O$_5$Cl (M+Cl) 417.1280, found 417.1280, 0.0 ppm.

2-[[1,1'-biphenyl]-2-yloxy]-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (4.9l): Following General Procedure A, 0.115 g (0.500 mmol) of compound 4.1 was reacted with 0.255 g (1.50 mmol) of 2-phenylphenol in the presence of 0.026 g (0.10 mmol) of Co(acac)$_2$ at 110 °C for 48 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–40% EtOAc in hexanes, furnishing 0.141 g (68% yield) of desired product 4.9l as a pale yellow solid (MP = 42 °C).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42–7.31 (m, 8 H), 7.29 (dd, $J = 7.31$, 1.53 Hz, 1 H), 6.56 (s, 2 H), 4.82 (td, $J = 7.11$, 4.18 Hz, 1 H), 3.85 (s, 3 H), 3.78 (s, 6 H), 2.32 (d, $J = 4.17$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.0, 147.0, 138.3, 137.8, 135.2, 131.3, 130.8, 129.3, 129.1, 128.5, 128.3, 128.1, 127.4, 125.9, 125.4, 122.6 (t, $J = 273.57$ Hz), 121.9, 104.9, 74.5 (t, $J = 31.33$ Hz), 60.9, 56.1

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –80.71 (dd, $J = 139.63$, 7.17 Hz, 1 F), –81.67 (dd, $J = 139.53$, 7.09 Hz, 1 F)

IR (film): 3454, 3059, 2940, 2838, 1595, 1506, 1479, 1463, 1422, 1325, 1264, 1236, 1189, 1127, 1070, 1009, 910, 838, 774, 736, 700, 661, 613, 566, 530, 474 cm$^{-1}$

HRMS (ESI+): calc. for C$_{23}$H$_{22}$F$_2$O$_5$K (M+K) 455.1072, found 455.1076, 0.9 ppm.
References:


Chapter 5 – Ongoing Metal-Catalyzed Dioxygenation Reactions of *gem*-Difluoroalkenes

5.1. Tunable Catalysis for Rapid Diversification

Medicinal chemists commonly diversify a single, common intermediate to access many products. This strategy streamlines synthetic effort, by enabling more efficient synthesis of many valuable compounds. However, late stage diversification requires many different reactions and the catalyst systems to reach the desired products. Exploiting catalyst systems, wherein a small change to the catalyst system produces divergent products, simplifies the workflow of late stage diversification.

Tunable, divergent catalyst systems are becoming more common, especially as C–H functionalization and directed reactions are developed. Often these divergent systems utilize distinct ligands to control the regioselectivity of transition metal catalyzed reactions. For example, in the Pd-catalyzed decarboxylative allylation of *α,α*-difluoroketones, distinct Buchwald monophosphine ligand control the site of nucleophilic addition to provide either linear or branched products (Scheme 5-1a). In a second example, using a Cu-based catalyst system, an allyl iodide and a diazo ester form an iodonium ylide, which undergoes a [2,3]-rearrangement in the presence of a pyridyl ligand, but undergoes a [1,2]-rearrangement in the presence of a phosphine ligand (Scheme 5-1b). Finally, a Pd catalyst couples naphthols with a vinylethylene carbonate, where a Buchwald ligand enables [3+2] cyclization, while bidentate phosphine ligands, particularly dppp, enable a [3+3] cyclization (Scheme 5-1c).
Scheme 5-1: Ligand Controlled Divergent Reactions

**a) Ligand Controlled Regio-Divergent Allylation of α,α-Difluoroketones**

\[
\begin{align*}
\text{R}^1\text{O} & \text{Ar} \\
\text{R}^2\text{O} & \text{O} \\
\text{F} & \text{F}
\end{align*}
\]

1,4-dioxane, 60 °C, N\(_2\)

\[
\begin{align*}
\text{Pd(OAc)}_2 & (3.0 \text{ mol\%}) \\
\text{'BuBrettPhos} & (6.0 \text{ mol\%})
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\text{O} & \text{Ar} \\
\text{R}^2\text{O} & \text{F} \\
\text{F} & \text{F}
\end{align*}
\]

1,4-dioxane, 90 °C, N\(_2\)

\[
\begin{align*}
\text{Pd(OAc)}_2 & (3.0 \text{ mol\%}) \\
\text{PhXPhos} & (5.0 \text{ mol\%})
\end{align*}
\]

via

**b) Ligand Controlled [2,3]- or [1,2]-Rearrangements of Iodonium Ylides**

\[
\begin{align*}
\text{R}^1\text{I} & \text{R}^2 \text{I} \\
\text{O} & \text{CO}_2 \text{R}
\end{align*}
\]

CH\(_2\)Cl\(_2\), –20 °C, N\(_2\)

\[
\begin{align*}
\text{[Cu(MeCN)}_4]\text{PF}_6 & (5.0 \text{ mol\%}) \\
\text{6,6'}\text{-Br}_2\text{-Bipyridine} & (6.0 \text{ mol\%})
\end{align*}
\]

CH\(_2\)Cl\(_2\), 45 °C, N\(_2\)

\[
\begin{align*}
\text{Pd(C}_3\text{H}_5\text{)}\text{Cl}_2 & (2.5 \text{ mol\%}) \\
\text{BrettPhos} & (5.0 \text{ mol\%})
\end{align*}
\]

K\(_2\)CO\(_3\)

PhMe, 90 °C, N\(_2\)

\[
\begin{align*}
\text{R}^2\text{Pd-PR}_3 \\
\text{PR}_3
\end{align*}
\]

**c) Ligand Controlled [3+2] or [3+3] Cycloadditions of Naphthols and Vinyl ether Carbonates**

\[
\begin{align*}
\text{O} & \text{O} \\
\text{R}^2 & \text{O} \\
\text{R}^2 & \text{O}
\end{align*}
\]

PhCF\(_3\), 90 °C, N\(_2\)

\[
\begin{align*}
\text{[Pd(C}_3\text{H}_3\text{Cl}_2]} & (2.5 \text{ mol\%}) \\
dppp & (5.0 \text{ mol\%})
\end{align*}
\]

K\(_2\)CO\(_3\)

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A second strategy exploits judicious solvent selection, for instance replacing polar protic solvents with polar aprotic solvents, to alter reactivity without any other changes to the reaction conditions. In the addition of α-cyano nucleophiles to benzyl electrophiles using Pd-based catalyst systems, the use of aromatic solvents vs. polar aprotic solvents switches between benzylation and arylation products (Scheme 5-2a). The aromatic solvent encourages the nitrile to re-arrange from an N-bound ligand to C-bound ligand, followed by reductive elimination with the Pd-benzyl complex. In contrast, polar protic solvents stabilize the N-bound species, encouraging nucleophilic addition of the ketenimine to the para-position of the Pd-benzyl species. In another example, solvent controlled the Co-catalyzed 1,2-oxazetidine cleavage by either stabilizing an N-Tosyl imine leaving group in protic solvents, or maintaining a Co-bound N-Tosyl imine and releasing formaldehyde in non-protic solvents, followed by C–H activation of heteroarenes (Scheme 5-2b).
A third strategy uses additives, such as an exogenous base or acid, to control the reaction outcome. For instance, the addition of amine bases to the decarboxylative benzylation reaction of \(\alpha,\alpha\)-difluoroketones controls the whether the nucleophile attacks the benzyl position or adds to the aryl ring of the benzyl electrophile (Scheme 5-3a). In a Ru-catalyzed [2+2+2] cycloaddition, a silver additive controls whether the reaction forms benzonitrile or pyridyl products (Scheme 5-3b). In this reaction, the silver additive alters the coordination sphere by removing a halide from the tetracoordinate, tetrahedral
Ru center, freeing a coordination site. Thus, the alkynyl nitrile coordinates through the N-center, allowing the [2+2+2] cyclization to occur on the nitrile. In the absence of silver, the halide stays bound to the Ru center. Thus, instead of an \(\eta^1\) binding event through the nitrile nitrogen, an \(\eta^3\) coordination of the alkyne occurs, changing the coordination sphere from tetrahedral to octahedral and enabling a [2+2+2] cyclization with the alkyne (Scheme 5-3b).^3f

Scheme 5-3: Additive Controlled Divergent Reactions

---

a) Amine Controlled Benzylation or Arylation of \(\alpha,\alpha\)-Difluoroketones

\[
\text{Pd(PPh}_3\text{)}_4 (2.5 \text{ mol\%}) \quad \text{o-Xylene, 120 °C, N}_2
\]

\[
(\text{Het})\text{Ar} - \text{O} \quad \text{O} \quad \text{Ar} \quad \text{F} \quad \text{F} \quad \text{Fluoroketones}
\]

\[
\text{Pd(PPh}_3\text{)}_4 (2.5 \text{ mol\%}) \quad \text{Et}_3\text{N} \quad \text{o-Xylene, 120 °C, N}_2
\]

\[
\text{Me} \quad \text{Ar} \quad \text{O} \quad \text{F} \quad \text{F}
\]

b) Silver Controlled [2+2+2] Cycloadditions of Diynes and AlkynylNitriles

\[
\text{CP}^*\text{Ru(COD)Cl (3.0 mol\%)} \quad \text{DME, R.T., Air}
\]

\[
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\]

\[
\text{NC} \quad \text{R}^3
\]

\[
\text{CP}^*\text{Ru(COD)Cl (3.0 mol\%)} \quad \text{AgOTf (3.0 mol\%)} \quad \text{DME, R.T., Air}
\]

\[
\text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\]

---

In contrast, exploiting minor changes in a catalyst system to control the final oxidation state of the products of oxidation reactions is relatively underexplored. Asymmetric
oxidation catalysts, such as the Sharpless dihydroxylation reagent, control the ultimate enantioselectivity through ligand control. However, a catalyst system in which minor changes selectively provide either an alcohol or a ketone product is relatively unknown. Such a controllable oxidation would eliminate additional oxidation or reduction steps, directly providing the desired final oxidation state.

One way to access a precursor which might enable selective control of an alcohol- or a ketone-based product is oxidative difunctionalization reactions of alkenes. Alkenes act as a synthetic handle for difunctionalization, providing a rapid method of diversification, directly forming densely functionalized products from simple starting materials. Many oxidative difunctionalization reactions of alkenes provide access to alcohol or ether derived products, through strategies such as epoxidation-nucleophilic addition or dihydroxylation reactions. However, few alkene difunctionalization reactions selectively functionalize each terminus of an alkene with two different oxygen functional groups in a single step. Such an unsymmetric difunctionalization typically requires two or more steps or provides a regioisomeric mixture of difunctionalized products.

The selective unsymmetric dioxygenation of a difluoroalkene under Co catalysis explored in Chapter 4 is one of the few reactions that selectively adds two different oxygen-based groups to an alkene. In this reaction, the distinct electronic character of the difluoroalkene substrate enables selective functionalization. This reaction only provides the benzylic alcohol product; however, in the absence of Co the same reaction provides a mixture of the benzyl alcohol and phenone products. Thus, reoptimization of the catalyst system to generate the phenone product should be possible. Herein, we present a series
of reactions using Pt-based catalyst systems, where a change from a basic to an acidic additive controls access to \( \beta \)-phenoxy-\( \beta \),\( \beta \)-difluorobenzyl alcohol or ketone products, and a Cu-based catalyst system to selectively provide \( \beta \)-phenoxy-\( \beta \),\( \beta \)-difluorobenzyl ketones.

5.2. *Platinum Catalysis to Access* \( \beta \)-Phenoxy-\( \beta \),\( \beta \)-Difluorobenzyl Alcohols

The catalytic addition of phenol to *gem*-difluoroalkenes using a platinum-based catalyst system provides similar reactivity to Co-based catalyst systems. In the presence of a basic additive, Pt(0)- and Pt(IV)-based precatalysts both selectively accessed the \( \beta \)-phenoxy-\( \beta \),\( \beta \)-difluorobenzyl alcohol product (*Table 5-1*, entries 1–2). Interested in exploring the benefits of a Pt-based catalyst system relative to a Co-based catalyst system, we optimized the reaction of a *gem*-difluoroalkene and a phenol to provide a \( \beta \)-phenoxy-\( \beta \),\( \beta \)-difluorobenzyl alcohol using a Pt-based catalyst system.

Initially, we attempted to simplify the Pt-based catalyst system, similar to the Co-based catalyst system in Chapter 4. To that end, we removed the base additive, unfortunately, both the yield and selectivity of the desired product decreased (*Table 5-1*, entries 3–4). Removing oxygen completely shut down the reaction (*Table 5-1*, entry 5). Notably, Pt(0)-, Pt(II)-, and Pt(IV)-based precatalysts all provided the desired product in moderate to good yield and selectivity, although PtO\(_2\) was the only successful Pt(IV)-based precatalyst (*Table 5-1*, entries 1–2, 19–20).

Exploring the basic co-catalyst, cyclic amine bases enabled the desired reactivity, with Dimethylaminopyridine (DMAP) providing the best yield and selectivity (*Table 5-1*, entries 6–11). Using DMAP as the co-catalyst, aromatic solvents and water provided the desired
alcohol product 5.3 in moderate to high yields and high selectivity. Other solvents reduced both the yield and selectivity of the desired product (Table 5-1, entries 12–18). Based on the similar reactivity of Pt(PPh₃)₄ and Pt(acac)₂ in the presence of DMAP, we settled on Pt(acac)₂ as the ideal catalyst, as Pt(acac)₂ is significantly less expensive per mole. However, Pt(acac)₂, unlike Pt(PPh₃)₄, required a phosphine-based ligand to provide consistent results. Gratifyingly, use of PPh₃ successfully improved the yield and selectivity of 5.3 over 5.4 when added to Pt(acac)₂ (Table 5-1, entries 21–23).
Table 5-1: Initial Optimization of Pt-Catalyzed Addition / Oxidation of Phenol to *gem*-Difluoroalkenes

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Base</th>
<th>Solvent</th>
<th>Conv.[b]</th>
<th>5.3[b]</th>
<th>5.4[b]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>PtO₂</td>
<td>TBD</td>
<td>DCB</td>
<td>98</td>
<td>68</td>
<td>15</td>
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<tr>
<td>2</td>
<td>Pt(PPh₃)₄</td>
<td>TBD</td>
<td>DCB</td>
<td>95</td>
<td>66</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>PtO₂</td>
<td>–</td>
<td>DCB</td>
<td>84</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Pt(PPh₃)₄</td>
<td>–</td>
<td>DCB</td>
<td>85</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>5[c]</td>
<td>PtO₂</td>
<td>–</td>
<td>DCB</td>
<td>34</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6[c]</td>
<td>Pt(PPh₃)₄</td>
<td>Et₃N</td>
<td>DCB</td>
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<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Pt(PPh₃)₄</td>
<td>2,6-Lutidine</td>
<td>DCB</td>
<td>92</td>
<td>1</td>
<td>8</td>
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<tr>
<td>8</td>
<td>Pt(PPh₃)₄</td>
<td>Imidazole</td>
<td>DCB</td>
<td>94</td>
<td>72</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>Pt(PPh₃)₄</td>
<td>DABCO</td>
<td>DCB</td>
<td>90</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>Pt(PPh₃)₄</td>
<td>DBU</td>
<td>DCB</td>
<td>87</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>Pt(PPh₃)₄</td>
<td>DMAP</td>
<td>DCB</td>
<td>94</td>
<td>85</td>
<td>3</td>
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<tr>
<td>12</td>
<td>Pt(PPh₃)₄</td>
<td>DMAP</td>
<td>H₂O</td>
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<td>1</td>
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<td>Pt(PPh₃)₄</td>
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<td>IPA</td>
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<td>0</td>
</tr>
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<td>Pt(PPh₃)₄</td>
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<td>1,4-Dioxane</td>
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<td>1</td>
<td>0</td>
</tr>
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<td>15</td>
<td>Pt(PPh₃)₄</td>
<td>DMAP</td>
<td>MeCN</td>
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<td>0</td>
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<tr>
<td>16</td>
<td>Pt(PPh₃)₄</td>
<td>DMAP</td>
<td>DMF</td>
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<td>1</td>
</tr>
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<td>17</td>
<td>Pt(PPh₃)₄</td>
<td>DMAP</td>
<td>DMSO</td>
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<td>2</td>
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<tr>
<td>18</td>
<td>Pt(PPh₃)₄</td>
<td>DMAP</td>
<td>PhMe</td>
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<td>1</td>
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<td>19</td>
<td>Pt₂(dba)₃</td>
<td>DMAP</td>
<td>DCB</td>
<td>83</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>Pt(acac)₂</td>
<td>DMAP</td>
<td>DCB</td>
<td>95</td>
<td>74</td>
<td>3</td>
</tr>
<tr>
<td>21[d]</td>
<td>Pt(acac)₂</td>
<td>DMAP</td>
<td>DCB</td>
<td>95</td>
<td>76</td>
<td>5</td>
</tr>
<tr>
<td>22[e]</td>
<td>Pt(acac)₂</td>
<td>DMAP</td>
<td>DCB</td>
<td>90</td>
<td>65</td>
<td>4</td>
</tr>
<tr>
<td>23[f]</td>
<td>Pt(acac)₂</td>
<td>DMAP</td>
<td>DCB</td>
<td>79</td>
<td>48</td>
<td>5</td>
</tr>
</tbody>
</table>

[a] Standard conditions: **5.1** (1.0 equiv., 0.10 mmol), **5.2** (3.0 equiv., 0.30 mmol), DMAP (10 mol%, 0.010 mmol), DCB (0.25 M, 0.40 mL), Pt(PPh₃)₄ (10 mol%, 0.010 mmol), 100 °C, for 18 h under an O₂ atmosphere. [b] Determined by ¹⁹F NMR analysis of the crude reaction mixture, standardized with 10 µL (0.080 mmol) of α,α,α-trifluorotoluene.
(TFT). [c] N\textsubscript{2} atmosphere. [d] 10% PPh\textsubscript{3}. [e] 20% PPh\textsubscript{3}. [f] 40% PPh\textsubscript{3}. DCB = 1,2-Dichlorobenzene. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. DABCO = 1,4-Diazabicyclo[2.2.2]octane. TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene.

Unfortunately, with more demanding substrates, such as electron-deficient or sterically congested gem-difluoroalkenes, the PPh\textsubscript{3}-ligated system failed to provide high yields. Thus, a variety of ligands were screened, and the use of three distinct ligands improved the reaction (Table 5-2). The use of PPh\textsubscript{3} [1:1 with Pt(acac)\textsubscript{2}] provided the best selectivity, but lower reactivity than bidentate phosphines (Table 5-2, entry 1). The use of DPPE or BINAP [0.5:1 with Pt(acac)\textsubscript{2}] improved the yield but reduced the selectivity (Table 5-2, entry 9 and 13). The use of DPPE balanced reactivity and selectivity better than BINAP, which provided the highest yield but the lowest selectivity of the three ligands. Thus, we settled on a catalyst system employing 10% Pt(acac)\textsubscript{2}, ligated with either 10% PPh\textsubscript{3} or 5% bidentate phosphine, with a 10% DMAP co-catalyst, in DCB at 100 °C for 24 h under an O\textsubscript{2} atmosphere.
Table 5-2: Ligand Screening of Pt-Catalyzed Addition of Phenols to *gem*-Difluoroalkenes

![Chemical structure image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (%)</th>
<th>Conv.[b]</th>
<th>5.9a[b]</th>
<th>5.10a[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃ (10%)</td>
<td>90</td>
<td>71</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>OPPh₃ (10%)</td>
<td>81</td>
<td>78</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>PCy₃ (10%)</td>
<td>67</td>
<td>58</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>P(4-CF₃Ph)₃ (10%)</td>
<td>88</td>
<td>73</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>SPhos (10%)</td>
<td>84</td>
<td>65</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>BrettPhos (10%)</td>
<td>82</td>
<td>69</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>tBu-XPhos (10%)</td>
<td>82</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>Xantphos (5%)</td>
<td>81</td>
<td>68</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>DPPE (5%)</td>
<td>91</td>
<td>84</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>DPPF (5%)</td>
<td>85</td>
<td>64</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>Bipyridine (5%)</td>
<td>89</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>Phenanthroline (5%)</td>
<td>86</td>
<td>52</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>BINAP (5%)</td>
<td>85</td>
<td>74</td>
<td>8</td>
</tr>
</tbody>
</table>

![Chemical structures of ligands]
[a] Standard conditions: 5.8a (1.0 equiv., 0.10 mmol), 5.2 (3.0 equiv., 0.30 mmol), DMAP (10 mol%, 0.010 mmol), DCB (0.25 M, 0.40 mL), Pt(PPh₃)₄ (10 mol%, 0.010 mmol), 130 °C, for 18 h under an O₂ atmosphere. [b] Determined by ¹⁹F NMR analysis of the crude reaction mixture, standardized with 10 µL (0.080 mmol) of TFT. 5.9c and 5.10c refer to Scheme 5-5.

Under these conditions, the Pt-based catalyst system performs similarly to the Co-based catalyst system for electron-rich and electron-neutral difluoroalkenes (Scheme 5-4, 5.6a–d). However, using the Pt-based systems the desired compounds are easier to purify than under the Co catalyzed conditions. Notably, the Pt-based catalyst system outperforms the Co-catalyst system for electron-deficient and ortho-substituted difluoroalkenes (5.6e, g–i). In these cases, the Pt-catalyst system routinely increased the yield of the desired product by 10–20%, without compromising selectivity. However, similar to the Co-based system, a 2,6-Me₂ substituted difluoroalkene failed to react (5.6f).
Scheme 5-4: Scope of gem-Difluoroalkenes in Pt-Catalyzed Addition / Oxidation of Phenols.[a]  

![Diagram showing the reaction scheme](image)

[a] Standard conditions: 5.5a–n (1.0 equiv., 0.50 mmol), 5.2 (3.0 equiv., 1.5 mmol), DMAP (10 mol%, 0.050 mmol), Ligand (5–10 mol%, 0.025–0.050 mmol), DCB (0.25 M, 2.0 mL), Pt(acac)$_2$ (10 mol%, 0.050 mmol), temperature as indicated, for 24 h under an O$_2$ atmosphere. The selectivity of alcohol:ketone was determined by $^{19}$F NMR analysis of
the crude reaction mixture, standardized with 50 µL (0.40 mmol) of TFT, and is reported in parentheses. Yields represent the average of 2 runs. [b] PPh₃ (10 mol%, 0.050 mmol). [c] DPPE (5 mol%, 0.025 mmol). [d] rac-BINAP (5 mol%, 0.025 mmol).

Using this system, heteroaryl difluoroalkenes reacted in much the same manner as aryl difluoroalkenes (Scheme 5-5). While the bulk of difluoroalkenes provided similar yields and selectivity under both the Pt- and Co-catalyst system, two cases demonstrate the complementary nature of these two systems. First, the electron rich, piperazine substituted thiazole, which required low temperature to avoid degradation using the Co-based catalyst system, degrades completely under Pt catalysis (5.9d). In the case of the bulky, 2-substituted benzothiophene, the Pt-based catalyst system outperforms the Co-based catalyst system (5.9c).

**Scheme 5-5: Scope of Heteroaryl gem-Difluoroalkenes in Pt-Catalyzed Addition / Oxidation of Phenols**[a]
[a] Standard conditions: 5.8a–d (1.0 equiv., 0.50 mmol), 5.2 (3.0 equiv., 1.5 mmol), DMAP (10 mol%, 0.050 mmol), Ligand (5–10 mol%, 0.050 mmol), DCB (0.25 M, 2.0 mL), Pt(acac)$_2$ (10 mol%, 0.050 mmol), temperature as indicated, for 24 h under an O$_2$ atmosphere. The selectivity of alcohol:ketone was determined by $^{19}$F NMR analysis of the crude reaction mixture, standardized with 50 µL (0.40 mmol) of TFT, and is reported in parentheses. Yields represent the average of 2 runs. [b] PPh$_3$ (10 mol%, 0.050 mmol). [c] DPPE (5 mol%, 0.025 mmol).

Subjecting diverse phenols to the Pt-catalyst system revealed no major difference between the Pt- and the Co-based catalyst systems (Scheme 5-6). Electron-rich, -neutral, and -deficient phenols all reacted well using the Pt-based catalyst system, providing the desired product in moderate to high yields and selectivities. Notably, ortho substituted phenols did not react favorably using the Pt-based catalyst systems compared to the Co-based catalyst systems. However, a hydroxypyridine substrate (5.12g), which did not activate using the Co-based catalyst system, did react well using the Pt-based catalyst system.
Scheme 5-6: Scope of Phenol Nucleophiles in Pt-Catalyzed Addition / Oxidation to \(\text{gem-}\) Difluoroalkenes\(^{[a]}\)

\[
\begin{array}{ccc}
\text{Ar} & \text{OH} & \text{Ar} \\
\text{F} & \text{F} & \text{F} \quad \text{HO} & \text{Ar} & \text{OH} \\
\text{OMe} & \text{Ar} & \text{OH} & \text{Br} & \text{Ar} & \text{OH} \\
\text{Ph} & \text{Ar} & \text{OH} & \text{Cl} & \text{Ar} & \text{OH} \\
\text{5.12a}^{[b]} & 68\% (>25:1) & 120 \, ^{\circ}\text{C} \\
\text{5.12b}^{[c]} & 50\% (24:1) & 130 \, ^{\circ}\text{C} \\
\text{5.3}^{[b]} & 70\% (23:1) & 130 \, ^{\circ}\text{C} \\
\text{5.12d}^{[b]} & 65\% (>25:1) & 120 \, ^{\circ}\text{C} \\
\text{5.12e}^{[b]} & 61\% (11:1) & 100 \, ^{\circ}\text{C} \\
\text{5.12f}^{[b]} & 63\% (>25:1) & 100 \, ^{\circ}\text{C} \\
\text{5.12g}^{[d]} & 79\% (20:1) & 120 \, ^{\circ}\text{C} \\
\text{5.12h}^{[c]} & 50\% (15:1) & 130 \, ^{\circ}\text{C} \\
\text{5.12i}^{[c]} & 47\% (>25:1) & 130 \, ^{\circ}\text{C} \\
\text{5.12j}^{[b]} & 46\% (7:1) & 120 \, ^{\circ}\text{C} \\
\end{array}
\]
[a] Standard conditions: 5.1 (1.0 equiv., 0.50 mmol), 5.11a-f (3.0 equiv., 1.5 mmol), DMAP (10 mol%, 0.050 mmol), Ligand (5–10 mol%, 0.050 mmol), DCB (0.25 M, 2.0 mL), Pt(acac)$_2$ (10 mol%, 0.050 mmol), temperature as indicated, for 24 h under an O$_2$ atmosphere. The selectivity of alcohol:ketone was determined by $^{19}$F NMR analysis of the crude reaction mixture, standardized with 50 µL (0.40 mmol) of TFT, and is reported in parentheses. Yields represent the average of 2 runs. [b] PPh$_3$ (10 mol%, 0.050 mmol). [c] DPPE (5 mol%, 0.025 mmol). [d] 5.1 (1.0 equiv., 0.10 mmol), 5.11g (3.0 equiv., 0.30 mmol), DMAP (20 mol%, 0.020 mmol), Pt(acac)$_2$ (20 mol%, 0.020 mmol), PPh$_3$ (20 mol%, 0.020 mmol)

Further, the Pt-based catalyst system, unlike the Co-based catalyst system, activates aliphatic alcohols and difluoroalkenes. Currently, these reactions do not selectively generate the desired product over the non-oxidized addition product and the trifluoroethyl benzene product. These reactions are still under development, as some re-optimization is required.
Scheme 5-7: Representative Reactions of Aliphatic Difluoroalkenes or Alcohols Using a Pt-Catalyst System\[a\]

\[
\begin{align*}
\text{F} & \quad \text{R} \\
\text{F} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{20\% Ligand} & \quad \text{20\% DMAP} & \quad \text{20\% Pt(acac)}_2 \\
120 \degree C, \text{DCB} & \quad 24 \text{ h, O}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{5.14a–c} & \quad \text{5.2} & \quad \text{5.15a–c} & \quad \text{5.16a–c} & \quad \text{5.17a–c} \\
\text{20\% Ligand} & \quad \text{20\% DMAP} & \quad \text{20\% Pt(acac)}_2 \\
120 \degree C, \text{DCB} & \quad 24 \text{ h, O}_2 \\
\text{Ar}^1 = 4-\text{Br-C}_8\text{H}_4 \\
\end{align*}
\]

\[
\begin{align*}
\text{5.15a} & \quad 26\% (>25:1) \\
\text{5.15b} & \quad 5\%–10\% (1:0:1) \\
\text{5.15c} & \quad 5\% (>25:1) \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{Ar}^2 \\
\text{R} & \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{20\% Ligand} & \quad \text{20\% DMAP} & \quad \text{20\% Pt(acac)}_2 \\
120 \degree C, \text{DCB} & \quad 24 \text{ h, O}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{5.1} & \quad \text{5.18a–d} & \quad \text{5.19a–d} & \quad \text{5.20a–d} & \quad \text{5.21a–d} \\
\text{20\% Ligand} & \quad \text{20\% DMAP} & \quad \text{20\% Pt(acac)}_2 \\
120 \degree C, \text{DCB} & \quad 24 \text{ h, O}_2 \\
\text{Ar}^2 = 3,4,5-(\text{OMe})_3\text{C}_8\text{H}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{5.19a} & \quad 10\% (2:0:1) \\
\text{5.19b} & \quad 10\% (3:0:1) \\
\text{5.19c} & \quad 8\% (1:0:1) \\
\text{5.19d} & \quad 5\% (1:0:2) \\
\end{align*}
\]

\[a\] Standard conditions: \textbf{5.1} or \textbf{5.14a–c} (1.0 equiv., 0.10 mmol), \textbf{5.2} or \textbf{5.18a–d} (3.0 equiv., 0.30 mmol), DMAP (20 mol\%, 0.020 mmol), PPh\textsubscript{3} (20 mol\%, 0.020 mmol), DCB (0.25 M, 0.40 mL), Pt(acac)\textsubscript{2} (20 mol\%, 0.020 mmol), 120 \degree C, for 24 h under an O\textsubscript{2} atmosphere. The yield and selectivity of \textbf{5.15:5.16:5.17} or \textbf{5.19:5.20:5.21} was determined by \textsuperscript{19}F NMR analysis of the crude reaction mixture, standardized with 10 \mu L (0.080 mmol) of TFT, and the selectivity is reported in parentheses.
5.3. Mechanistic Considerations

The Co-based catalyst system provides the desired β-phenoxy-β,β-difluorobenzyl alcohol product via a one-electron process. While comprehensive mechanistic studies have not been undertaken, the Pt-based catalyst system might employ a two-electron process to affect the oxidative addition of phenol to difluoroalkenes. Pt(0)-, Pt(II)-, and Pt(IV)-precatalysts all provided highly selective access to the desired product, which implies that two-electron oxidative addition at Pt occurs. Further, the reaction requires a base co-catalysis to promote addition of phenol, indicating the involvement of a phenoxy intermediate. Finally, there are few examples of Pt(III) in catalytic reactions.

5.4. Copper Catalysis to Access β-Phenoxy-β,β-Difluorobenzyl Ketones

While a co-catalytic system of Pt and base enabled the production of β-phenoxy-β,β-difluorobenzyl alcohols, a co-catalytic system of Pt and acid provided the β-phenoxy-β,β-difluorobenzyl ketone products in high selectivity and low yield. Screening of various acids revealed para-toluene sulfonic acid (PTSA) as optimal, with other sulfonic acids not improving the reaction, reducing the selectivity for the ketone-derived product (Table 5-3). From a screen of ligands, pyridyl ligands demonstrated improved selectivity, with multi-dentate pyridyl ligands such as terpyridine and phenanthroline proving superior (Table 5-4, entries 1–3).
Table 5-3: Optimization of Pt-Catalyzed Addition / Oxidation of Phenols to gem-Difluoroalkenes to Provide β-Phenoxy-β,β-Difluorobenzyl Ketones[a]

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Conv.[b]</th>
<th>5.3[b]</th>
<th>5.4[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$SO$_4$</td>
<td>79</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>72</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>92</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>Proline</td>
<td>25</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>PTSA-H$_2$O</td>
<td>&gt;99</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>MsOH</td>
<td>&gt;99</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>SDS</td>
<td>60</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Isoquinoline-5-SO$_4$</td>
<td>40</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>9[c]</td>
<td>PTSA-H$_2$O</td>
<td>76</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>10[d]</td>
<td>PTSA-H$_2$O</td>
<td>57</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>11[e]</td>
<td>PTSA-H$_2$O</td>
<td>52</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>12[c,f]</td>
<td>PTSA-H$_2$O</td>
<td>76</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>13[c,f]</td>
<td>4-NH$_2$-C$_6$H$_4$-SO$_3$H</td>
<td>60</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>14[c,f]</td>
<td>4-Cl-C$_6$H$_4$-SO$_3$H</td>
<td>12</td>
<td>trace</td>
<td>18</td>
</tr>
<tr>
<td>15[c,f]</td>
<td>C$_6$H$_5$-SO$_3$H</td>
<td>80</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>16[c,f]</td>
<td>2,4-Me$_2$-C$_6$H$_5$-SO$_3$H</td>
<td>84</td>
<td>9</td>
<td>23</td>
</tr>
</tbody>
</table>

[a] Standard conditions: 5.1 (1.0 equiv., 0.10 mmol), 5.2 (3.0 equiv., 0.30 mmol), Acid (1 equiv., 0.10 mmol), DCB (0.25 M, 0.40 mL), Pt(PPh$_3$)$_4$ (10 mol%, 0.010 mmol), 100 °C, for 18 h under an O$_2$ atmosphere. [b] Determined by $^{19}$F NMR analysis of the crude reaction mixture, standardized with 10 µL (0.080 mmol) of TFT. [c] 50% Acid. [d] 25% Acid. [e] 10% Acid. [f] 120 °C. TFA = Trifluoroacetic Acid. MsOH = Methane Sulfonic Acid. SDS = Sodium Dodecyl Sulfate.
Further optimization failed to increase the yield of the desired ketone in a more challenging substrate (5.10c) beyond 50%. Thinking that more oxidizing conditions might increase reactivity, we attempted Wacker-type conditions (Table 5-4, entries 4–7),\textsuperscript{11} which increased yield. Further studies revealed that these conditions did not require Pt, instead operating exclusively through the Cu-based catalyst (Table 5-4, entry 11). Thus, further optimization was conducted using Cu.

**Table 5-4:** Initial Discovery of Cu-Catalyzed Addition / Oxidation of Phenols to gem-Difluoroalkenes to Provide β-Phenoxy-β,β-Difluorobenzyl Ketones\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Ligand</th>
<th>Conv.\textsuperscript{[b]}</th>
<th>5.9c\textsuperscript{[b]}</th>
<th>5.10c\textsuperscript{[b]}</th>
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<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>Bipyridine</td>
<td>89</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>Phenanthroline</td>
<td>82</td>
<td>0</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>Terpyridine</td>
<td>89</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>CuCl\textsubscript{2}</td>
<td>PPh\textsubscript{3}</td>
<td>&gt;99</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>CuCl\textsubscript{2}</td>
<td>Bipyridine</td>
<td>84</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>CuCl\textsubscript{2}</td>
<td>Phenanthroline</td>
<td>80</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>CuCl\textsubscript{2}</td>
<td>Terpyridine</td>
<td>89</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>CuCl\textsubscript{2}</td>
<td>Bipyridine</td>
<td>81</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>CuCl\textsubscript{2}</td>
<td>Phenanthroline</td>
<td>81</td>
<td>0</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>CuCl\textsubscript{2}</td>
<td>Terpyridine</td>
<td>81</td>
<td>0</td>
<td>64</td>
</tr>
<tr>
<td>11\textsuperscript{[c,d]}</td>
<td>CuCl\textsubscript{2}</td>
<td>Terpyridine</td>
<td>84</td>
<td>14</td>
<td>64</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Initial discovery; \textsuperscript{[b]} Conv. = Conversion; \textsuperscript{[c]} CuCl\textsubscript{2} loading 20%; \textsuperscript{[d]} CuCl\textsubscript{2} loading 10%.
[a] Standard conditions: 5.8c (1.0 equiv., 0.10 mmol), 5.2 (3.0 equiv., 0.30 mmol), Acid (50 mol%, 0.050 mmol), Ligand (5.0 mol%, 0.0050 mmol), DCB (0.25 M, 0.40 mL), Pt(PPh₃)₄ (10 mol%, 0.010 mmol), 140 °C, for 18 h under an O₂ atmosphere. [b] Determined by ¹⁹F NMR analysis of the crude reaction mixture, standardized with 10 µL (0.080 mmol) of TFT. [c] 0% Acid. [d] 0% Pt, 20% Terpyridine. 5.9c and 5.10c refer to Scheme 5-5.

Under these conditions, terpyridine remained the optimal ligand; however, acidic co-catalysts were no longer useful (Table 5-4, entries 8–11). Instead, the solvent controlled the reactivity of the system (Table 5-5). The use of aromatic solvents provided high yields with moderate selectivity, generally 1:3 for 5.9c:5.10c (Table 5-5, entry 10). The use of dimethylsulfoxide (DMSO) improved the selectivity, providing undetectable amounts of the undesired alcohol side product 5.9c, but unfortunately the yield of 5.10c was low (Table 5-5, entry 12). The combination of DMSO and DCB prevented formation of the undesired side product 5.9c without reducing the yield of 5.10c (Table 5-5, entries 15–17). We settled on an optimal catalyst system of 20% CuCl₂ ligated with 20% terpyridine in 95:5 DCB:DMSO at 100 °C in an O₂ atmosphere for 24 h.
Table 5-5: Optimization of Cu-Catalyzed Addition / Oxidation of Phenols to gem-Difluoroalkenes to Provide β-Phenoxy-β,β-Difluorobenzyl Ketones

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Conv.</th>
<th>5.9c</th>
<th>5.10c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂</td>
<td>Bipyridine</td>
<td>DCB</td>
<td>75</td>
<td>16</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>CuCl₂</td>
<td>Phenanthroline</td>
<td>DCB</td>
<td>81</td>
<td>18</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>CuCl₂</td>
<td>Terpyridine</td>
<td>DCB</td>
<td>76</td>
<td>16</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>CuSO₄</td>
<td>Terpyridine</td>
<td>DCB</td>
<td>89</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂</td>
<td>Terpyridine</td>
<td>DCB</td>
<td>80</td>
<td>11</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)₂</td>
<td>Phenanthroline</td>
<td>DCB</td>
<td>82</td>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)₂</td>
<td>Bathophenanthroline</td>
<td>DCB</td>
<td>75</td>
<td>9</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)₂</td>
<td>Me₄-Phenanthroline</td>
<td>DCB</td>
<td>91</td>
<td>10</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)₂</td>
<td>(OMe)₂-Phenanthroline</td>
<td>DCB</td>
<td>82</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>CuCl₂</td>
<td>Phenanthroline</td>
<td>PhMe</td>
<td>80</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>CuCl₂</td>
<td>Phenanthroline</td>
<td>DMF</td>
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<td>0</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>CuCl₂</td>
<td>Phenanthroline</td>
<td>DMSO</td>
<td>40</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>CuCl₂</td>
<td>Phenanthroline</td>
<td>Diglyme</td>
<td>67</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>14[c]</td>
<td>Cu(OAc)₂</td>
<td>Terpyridine</td>
<td>3:1 DCB:Diglyme</td>
<td>94</td>
<td>18</td>
<td>81</td>
</tr>
<tr>
<td>15[c]</td>
<td>Cu(OAc)₂</td>
<td>Terpyridine</td>
<td>3:1 DCB:DMSO</td>
<td>61</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>16[c,d]</td>
<td>Cu(OAc)₂</td>
<td>Terpyridine</td>
<td>95:5 DCB:DMSO</td>
<td>&gt;99</td>
<td>7</td>
<td>83</td>
</tr>
<tr>
<td>17[c,d]</td>
<td>Cu(OAc)₂</td>
<td>Terpyridine</td>
<td>3:1 DCB:DMSO</td>
<td>87</td>
<td>2</td>
<td>65</td>
</tr>
</tbody>
</table>

[a] Standard conditions: 5.8c (1.0 equiv., 0.10 mmol), 5.2 (3.0 equiv., 0.30 mmol), Ligand (20 mol%, 0.020 mmol), DCB (0.25 M, 0.40 mL), Cu (20 mol%, 0.020 mmol), 120 °C, for 18 h under an O₂ atmosphere. [b] Determined by ¹⁹F NMR analysis of the crude reaction mixture, standardized with 10 µL (0.080 mmol) of TFT. [c] 100 °C. [d] 5.1 in place of 5.8c.
A variety of substrates were screened using the optimized conditions. Electron-rich difluoroalkenes provided high selectivity but low conversion. Alternately, electron-deficient difluoroalkenes gave moderate to low selectivity and conversion. A 2,6-dimethylsubstituted difluoroalkene showed low reactivity; however, some formation of product was observed (5.7f). Heteroaryl difluoroalkenes provided moderate to good selectivity, but moderate conversion (5.10a, c). Phenols provided low conversion, but what converted generally provided yield in good selectivity. However, a 4-OMe substituted phenol gave high conversion, poor yield, and poor selectivity (5.13a).
Scheme 5-8: Initial Scope of Cu-Catalyzed Addition / Oxidation of Phenols to gem-Difluoroalkenes\textsuperscript{[a]}

\[ \text{Scheme 5-8: Initial Scope of Cu-Catalyzed Addition / Oxidation of Phenols to gem-Difluoroalkenes} \]

\[ \text{5.5a–i} \quad \text{5.2} \quad \text{20 \% Terpyridine} \quad \text{20 \% Cu(OAc)}_2 \quad \text{DCB:DMSO (95:5)} \quad 100 \, ^{\circ}\text{C}, 24 \, \text{h, O}_2 \]

\[ \text{5.6a-i} \quad \text{5.7a-i} \]

\[ \begin{align*}
\text{5.7a} & \quad \text{MeO} \\
& \quad 44\% (15:1) \\
\text{5.7f} & \quad \text{Me} \\
& \quad 1\%
\end{align*} \]

\[ \begin{align*}
\text{5.7j} & \quad \text{O} \quad \text{N} \\
& \quad 23\% (>25:1) \\
\text{5.4} & \quad \text{MeO} \\
& \quad 83\% (12:1) \\
\text{5.13a} & \quad \text{Ar}^2 \quad \text{Ar} \quad \text{O} \\
& \quad 12\% (12:1)
\end{align*} \]

\[ \begin{align*}
\text{5.7h} & \quad \text{NC} \\
& \quad 13\% (2:1) \\
\text{5.10a} & \quad \text{N} \quad \text{Ph} \\
& \quad 31\% (>25:1) \\
\text{5.13g} & \quad \text{Ar}^2 \quad \text{Ar} \quad \text{O} \\
& \quad 16\% (>25:1)
\end{align*} \]

\[ Ar^1 = 4-\text{Br}(\text{C}_6\text{H}_4) \]
\[ Ar^2 = 3,4,5-(\text{OMe})_3(\text{C}_6\text{H}_2) \]

\[ [a] \text{Standard conditions: 5.1, 5.5, or 5.8 (1.0 equiv., 0.10 mmol), 5.2 or 5.11 (3.0 equiv., 0.30 mmol), Terpyridine (20 mol\%, 0.020 mmol), CuCl}_2 (20 \text{ mol\%, 0.020 mmol), DCB (0.38 mL), DMSO (0.020 mL), 100 \, ^{\circ}\text{C, for 24 h under an O}_2 \text{ atmosphere. Yield of 5.7, 5.10, or 5.12 and selectivity versus 5.6, 5.9, or 5.11 determined by }^{19}\text{F NMR analysis of} }\]

450
the crude reaction mixture, standardized with 10 µL (0.080 mmol) of TFT. [c] 100 °C. [d] 5.1 in place of 5.8c.

Overall, the current reaction provides a basis from which to finalize the Cu-based catalyst system for the selective synthesis of β-phenoxy-β,β-difluorobenzyl ketones from gem-difluoroalkenes and phenols. Currently, the catalyst system does not fully convert gem-difluoroalkenes to β-phenoxy-β,β-difluorobenzyl ketones, presenting several potential pathways forwards. First, the temperature can increase from 100 °C, as the current solvent system of DCB:DMSO (95:5) contains two high boiling solvents. However, some substrates (5.7f, 5.13a, 5.7h) give low yield with moderately high conversions, indicating that simply increasing temperature will not solve the issue. Thus, a second strategy is the addition of an external oxidant, such as tert-butyl hydroperoxide, commonly employed in Cu-based oxidation reactions. Finally, alternate solvent systems, or alternate metal catalysts, might enable improved oxidation conditions. However, initial attempts at Fe-based catalyst systems did not improve the yield or selectivity of β-phenoxy-β,β-difluorobenzyl ketones.

5.5. Conclusions

In conclusion, a Pt-based catalyst system provides similar reactivity to the Co-based catalyst system detailed in Chapter 4, where in the presence of a basic co-catalyst a phenolic nucleophile and O₂ are added to gem-difluoroalkenes to provide β-phenoxy-β,β-difluorobenzyl alcohols. This catalyst system outperforms the Co-based catalyst system from Chapter 4 for electron-deficient and ortho-substituted gem-difluoroalkenes, but
otherwise performs similarly. Furthermore, the Pt-based catalyst system activates both aliphatic $gem$-difluoroalkenes and alcohols, although further optimization is required.

Additionally, a Pt-based catalyst system provided tunable reactivity to generate $\beta$-phenoxy-$\beta,\beta$-difluorobenzyl ketone products. This reactivity required the exchange of the base co-catalyst for an acid co-catalyst, although the yield could not increase beyond 50%. However, changing to a Cu-based catalyst system improved reactivity, and the current optimized conditions provide $\beta$-phenoxy-$\beta,\beta$-difluorobenzyl ketone products from a variety of $gem$-difluoroalkenes and phenols. This reaction requires the final development of the reaction conditions and the substrate tables.
5.6. References for Chapter 5


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General Considerations:

Unless otherwise noted, reactions were performed under an atmosphere of air using oven-dried glassware. Selective dioxygenation reactions of phenols and difluorostyrenes were performed in 20 mL borosilicate glass scintillation vials sealed with a PTFE-lined screw-top cap. All other reactions were performed in round-bottom flasks sealed with rubber septa. Stainless-steel syringes were used to transfer air- and moisture-sensitive liquid reagents. Reactions were monitored by either $^{19}$F NMR with an internal standard of $\alpha,\alpha,\alpha$-trifluorotoluene or by thin-layer chromatography (TLC) on UNIPLATE Silica Gel HLF plates, visualized by quenching of fluorescence. Column chromatography was conducted using a Teledyne Isco CombiFlash Rf 200 system utilizing gradient elution. Isolated yields reported in the manuscript represent an average of at least 2 independent runs of final compound 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. Cobalt(II) 2,4-pentanedionate [Co(acac)$_2$] was purchased from Alfa Aesar. 1,2–Dichlorobenzene (DCB, anhydrous, 99+%) and N-methylpyrrolidine (NMP, anhydrous) were purchased from Sigma Aldrich. Solvents, including dimethylformamide (DMF), toluene (PhMe), dichloromethane (DCM), methanol (MeOH), acetonitrile (MeCN), and tetrahydrofuran (THF) were used directly from a solvent purification system, in which
solvent was dried by passage through two columns of activated alumina under argon. Other chemical abbreviations utilized in this document include: $\alpha,\alpha,\alpha$-trifluorotoluene (TFT), sodium sulfate (Na$_2$SO$_4$), magnesium sulfate (MgSO$_4$), ethyl acetate (EtOAc), diethyl ether (Et$_2$O), ammonium chloride (NH$_4$Cl), n-butyllithium ("BuLi), sodium hydroxide (NaOH), room temperature (R.T.), n-butylicarbonate anhydride (Boc$_2$O), potassium carbonate (K$_2$CO$_3$), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and hydrochloric acid (HCl).

Proton nuclear magnetic resonance ($^1$H NMR) and fluorine nuclear magnetic resonance ($^{19}$F NMR) were taken on a Bruker AVIIIHD 400 AVANCE spectrometer (400 and 376 MHz respectively). Proton and carbon nuclear magnetic resonance ($^{13}$C NMR) were taken on a Bruker AVIII 500 Avance spectrometer with a CPDUL cryoprobe (500 and 126 MHz respectively). Chemical shifts ($\delta$) for protons are reported in parts per million (ppm) downfield from tetramethylsilane, and are referenced to the proton resonance of residual solvent in the NMR solvent (CHCl$_3$: $\delta = 7.26$ ppm; DMSO: $\delta = 2.50$ ppm). Chemical shifts ($\delta$) for carbon are reported in ppm downfield from tetramethylsilane, and are referenced to the carbon resonance of the solvent residual peak (CDCl$_3$: $\delta = 77.2$ ppm; DMSO: $\delta = 39.52$ ppm). Chemical shifts for fluorine are reported uncorrected in ppm upfield from trichlorofluoromethane (0 ppm). NMR data are represented as follows: chemical shift (ppm), multiplicity (s = singlet, $\delta$ = doublet, t = triplet, q = quartet, p = pentet,
m = multiplet), coupling constant in Hertz (Hz), integration. Electron paramagnetic resonance (EPR) were taken on a Bruker EMXplus EPR spectrometer with an Oxford cryostat. 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 on a Perkin Elmer Spectrum Two Fourier Transform Infrared Spectrometer by drying samples on a diamond ATR Sample base plate. Uncorrected melting points were measured on a Thomas Hoover Capillary Melting Point apparatus.

**Preparation and Characterization of Gem-Difluoroalkenes**

![](image)

**5-(2,2-difluorovinyl)-1,2,3-trimethoxybenzene (5.1):** Compound 5.1 corresponds to compound 2.1 in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
1-(2,2-difluorovinyl)-4-methoxybenzene (5.5a): Compound 5.5a corresponds to compound 2.5a in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

1-(benzyloxy)-4-(2,2-difluorovinyl)-2-methoxybenzene (5.5b): Compound 5.5b corresponds to compound 2.5h in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
1-(tert-butyl)-4-(2,2-difluorovinyl)benzene (5.5c): Compound 5.5c corresponds to compound 3.8f in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.

![5.5d](image)

1-(2,2-difluorovinyl)-3,5-dimethylbenzene (5.5d): Compound 5.5d corresponds to compound 3.8g in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.

![5.5e](image)

1-(2,2-difluorovinyl)-2,4-dimethylbenzene (5.5e): Compound 5.5e corresponds to compound 3.8h in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.
2-(2,2-difluorovinyl)-1,3-dimethylbenzene (5.5f): Compound 5.5f corresponds to compound 3.8i in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.

4’-(tert-butyl)-2-(2,2-difluorovinyl)-1,1’-biphenyl (5.5g): Compound 5.5g corresponds to compound 2.5g in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
ethyl (E)-3-(3-(2,2-difluorovinyl)phenyl)acrylate (5.5h): Compound 5.5h corresponds to compound 2.5j in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

4-(2,2-difluorovinyl)-N,N-diisopropylbenzamide (5.5i): Compound 5.5i corresponds to compound 3.8q in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.
4-(2,2-difluorovinyl)-1-phenyl-1H-pyrazole (5.8a): Compound 5.8a corresponds to compound 2.7c in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

3-(2,2-difluorovinyl)-1-tosyl-1H-indole (5.8b): Compound 5.8b corresponds to compound 2.7a in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

4-(2,2-difluorovinyl)dibenzo[b,d]thiophene (5.8c): Compound 5.8c corresponds to compound 2.7d in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.
tert-butyl 4-(5-(2,2-difluorovinyl)thiazol-2-yl)piperazine-1-carboxylate (5.8d):

Compound 5.8d corresponds to compound 2.7f in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

**General Procedure for the Selective Unsymmetric Dioxygenation of Difluoroalkenes with Phenols (A-1):**

An oven-dried 20 mL scintillation vial, equipped with a magnetic stirbar, was charged with difluoroalkene (0.50 mmol), phenol (1.50 mmol), DMAP (0.05 mmol), PPh$_3$ (0.05 mmol), and Pt(acac)$_2$ (0.05 mmol). The system was purged with O$_2$ gas for 1 min before anhydrous DCB (2.0 mL) was added to the system under a stream of O$_2$ gas. The system was sealed with a PTFE-lined screw-top cap and stirred for 1 min at R.T. Subsequently, the vial was placed into a pre-heated reaction block and stirred vigorously at 90–140 °C for 24 h. The vial was cooled to R.T., and 50 µL (0.40 mmol) of TFT was added via microsyringe. The solution was diluted with approximately 1 mL of DCM and then stirred...
at R.T. for 10 min to allow adequate mixing. After mixing, an aliquot was removed from the vial and passed through a pad of silica gel into an NMR tube using acetone as eluent to remove Pt(acac)_2, after which the reaction was analyzed by ^19_F NMR for completion and selectivity. After ^19_F NMR analysis, the aliquot was sampled for TLC analysis (visualized with 10% phosphomolybdic acid in EtOH) then returned to the vial. Aqueous base (sat. NaOH or Na_2CO_3) was added to the solution and stirred for 30 min, and then extracted with DCM (four times). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and then purified by flash chromatography using EtOAc and hexanes.

**General Procedure for the Selective Unsymmetric Dioxygenation of Difluoroalkenes with Phenols (A-2):**

An oven-dried 20 mL scintillation vial, equipped with a magnetic stirbar, was charged with difluoroalkene (0.50 mmol), phenol (1.50 mmol), DMAP (0.05 mmol), DPPE (0.025 mmol), and Pt(acac)_2 (0.05 mmol). The system was purged with O_2 gas for 1 min before anhydrous DCB (2.0 mL) was added to the system under a stream of O_2 gas. The system was sealed with a PTFE-lined screw-top cap and stirred for 1 min at R.T. Subsequently, the vial was placed into a pre-heated reaction block and stirred vigorously at 90–140 °C for 24 h. The vial was cooled to R.T., and 50 µL (0.40 mmol) of TFT was added via microsyringe. The solution was diluted with approximately 1 mL of DCM and then stirred.
at R.T. for 10 min to allow adequate mixing. After mixing, an aliquot was removed from the vial and passed through a pad of silica gel into an NMR tube using acetone as eluent to remove Pt(acac)$_2$, after which the reaction was analyzed by $^{19}$F NMR for completion and selectivity. After $^{19}$F NMR analysis, the aliquot was sampled for TLC analysis (visualized with 10% phosphomolybdic acid in EtOH) then returned to the vial. Aqueous base (sat. NaOH or Na$_2$CO$_3$) was added to the solution and stirred for 30 min, and then extracted with DCM (four times). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, concentrated in vacuo, and then purified by flash chromatography using EtOAc and hexanes.

**General Procedure for the Selective Unsymmetric Dioxygenation of Difluoroalkenes with Phenols (A-3):**

An oven-dried 20 mL scintillation vial, equipped with a magnetic stirbar, was charged with difluoroalkene (0.50 mmol), phenol (1.50 mmol), DMAP (0.05 mmol), rac-BINAP (0.025 mmol), and Pt(acac)$_2$ (0.05 mmol). The system was purged with O$_2$ gas for 1 min before anhydrous DCB (2.0 mL) was added to the system under a stream of O$_2$ gas. The system was sealed with a PTFE-lined screw-top cap and stirred for 1 min at R.T. Subsequently, the vial was placed into a pre-heated reaction block and stirred vigorously at 90–140 °C for 24 h. The vial was cooled to R.T., and 50 µL (0.40 mmol) of TFT was added via microsyringe. The solution was diluted with approximately 1 mL of DCM and
then stirred at R.T. for 10 min to allow adequate mixing. After mixing, an aliquot was removed from the vial and passed through a pad of silica gel into an NMR tube using acetone as eluent to remove Pt(acac)₂, after which the reaction was analyzed by ¹⁹F NMR for completion and selectivity. After ¹⁹F NMR analysis, the aliquot was sampled for TLC analysis (visualized with 10% phosphomolybdic acid in EtOH) then returned to the vial. Aqueous base (sat. NaOH or Na₂CO₃) was added to the solution and stirred for 30 min, and then extracted with DCM (four times). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo, and then purified by flash chromatography using EtOAc and hexanes.

**Preparation and Characterization of Compounds in Table 5-1:**

2-(4-bromophenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.3):

Following General Procedure A-1, 0.115 g (0.500 mmol) of compound 5.1 was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.007 g (0.050 mmol) of
DMAP, 0.014 g (0.050 mmol) of PPh₃, and 0.020 g (0.050 mmol) of Pt(acac)₂ at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.148 g (71% yield) of desired product 5.3 as a yellow solid (MP = 93–95 °C).

¹H NMR (400 MHz, CDCl₃): δ 7.45–7.41 (m, 2 H), 7.03–6.99 (m, 2 H), 6.74 (s, 2 H), 5.00 (td, J = 7.24, 3.49 Hz, 1 H), 3.86 (s, 6H), 3.85 (s, 3 H), 3.14 (d, J = 3.74 Hz, 1 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.1, 149.1 (t, J = 2.05 Hz), 138.4 (d, J = 2.06 Hz), 132.6, 131.0, 123.6, 122.4 (t, J = 273.70 Hz), 119.0, 105.0, 74.2 (t, J = 31.70 Hz), 61.0, 56.3

¹⁹F NMR (376 MHz, CDCl₃): δ –81.65 (dd, J = 141.05, 6.98 Hz, 1 F), –82.16 (dd, J = 140.99, 7.23 Hz, 1 F)

IR (film): 3450, 2939, 1595, 1508, 1485, 1464, 1422, 1326, 1253, 1129, 1068, 1011, 829, 750, 710 cm⁻¹

HRMS (ESI+): calc. for C₁₇H₁₇BrF₂O₅ (M⁺) 418.0227, found 418.0212, 3.6 ppm.
Experimental Procedures for Table 5-1:

Following General Procedure A-1, 0.023 g (0.10 mmol) of 5.1 was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.010 mmol of base and 0.010 mmol of a Pt salt in 0.40 mL of DCB at 100 °C for 18 h. The reactions were cooled to R.T., and 10 μL (0.080 mmol) of TFT were added. The reactions were diluted with 2.0 mL of DCM,
and allowed to stir for 5 min. An aliquot was removed and passed through a silica gel plug to remove the Pt, and then analyzed by $^{19}$F NMR for completion, yield, and selectivity.
Experimental Procedures for Table 5-2:

**Scheme 5.1:**

Experimental procedure for Table 5-2:

5.8c + 5.2 Br → 5.9c + 5.10c

- 10% DMAP
- 5–10% Ligand
- 10% Pt(acac)₂
- 130 °C, DCB
- O₂, 18 h

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<th>Entry</th>
<th>Ligand (%)</th>
<th>Conv.[b]</th>
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<th>5.10a[b]</th>
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<td>PCy₃ (10%)</td>
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<td>4</td>
<td>P(4-CF₃Ph)₃ (10%)</td>
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<td>SPhos (10%)</td>
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<tr>
<td>6</td>
<td>BrettPhos (10%)</td>
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<td>8</td>
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<td>7</td>
<td>tBu-XPhos (10%)</td>
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<td>Xantphos (5%)</td>
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<td>DPPE (5%)</td>
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<tr>
<td>10</td>
<td>DPPF (5%)</td>
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<td>64</td>
<td>17</td>
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<td>11</td>
<td>Bipyridine (5%)</td>
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<tr>
<td>12</td>
<td>Phenanthroline (5%)</td>
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<tr>
<td>13</td>
<td>BINAP (5%)</td>
<td>85</td>
<td>74</td>
<td>8</td>
</tr>
</tbody>
</table>

**SPhos**

```
   OMe
 P(Cy)₂
P(Cy)₂
MeO
```

**BrettPhos**

```
   OMe
  iPr
P(Cy)₂
```

**tBu-XPhos**

```
   P(tBu)₂
```

**Xantphos**

```
   Me
Me
```

**Bipyridine**

```
   Fe
```

**DPPF**

```
   Ph₂P
```

**BINAP**

```
   PPh₂
```
Following General Procedure A-1, 0.025 g (0.10 mmol) of 5.8c was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.001 g (0.010 mmol) of DMAP, 0.0050 or 0.010 mmol of ligand, and 0.004 g (0.010 mmol) of Pt(acac)$_2$ in 0.40 mL of DCB at 130 °C for 18 h. The reactions were cooled to R.T., and 10 µL (0.080 mmol) of TFT were added. The reactions were diluted with 2.0 mL of DCM, and allowed to stir for 5 min. An aliquot was removed and passed through a silica gel plug to remove the Pt, and then analyzed by $^{19}$F NMR for completion, yield, and selectivity.

Experimental Procedures and Characterization of Compounds in Scheme 5-4:

2-(4-bromophenoxy)-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-ol (5.6a): Following General Procedure A-1, 0.085 g (0.50 mmol) of compound 5.5a was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.013 g (0.050 mmol) PPh$_3$, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 90 °C for 24 h. After
workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.110 g (61% yield) of desired product 5.6a as a pale yellow solid (MP = 51–53 °C).

\textbf{1H NMR (400 MHz, CDCl}_3\textbf{): }\delta 7.47 (d, J = 8.64 Hz, 2 H), 7.44–7.41 (m, 2 H), 7.01 (d, J = 8.91 Hz, 2 H), 6.96–6.92 (m, 2H), 5.04 (td, J = 7.18, 4.29 Hz, 1 H), 3.83 (s, 3 H), 2.57 (d, J = 4.27 Hz, 1 H)

\textbf{13C NMR (126 MHz, CDCl}_3\textbf{): }\delta 160.3, 149.2 (t, J = 2.40 Hz), 132.6, 129.1, 127.4, 123.6, 122.6 (t, J = 272.76 Hz), 119.0, 113.9, 74.1 (t, J = 31.82 Hz), 55.4

\textbf{19F NMR (376 MHz, CDCl}_3\textbf{): }\delta –82.39 (d, J = 7.21 Hz, 2 F)

\textbf{IR (film): }3424, 2957, 2911, 2838, 1891, 1613, 1586, 1515, 1485, 1465, 1442, 1399, 1346, 1305, 1246, 1197, 1177, 1144, 1117, 1065, 1032, 1012, 939, 827, 800, 756, 745, 716, 691, 636, 593, 535, 493 cm\textsuperscript{-1}

\textbf{HRMS (ESI–): }calc. for C\textsubscript{15}H\textsubscript{13}BrF\textsubscript{2}O\textsubscript{3}Cl (M+Cl) 392.9705, found 392.9709, 1.0 ppm.
1-(4-(benzyloxy)-3-methoxyphenyl)-2-(4-bromophenoxy)-2,2-difluoroethan-1-ol (5.6b): Following General Procedure A-1, 0.131 g (0.500 mmol) of compound 5.5b was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.014 g (0.050 mmol) of PPh₃, and 0.020 g (0.050 mmol) of Pt(acac)₂ at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.156 g (70% yield) of desired product 5.6b as a light orange solid (MP = 87–88 °C)

$^1$H NMR (400 MHz, CDCl₃): δ 7.44 (td, $J = 7.21$, 6.81, 1.94 Hz, 4 H), 7.41–7.34 (m, 2 H), 7.34–7.28 (m, 1 H), 7.11 (d, $J = 1.93$ Hz, 1 H), 7.06–6.96 (m, 3 H), 6.89 (d, $J = 8.29$ Hz, 1 H), 5.17 (s, 2 H), 5.00 (t, $J = 7.12$ Hz, 1 H), 3.90 (s, 3H), 2.83 (bs, 1 H)

$^{13}$C NMR (126 MHz, CDCl₃): δ 149.6, 149.1 (d, $J = 2.75$ Hz), 148.8, 137.0, 132.5, 128.7, 128.3, 128.0, 127.4, 123.6, 122.5 (t, $J = 272.85$ Hz), 120.6, 119.0, 113.4 (d, $J = 1.62$ Hz), 111.3, 74.1 (t, $J = 31.44$ Hz), 71.0, 56.2
\(^{19}\text{F NMR (376 MHz, CDCl}_3\):} \delta -81.89 (dd, \(J = 141.33, 7.27\) Hz, 1 F), -82.28 (dd, \(J = 141.33, 7.27\) Hz, 1 F)

\textbf{IR (film):} 3458, 3033, 2917, 2849, 1735, 1607, 1594, 1514, 1484, 1464, 1454, 1421, 1382, 1337, 1252, 1202, 1138, 1065, 1033, 1012, 914, 844, 827, 800, 738, 696, 648, 551, 494 cm\(^{-1}\)

\textbf{HRMS (ESI+):} calc. for C\(_{22}\)H\(_{19}\)BrF\(_2\)O\(_4\)K (M+K) 503.0072, found 503.0078, 1.2 ppm.

\[ \text{Br} \]
\[ \text{O} \]
\[ \text{F} \]
\[ \text{F} \]
\[ \text{tBu} \]
\[ \text{OH} \]
\[ 5.6c \]

\textbf{2-(4-bromophenoxy)-1-(4-(tert-butyl)phenyl)-2,2-difluoroethan-1-ol (5.6c):} Following General Procedure A-1, 0.098 g (0.50 mmol) of compound 5.5c was reacted with 0.0259 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.013 g (0.050 mmol) of PPh\(_3\), and 0.020 g (0.050 mmol) or Pt(acac)\(_2\) at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–15% EtOAc in hexanes, furnishing 0.094 g (49% yield) as an orange oil.
\[ ^1H \text{ NMR (500 MHz, CDCl}_3\] \delta 7.47 (d, \( J = 8.62 \text{ Hz}, 2 \text{ H})\), 7.44–7.43 (m, 4 \text{ H}), 7.02 (d, \( J = 8.83 \text{ Hz}, 2 \text{ H})\), 5.06 (td, \( J = 7.18, 4.50 \text{ Hz}, 1 \text{ H})\), 2.56 (d, \( J = 4.50 \text{ Hz}, 1 \text{ H})\), 1.34 (s, 9 \text{ H})

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3\] \delta 152.3, 149.2, 132.6, 132.3, 127.5, 125.5, 123.6, 122.6 (t, \( J = 272.79 \text{ Hz})\), 119.0, 74.4 (t, \( J = 31.60 \text{ Hz})\), 34.8, 31.4

\[ ^{19}F \text{ NMR (376 MHz, CDCl}_3\] \delta –82.82 (dd, \( J = 140.87, 7.24 \text{ Hz}, 1 \text{ F}), –83.22 (dd, \( J = 140.93, 7.21 \text{ Hz}, 1 \text{ F})

HRMS (ESI–): calc. for \( \text{C}_{18}\text{H}_{19}\text{BrF}_{2}\text{O}_{2}\text{Cl} \text{ (M+Cl)} 419.0225\), found 419.0240, 3.6 ppm.

2-(4-bromophenoxy)-1-(3,5-dimethylphenyl)-2,2-difluoroethan-1-ol (5.6d): Following General Procedure A-1, 0.084 g (0.50 mmol) of compound 5.5d was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.013 g (0.050 mmol) of PPh\textsubscript{3}, and 0.020 g (0.050 mmol) of Pt(acac)\textsubscript{2} at 130 °C for 24 h. After
workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–15% EtOAc in hexanes, furnishing 0.103 g (58% yield) of desired product 5.6d as a tan solid (MP = 79–81 °C)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 (d, $J = 8.88$ Hz, 2 H), 7.16 (bs, 2 H), 7.04 (bs, 2 H), 7.02 (bs, 1 H), 5.00 (t, $J = 7.25$ Hz, 1 H), 2.74 (bs, 1 H), 2.36 (s, 6 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.2, 138.1, 135.2, 132.5, 130.9, 125.6 (d, $J = 1.49$ Hz), 123.6, 122.5 (t, $J = 272.07$ Hz), 118.9, 74.6 (t, $J = 31.54$ Hz), 21.5

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.59 (dd, $J = 140.92$, 7.09 Hz, 1 F), –82.16 (dd, $J = 140.89$, 7.38 Hz, 1 F)

IR (film): 3395, 3011, 2919, 2051, 1891, 1760, 1609, 1583, 1484, 1399, 1379, 1345, 1251, 1199, 1143, 1114, 1066, 1012, 953, 938, 905, 886, 828, 803, 786, 762, 744, 716, 699, 686, 645, 561, 536, 493 cm$^{-1}$

HRMS (ESI–): calc. for C$_{16}$H$_{15}$BrF$_2$O$_2$Cl (M+Cl) 390.9912, found 390.9921, 2.3 ppm.
2-(4-bromophenoxy)-1-(2,4-dimethylphenyl)-2,2-difluoroethan-1-ol (5.6e): Following General Procedure A-1, 0.084 g (0.50 mmol) of compound 5.5e was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.013 g (0.050 mmol) PPh₃, and 0.020 g (0.050 mmol) of Pt(acac)₂ at 120 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–20% EtOAc in hexanes, furnishing 0.114 g (64% yield) of desired product 5.6e as a pale oil

¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, J = 7.96 Hz, 1 H), 7.43 (d, J = 8.90 Hz, 2 H), 7.11 (d, J = 8.24 Hz, 1 H), 7.04 (d, J = 2.23 Hz, 2 H), 7.02 (s, 1 H), 5.35 (td, J = 7.18, 3.79 Hz, 1 H), 2.85 (d, J = 4.35 Hz, 1 H), 2.40 (s, 3 H), 2.35 (s, 3 H)

¹³C NMR (126 MHz, CDCl₃): δ 149.1 (t, J = 2.25 Hz), 138.7, 136.7, 132.5, 131.3, 130.9, 127.3 (t, J = 1.73 Hz), 127.1, 123.5, 123.0 (t, J = 273.10 Hz), 118.8, 70.3 (t, J = 31.67 Hz), 21.2, 19.6
$^{19}\text{F NMR (376 MHz, CDCl}_3\text{):}$ δ –81.41 (dd, $J = 140.67$, 7.53 Hz, 1 F), –81.85 (dd, $J = 140.45$, 7.12 Hz, 1 F)

**IR (film):** 3381, 2923, 1616, 1583, 1484, 1249, 1196, 1142, 1065, 1012, 826, 809, 760, 748, 720, 691, 494 cm$^{-1}$

**HRMS (ESI+):** calc. for C$_{16}$H$_{15}$BrF$_2$O$_2$Cl (M+Cl) 390.9912, found 390.9920, 2.0 ppm.

2-(4-bromophenoxy)-1-(4′-(tert-butyl)-[1,1′-biphenyl]-2-yl)-2,2-difluoroethan-1-ol (5.6g): Following General Procedure A-2, 0.136 g (0.500 mmol) of compound 5.5g was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.026 g (0.100 mmol) of 0.006 g (0.050 mmol) of DMAP, 0.010 g (0.025 mmol) DPPE, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–25% EtOAc in hexanes, furnishing 0.115 g (50% yield) of desired product 5.6g as an orange oil.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.81 (t, $J = 1.66$ Hz, 1 H), 7.66 (dt, $J = 7.39$, 1.71 Hz, 1 H), 7.60 (d, $J = 8.45$ Hz, 2 H), 7.52 (d, $J = 2.18$ Hz, 2 H), 7.52–7.49 (m, 2 H), 7.45 (d, $J = 8.86$ Hz, 2 H), 7.04 (d, $J = 8.77$ Hz, 2 H), 5.16 (t, $J = 7.11$ Hz, 1 H), 3.00 (bs, 1 H), 1.40 (s, 9 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 150.7, 149.1, 141.3, 137.9, 135.8, 132.5, 128.8, 127.8, 126.9, 126.5, 126.4, 125.9, 123.6, 122.5 (t, $J = 272.36$ Hz), 119.0, 74.5 (t, $J = 31.35$ Hz), 34.7, 31.5

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.63 (dd, $J = 140.63$, 7.08 Hz, 1 F), –82.03 (dd, $J = 140.63$, 7.16 Hz, 1 H)

IR (film): 3401, 3065, 2962, 2904, 2867, 1580, 1483, 1399, 1363, 1252, 1209, 1140, 1115, 1067, 1012, 954, 906, 881, 839, 825, 766, 739, 705, 675, 645, 632, 585, 545, 522, 492 cm$^{-1}$

HRMS (ESI+): calc. for C$_{24}$H$_{24}$BrF$_2$O$_2$ (M+H) 461.0928, found 461.1971, 2.0 ppm.
ethyl (E)-3-(3-(2-(4-bromophenoxy)-2,2-difluoro-1-hydroxyethyl)phenyl)acrylate (5.6h): Following General Procedure A-3, 0.119 g (0.500 mmol) of compound 5.5h was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.016 g (0.025 mmol) of rac-BINAP, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 140 °C for 24 h. After workup with sat. Na$_2$CO$_3$ (aq.), the product was purified by flash chromatography using a gradient of 5–35% EtOAc in hexanes, furnishing 0.110 g (51% yield) of desired product 5.6h as an orange oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.68 (d, $J = 16.16$ Hz, 2 H), 7.56 (d, $J = 7.42$ Hz, 1 H), 7.52 (dt, $J = 7.88, 1.47$ Hz, 1 H), 7.42–7.38 (m, 3 H), 6.98 (m, 2 H), 6.45 (d, $J = 16.02$ Hz, 1 H), 5.10 (t $J = 7.05$ Hz, 1 H), 4.25 (q, $J = 7.11$ Hz, 2 H), 3.53 (bs, 1 H), 1.32 (t, $J = 7.13$ Hz, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 167.2, 148.9 (t, $J = 2.32$ Hz), 144.4, 136.3, 134.5, 132.5, 129.7, 128.9, 128.6, 127.5, 122.3 (t, $J = 273.04$ Hz), 119.0, 118.7, 73.8 (t, $J = 31.46$ Hz), 60.8, 14.4
$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.74 (dd, $J = 140.69$, 6.93 Hz, 1 F), –82.25 (dd, $J = 140.78$, 7.25 Hz, 1 F)

IR (film): 3418, 2982, 2051, 1891, 1693, 1484, 1438, 1397, 1368, 1252, 1225, 1188, 1148, 1113, 1098, 1066, 1012, 983, 863, 843, 825, 794, 757, 734, 696, 651, 581, 558, 493, 465 cm$^{-1}$

HRMS (ESI–): calc. for C$_{19}$H$_{17}$BrF$_2$O$_4$Cl (M+Cl) 460.9967, found 460.9999, 6.9 ppm.

4-(2-(4-bromophenoxy)-2,2-difluoro-1-hydroxyethyl)-N,N-diisopropylbenzamide (5.6i): Following General Procedure A-3, 0.134 g (0.500 mmol) of compound 5.5i was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.016 g (0.025 mmol) of rac-BINAP, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 140 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified
by flash chromatography using a gradient of 15–50% EtOAc in hexanes, furnishing 0.096 g (49% yield) of desired product 5.6i as a white solid (MP = 182–183 °C)

\(^1\)H NMR (500 MHz, DMSO-D\(_6\), 60 °C): δ 7.57 (dd, \(J = 8.45, 3.06\) Hz, 4 H), 7.29 (d, \(J = 7.74\) Hz, 2 H), 7.08 (d, \(J = 8.34\) Hz, 2 H), 6.51 (d, \(J = 5.64\) Hz, 1 H), 5.10 (q, \(J = 7.08\) Hz, 1 H), 3.66–3.63 (m, 2 H), 1.28 (bs, 12 H)

\(^1^3\)C NMR (126 MHz, DMSO-D\(_6\), 60 °C): δ 169.3, 148.8 (d, \(J = 2.31\) Hz), 138.7, 137.2, 132.3, 127.7, 124.7, 123.2, 122.6 (t, \(J = 272.21\) Hz), 117.7, 72.0 (t, \(J = 31.34\) Hz), 54.5, 20.2

\(^1^9\)F NMR (376 MHz, CDCl\(_3\)): δ –81.80 (dd, \(J = 140.26, 7.03\) Hz, 1 F), –82.22 (dd, \(J = 140.26, 6.48\) Hz, 1 F)

IR (film): 3250, 2974, 2935, 1602, 1515, 1483, 1457, 1407, 1381, 1372, 1349, 1275, 1252, 1209, 1195, 1161, 1141, 1082, 1064, 1038, 1012, 919, 883, 854, 808, 765, 750, 681, 631, 610, 577, 548, 527, 497 cm\(^{-1}\)

HRMS (ESI+): calc. for C\(_{21}\)H\(_{24}\)BrF\(_2\)NO\(_3\)Na (M+Na) 478.0805, found 478.0813, 1.7 ppm.
Experimental Procedures and Characterization of Compounds in Scheme 5-5:

2-(4-bromophenoxy)-2,2-difluoro-1-(1-phenyl-1H-pyrazol-4-yl)ethan-1-ol \( (5.9a) \):

Following General Procedure A-1, 0.103 g (0.500 mmol) of compound \( 5.9a \) was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.007 g (0.050 mmol) of DMAP, 0.014 g (0.050 mmol) of \( \text{PPh}_3 \), and 0.020 g (0.050 mmol) of \( \text{Pt(acac)}_2 \) at 100 °C for 24 h. After workup with 1 N \( \text{NaOH} \) (aq.), the product was purified by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.083 g (42% yield) of desired product \( 5.9a \) as a yellow solid (MP = 70–72 °C)

\( ^1\text{H NMR (400 MHz, CDCl}_3 \): \( \delta \) 8.04 (s, 1 H), 7.82 (s, 1 H), 7.65 (d, \( J = 7.51 \) Hz, 2 H), 7.43 (dd, \( J = 8.90, 7.22 \) Hz, 4 H), 7.29 (t, \( J = 7.45 \) Hz, 1 H), 7.04 (d, \( J = 8.57 \) Hz, 2 H), 5.16 (td, \( J = 6.91, 3.91 \) Hz, 1 H), 3.59 (d, \( J = 5.46 \) Hz, 1 H)
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.0, 140.1 (d, $J = 1.95$ Hz), 139.8, 132.6, 129.6, 127.0, 126.6 (d, $J = 1.86$ Hz), 123.6, 122.5 (t, $J = 271.91$ Hz), 119.4, 119.1, 118.9 (d, $J = 1.87$ Hz), 67.7 (t, $J = 33.26$ Hz)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –82.60 (dd, $J = 140.85$, 6.21 Hz, 1 F), –83.07 (dd, $J = 141.08$, 6.84 Hz, 1 F)

IR (film): 3279, 2923, 1680, 1600, 1572, 1504, 1485, 1405, 1257, 1209, 1148, 1114, 1067, 1043, 1012, 955, 904, 826, 804, 756, 690, 492 cm$^{-1}$

HRMS (ESI+): calc. for C$_{17}$H$_{14}$BrF$_2$N$_2$O$_2$ (M+H) 395.0207, found 395.0220, 3.3 ppm.

2-(4-bromophenoxy)-2,2-difluoro-1-(1-tosyl-1H-indol-3-yl)ethan-1-ol (5.9b):

Following General Procedure A-1, 0.167 g (0.500 mmol) of compound 5.8b was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.007 g (0.050 mmol) of DMAP, 0.014 g (0.050 mmol) of PPh$_3$, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 120 °C
for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.151 g (58% yield) of desired product **5.9b** as an orange solid (MP = 53–55 °C).

**¹H NMR (400 MHz, CDCl₃):** δ 7.99 (dt, J = 8.49, 0.88 Hz, 1 H), 7.77 (d, J = 8.53 Hz, 3 H), 7.73 (d, J = 7.75 Hz, 1 H), 7.45–7.41 (m, 2 H), 7.34 (ddd, J = 8.38, 7.16, 1.28 Hz, 1 H), 7.28–7.24 (m, 1 H), 7.21 (d, J = 7.65 Hz, 2 H), 6.98 (dd, J = 8.76, 1.07 Hz, 2 H), 5.35 (td, J = 6.73, 4.53 Hz, 1 H), 2.68 (d, J = 4.95 Hz, 1 H), 2.34 (s, 3 H)

**¹³C NMR (126 MHz, CDCl₃):** δ 149.0 (d, J = 1.96 Hz), 145.4, 135.2, 132.6, 130.1, 129.1, 127.0, 125.8 (d, J = 2.00 Hz), 125.2, 123.6, 123.5, 122.5 (t, J = 272.36 Hz), 120.9 (d, J = 1.82 Hz), 119.2, 117.0 (d, J = 1.66 Hz), 113.8, 69.1 (t, J = 33.67 Hz), 21.7

**¹⁹F NMR (376 MHz, CDCl₃):** δ −81.47 (dd, J = 140.26, 6.78 Hz, 1 F), −82.05 (dd, J = 140.24, 7.22 Hz, 1 F)

**IR (film):** 3509, 3113, 2924, 2052, 1913, 1596, 1566, 1485, 1447, 1340, 1368, 1278, 1255, 1189, 1172, 1122, 1084, 1066, 1012, 972, 907, 834, 811, 764, 744, 733, 703, 678, 657, 599, 571, 537, 492 cm⁻¹

**HRMS (ESI−):** calc. for C₂₃H₁₈F₂NO₄S (M−) 520.0030, found 520.0041, 2.1 ppm.
2-(4-bromophenoxy)-1-(dibenzo[b,d]thiophen-4-yl)-2,2-difluoroethan-1-ol (5.9c):

Following General Procedure A-2, 0.123 g (0.500 mmol) of compound 5.8c was reacted with 0.260 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.016 g (0.025 mmol) of rac-BINAP, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–20% EtOAc in hexanes, furnishing 0.103 g (49% yield) of desired product 5.9c as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.16 (ddd, $J = 7.05, 3.87, 1.88$ Hz, 2 H), 7.86–7.84 (m, 1 H), 7.72 (d, $J = 7.45$ Hz, 1 H), 7.53–7.46 (m, 3 H), 7.40–7.38 (m, 2 H), 7.00 (d, $J = 8.59$ Hz, 2 H), 5.45 (td, $J = 9.07, 2.82$ Hz, 1 H), 3.20 (d, $J = 3.92$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 149.0 (d, $J = 3.01$ Hz), 139.5, 139.2, 136.4, 135.3, 132.5, 129.9, 127.1, 126.2, 124.7, 124.6, 123.4, 122.7, 122.3, 121.7, 118.9, 73.7 (t, $J = 32.23$ Hz)
\(^{19}\text{F NMR (376 MHz, CDCl}_3\):} \delta -81.01 (dd, \(J = 139.12, 6.75 \text{ Hz, 1 F}) , -81.76 (dd, \(J = 139.29, 7.33 \text{ Hz, 1 F})

\text{IR (film):} 3412, 3064, 2922, 1888, 1762, 1583, 1550, 1484, 1444, 1401, 1342, 1276, 1250, 1196, 1147, 1111, 1099, 1066, 1038, 1021, 1012, 938, 904, 827, 793, 750, 706, 688, 646, 627, 577, 556, 492 \text{ cm}^{-1}

\text{HRMS (ESI–):} \text{ calc. for } C_{20}H_{13}BrF_2O_2SCl (M+Cl) 468.9476, \text{ found 468.9471, 1.1 ppm.}

\text{Experimental Procedures and Characterization of Compounds in Scheme 5-6:}

\text{2,2-difluoro-2-(4-methoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12a):} Following General Procedure A-1, 0.115 g (0.50 mmol) of compound 5.1 was reacted with 0.186 g (1.50 mmol) of 4-methoxyphenol in the presence of 0.006 g (0.050 mmol) of
DMAP, 0.013 g (0.050 mmol) of PPh$_3$, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 120 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–35% EtOAc in hexanes, furnishing 0.126 g (68% yield) of desired product **5.12a** as an orange oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.05 (d, $J = 8.88$ Hz, 2 H), 6.82 (d, $J = 9.13$ Hz, 2 H), 6.77 (s, 2 H), 5.00 (t, $J = 7.10$ Hz, 1 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.13 (s, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 157.5, 153.1, 131.2, 123.1, 122.4 (t, $J = 270.28$ Hz), 120.1, 115.0, 114.4, 105.0, 74.4 (t, $J = 31.76$ Hz), 60.9, 56.2, 55.6

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –81.60 (dd, $J = 141.70$, 6.94 Hz, 1 F), –82.23 (dd, $J = 141.70$, 7.41 Hz, 1 F)

HRMS (ESI–): calc. for C$_{18}$H$_{20}$F$_2$O$_6$Cl (M+Cl) 405.0916, found 405.0911, 1.2 ppm
2,2-difluoro-2-phenoxy-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12b): Following General Procedure A-2, 0.115 g (0.500 mmol) of compound 5.1 was reacted with 0.141 g (1.50 mmol) of phenol in the presence of 0.006 g (0.05 mmol) of DMAP, 0.010 g (0.025 mmol) of DPPE, and 0.019 g (0.050 mmol) of Pt(acac)$_2$ at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 15–40% EtOAc in hexanes, furnishing 0.098 g (58% yield) of desired product 5.12b as an off-white solid (MP = 100–101 °C).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.32 (dd, $J = 8.53$, 7.23 Hz, 2 H), 7.20 (t, $J = 7.42$ Hz, 1 H), 7.14 (d, $J = 7.18$ Hz, 2 H), 6.78 (s, 2 H), 5.03 (ddd, $J = 9.10$, 6.73, 2.85 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.07 (d, $J = 3.91$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 153.1, 150.0, 138.4, 131.1, 129.5, 125.8, 122.5 (t, $J = 271.92$ Hz), 121.7, 105.0, 74.5 (t, $J = 31.90$ Hz), 61.0, 58.2

$^{19}$F NMR (376 MHz, CDCl$_3$): δ –81.49 (dd, $J = 141.10$, 6.77 Hz, 1 F), –81.97 (dd, $J = 141.10$, 7.31 Hz, 1 F)

IR (film): 3442, 2940, 2839, 1771, 1592, 1508, 1491, 1462, 1422, 1325, 1291, 1235, 1194, 1125, 1078, 1062, 1026, 1003, 921, 898, 839, 787, 754, 732, 702, 690, 660, 558, 530, 485 cm$^{-1}$

HRMS (ESI+): calc. for C$_{17}$H$_{19}$F$_2$O$_5$ (M+H) 341.1201, found 341.1195, 1.8 ppm.
2,2-difluoro-2-(o-tolyloxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12c): Following General Procedure A-2, 0.115 g (0.500 mmol) of compound 5.1 was reacted with 0.16 mL (1.50 mmol) of o-cresol in the presence of 0.007 g (0.050 mmol) of DMAP, 0.010 g (0.025 mmol) of DPPE, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–25% EtOAc in hexanes, furnishing 0.082 g (46% yield) of desired product 5.12c as an orange oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.21–7.07 (m, 4 H), 6.80 (s, 2 H), 5.07 (dd, $J = 7.79, 5.83$ Hz, 1 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.93 (bs, 1 H), 2.05 (s, 3 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.2, 148.4 (d, $J = 2.00$ Hz), 138.6, 131.30, 131.25, 131.18, 126.8, 125.9, 122.7 (t, $J = 271.11$ Hz), 122.0 (d, $J = 1.66$ Hz), 105.1, 74.7 (t, $J = 31.83$ Hz), 61.0, 56.3, 16.3

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –80.33 (dd, $J = 141.28, 5.87$ Hz, 1 F), –82.40 (dd, $J = 141.25, 7.82$ Hz, 1 F)
**IR (film):** 3445, 2939, 2839, 1594, 1492, 1461, 1421, 1325, 1251, 1234, 1178, 1125, 1062, 1030, 922, 844, 819, 787, 745, 712, 694, 660, 559, 527 cm$^{-1}$

**HRMS (ESI+):** calc. for C$_{18}$H$_{20}$F$_2$O$_5$Na (M+Na) 377.1177, found 377.1179, 0.5 ppm.

![Structure of 5.12d](image)

2-([1,1'-biphenyl]-4-yloxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12d): Following General Procedure A-1, 0.115 g (0.500 mmol) of compound 5.1 was reacted with 0.255 g (1.50 mmol) of 4-phenylphenol in the presence of 0.007 g (0.050 mmol) of DMAP, 0.013 (0.050 mmol) of PPh$_3$, and 0.020 g (0.050 mmol) of Pt(acac)$_2$ at 120 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 5–40% EtOAc in hexanes, furnishing 0.147 g (71% yield) of desired product 5.12d as a pale yellow solid MP = 54–56 °C.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.55 (d, $J = 8.54$ Hz, 4 H), 7.43 (t, $J = 7.50$ Hz, 2 H), 7.37–7.33 (m, 1 H), 7.22 (dd, $J = 8.65$, 0.91 Hz, 2 H), 6.81 (s, 2 H), 5.06 (td, $J = 7.09$, 3.94 Hz, 1 H), 3.90 (s, 6 H), 3.88 (s, 3 H), 2.90 (d, $J = 4.01$ Hz, 1 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 153.2, 149.4, 140.3, 139.1, 138.5, 131.0, 129.0, 128.2, 127.5, 127.2, 122.6 (t, $J = 272.36$ Hz), 122.0, 105.1, 74.6 (t, $J = 31.88$ Hz), 61.0, 56.3

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –81.48 (dd, $J = 141.06$, 6.88 Hz, 1 F), –81.99 (dd, $J = 141.05$, 7.20 Hz, 1 F)

IR (film): 3443, 2939, 2838, 2251, 1903, 1594, 1509, 1486, 1462, 1421, 1325, 1289, 1235, 1184, 1125, 1064, 1008, 909, 842, 807, 758, 730, 698, 651, 551, 531, 500 cm$^{-1}$

HRMS (ESI+): calc. for C$_{23}$H$_{22}$F$_2$O$_5$Na (M+Na) 439.1333, found 439.1344, 2.5 ppm.
2-(2,4-dichlorophenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12e):
Following General Procedure A-1, 0.115 g (0.500 mmol) of compound 5.1 was reacted with 0.245 g (1.50 mmol) of 2,4-dichlorophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.013 g (0.050 mmol) of PPh₃, and 0.020 g (0.050 mmol) of Pt(acac)₂ at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–40% EtOAc in hexanes, furnishing 0.127 g (62% yield) of desired product 5.12e as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 7.42 (d, J = 2.43 Hz, 1 H), 7.28–7.25 (m, 1 H), 7.21 (dd, J = 8.81, 2.42 Hz, 1 H), 6.79 (s, 2 H), 5.09 (t, J = 7.27 Hz, 1 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.89 (bs, 1 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.1, 144.7 (d, J = 1.88 Hz), 138.6, 131.6, 130.3, 130.2, 128.1, 127.8, 123.8 (t, J = 1.84 Hz), 122.6 (t, J = 275.45 Hz), 105.0, 74.4 (t, J = 30.98 Hz), 60.9, 56.2

¹⁹F NMR (376 MHz, CDCl₃): δ −81.59 (dd, J = 138.37, 6.85 Hz, 1 F), −82.67 (dd, J = 138.48, 7.65 Hz, 1 F)

IR (film): 3444, 3081, 2940, 2839, 2251, 1594, 1508, 1475, 1463, 1422, 1384, 1325, 1261, 1235, 1185, 1125, 1096, 1075, 1002, 910, 868, 841, 812, 791, 770, 734, 687, 663, 632, 568, 530 cm⁻¹

HRMS (ESI+): calc. for C₁₇H₁₆Cl₂F₂O₅K (M+K) 446.9980, found 446.9998, 4.0 ppm.
2,2-difluoro-2-(3-iodophenoxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12f):

Following General Procedure A-1, 0.115 g (0.500 mmol) of compound 5.1 was reacted in the dark with 0.330 g (1.50 mmol) of 3-iodophenol in the presence of 0.007 g (0.050 mmol) of DMAP, 0.014 g (0.050 mmol) of PPh₃, and 0.020 g (0.050 mmol) of Pt(acac)₂ at 100 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 10–35% EtOAc in hexanes, furnishing 0.147 g (63% yield) of desired product 5.12f as a pale solid (MP = 123–126 °C).

¹H NMR (400 MHz, CDCl₃): δ 7.56 (dt, J = 7.82, 1.28 Hz, 1 H), 7.51 (t, J = 1.90 Hz, 1 H), 7.13 (ddd, J = 8.34, 2.23, 1.03 Hz, 1 H), 7.06 (t, J = 8.00 Hz, 1 H), 6.77 (s, 2 H), 5.02 (td, J = 7.14, 3.90 Hz, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 2.67 (d, J = 3.26 Hz, 1 H)

¹³C NMR (126 MHz, CDCl₃): δ 153.3, 150.3 (t, J = 2.14 Hz), 135.1, 131.0, 130.9, 130.6, 122.5 (t J = 272.99 Hz), 121.2, 105.0, 93.7, 74.4 (t, J = 31.16 Hz), 61.0, 56.4
\[^{19}\text{F} \text{NMR (376 MHz, CDCl}_3\):} \delta -81.89 (ddd, \ J = 141.02, 7.26, 7.02 \text{ Hz, 2 F})

\text{IR (film):} 3448, 2936, 1580, 1508, 1500, 1466, 1422, 1336, 1326, 1238, 1129, 997, 845, 758, 706 \text{ cm}^{-1}

\text{HRMS (ESI\textendash):} \text{calc. for C}_{17}\text{H}_{17}\text{F}_2\text{I}_5\text{O}_5\text{Cl (M+Cl) 500.9777, found 500.9782, 1.0 ppm.}

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{MeO} \\
\text{MeO} \\
\text{OMe} \\
\text{5.12g}
\end{array}
\]

\textbf{2,2-difluoro-2-(pyridin-2-yloxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12g):}

Following General Procedure A-1, 0.023 g (0.10 mmol) of compound 5.1 was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.003 g (0.020 mmol) of DMAP, 0.006 g (0.020 mmol) of PPh\textsubscript{3}, and 0.007 g (0.020 mmol) of Pt(acac)\textsubscript{2} in 0.40 mL of DCB at 120 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–45% EtOAc in hexanes, furnishing 0.027 g (79% yield) of desired product 5.12g as a red oil.
1H NMR (500 MHz, CDCl₃): δ 7.45 (d, J = 8.92 Hz, 2 H), 7.02 (d, J = 8.90 Hz, 2 H), 6.77 (s, 2 H), 5.02 (td, J = 7.10, 4.13 Hz, 1 H), 3.88 (s, 6 H), 3.87 (s, 3 H), 2.74 (d, J = 3.97 Hz, 1 H)

13C NMR (126 MHz, CDCl₃): δ 153.3, 149.2, 138.9, 132.7, 130.8, 123.6, 122.5 (J = 273.33 Hz), 119.1, 105.2, 74.6 (t, J = 31.42 Hz), 61.0, 56.4

19F NMR (376 MHz, CDCl₃): δ –82.74 (dd, J = 141.16, 7.10 Hz, 1 F), –83.17 (dd, J = 141.09, 7.47 Hz, 1 F)

2-(1,1'-biphenyl)-2-yloxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12h): Following General Procedure A-2, 0.115 g (0.50 mmol) of compound 5.1 was reacted with 0.256 g (1.50 mmol) 2-phenylphenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.010 (0.025 mmol) of DPPE, and 0.019 g (0.050 mmol) of Pt(acac)₂ at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash
chromatography using a gradient of 0–15% EtOAc in hexanes, furnishing 0.116 g (56% yield) of desired compound \textbf{5.12h} as a pale yellow solid (MP = 42 °C).

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}: \(\delta\) 7.42–7.31 (m, 8 H), 7.29 (dd, \(J = 7.31, 1.53\) Hz, 1 H), 6.56 (s, 2 H), 4.82 (td, \(J = 7.11, 4.18\) Hz, 1 H), 3.85 (s, 3 H), 3.78 (s, 6 H), 2.32 (d, \(J = 4.17\) Hz, 1 H)

\textbf{\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3})}: \(\delta\) 153.0, 147.0, 138.3, 137.8, 135.2, 131.3, 130.8, 129.3, 129.1, 128.5, 128.3, 128.1, 127.4, 125.9, 125.4, 122.6 (t, \(J = 273.57\) Hz), 121.9, 104.9, 74.5 (t, \(J = 31.33\) Hz), 60.9, 56.1

\textbf{\textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3})}: \(\delta\) –80.71 (dd, \(J = 139.63, 7.17\) Hz, 1 F), –81.67 (dd, \(J = 139.53, 7.09\) Hz, 1 F)

\textbf{IR (film)}: 3454, 3059, 2940, 2838, 1595, 1506, 1479, 1463, 1422, 1325, 1264, 1236, 1189, 1127, 1070, 1009, 910, 838, 774, 736, 700, 661, 613, 566, 530, 474 cm\textsuperscript{-1}

\textbf{HRMS (ESI\textsuperscript{+})}: calc. for C\textsubscript{23}H\textsubscript{22}F\textsubscript{2}O\textsubscript{5}K (M+K) 455.1072, found 455.1076, 0.9 ppm.
**2,2-difluoro-2-(2-isopropylphenoxy)-1-(3,4,5-trimethoxyphenyl)ethan-1-ol (5.12i):**

Following General Procedure A-2, 0.115 g (0.50 mmol) of compound 5.1 was reacted with 0.21 mL (1.50 mmol) 2-isopropylphenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.010 (0.025 mmol) of DPPE, and 0.019 g (0.050 mmol) of Pt(acac)$_2$ at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–15% EtOAc in hexanes, furnishing 0.085 g (44% yield) of desired compound 5.12i as a black semisolid.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.24 (dt, $J = 7.74$, 2.51 Hz, 2 H), 7.15 (ddd, $J = 8.03$, 5.34, 2.08 Hz, 2 H), 6.81 (s, 2 H), 5.09 (dt, $J = 8.66$, 4.45 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 2.82 (p, $J = 6.92$ Hz, 1 H), 2.74 (d, $J = 3.95$ Hz, 1 H), 1.03 (dd, $J = 6.92$, 1.01 Hz, 6 H)

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 153.3, 147.1 (d, $J = 2.01$ Hz), 141.5, 138.6, 131.2 (d, $J = 1.87$ Hz), 126.7, 126.6, 126.2, 122.7 (dd, $J = 271.38$, 2.53 Hz), 121.8, 105.1, 74.9 (dd, $J = 32.84$, 30.16 Hz), 61.0, 56.3, 26.4, 23.1 (d, $J = 16.51$ Hz)
\[^{19}\text{F NMR (376 MHz, CDCl}_3\text{)}: \delta -79.34 (dd, J = 140.88, 4.75 Hz, 1 F), -83.16 (dd, J = 140.73, 8.56 Hz, 1 F)\]

IR (film): 3452, 2964, 2840, 1595, 1508, 1488, 1461, 1422, 1385, 1363, 1325, 1275, 1250, 1234, 1179, 1126, 1084, 1060, 1033, 1004, 910, 836, 812, 785, 754, 732, 698, 661, 573, 530, 473 cm\(^{-1}\)

HRMS (ESI–): calc. for C\(_{20}\)H\(_{24}\)F\(_2\)O\(_5\)Cl (M+Cl) 417.1280, found 417.1280, 0.0 ppm.

2-(4-(2-bromoethyl)phenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-ol

(5.12j): Following General Procedure A-1, 0.115 g (0.50 mmol) of compound 5.1 was reacted with 0.302 g (1.50 mmol) 4-(2-bromoethyl)phenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.013 (0.050 mmol) of PPh\(_3\), and 0.019 g (0.050 mmol) of Pt(acac)\(_2\) at 130 °C for 24 h. After workup with 1 N NaOH (aq.), the product was purified
by flash chromatography using a gradient of 0–15% EtOAc in hexanes, furnishing 0.103 g (46% yield) of desired compound 5.12j as a red oil.

**1H NMR (400 MHz, CDCl₃):** δ 7.16 (d, J = 8.56 Hz, 2 H), 7.08 (d, J = 8.21 Hz, 2 H), 6.77 (s, 2 H), 5.02 (td, J = 7.24, 3.11 Hz, 1 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.54 (t, J = 7.49 Hz, 2 H), 3.12 (t, J = 7.47 Hz, 2 H)

**13C NMR (126 MHz, CDCl₃):** δ 153.2, 148.9 (t, J = 2.37 Hz), 138.5 (d, J = 1.63 Hz), 136.6, 130.9, 129.8, 122.5 (t, J = 271.38 Hz), 121.9, 105.0, 74.4 (t, J = 31.77 Hz), 61.0, 56.3, 38.7, 32.9

**19F NMR (376 MHz, CDCl₃):** δ –81.56 (dd, J = 141.41, 7.45 Hz, 1 F), –81.99 (dd, J = 141.40, 7.81 Hz, 1 F)

**IR (film):** 3446, 2939, 2839, 2250, 1758, 1593, 1507, 1462, 1421, 1325, 1235, 1200, 1125, 1064, 1019, 1002, 910, 831, 809, 764, 751, 731, 697, 646, 551, 531 cm⁻¹

**HRMS (ESI–):** calc. for C₁₉H₂₁BrF₂O₅Cl (M+Cl) 481.0229, found 481.0247, 3.7 ppm.

**General Procedure for the Cu-Catalyzed Selective Unsymmetric Dioxygenation of Difluoroalkenes with Phenols (B):**

An oven-dried one-dram vial, equipped with a magnetic stirbar, was charged with difluoroalkene (0.10 mmol), phenol (0.30 mmol), terpyridine (0.02 mmol), CuCl₂ (0.02
mmol). The system was purged with O₂ gas for 1 min before anhydrous DCB (2.0 mL) was added to the system under a balloon of O₂ gas. The system was sealed with a PTFE-lined screw-top cap and stirred for 1 min at R.T. Subsequently, the vial was placed into a pre-heated reaction block and stirred vigorously at 100 °C for 24 h. The vial was cooled to R.T., and 10 µL (0.080 mmol) of TFT was added via microsyringe. The solution was diluted with approximately 1 mL of DCM and then stirred at R.T. for 10 min to allow adequate mixing. After mixing, an aliquot was removed from the vial and analyzed by ¹⁹F NMR for completion and selectivity.
Experimental Procedures for Table 5-3:

Following General Procedure B, 0.023 g (0.10 mmol) of 5.1 was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.050 mmol of acid and 0.012 g (0.010 mmol) of Pt(PPh3)4 in 0.40 mL of DCB at 100 °C for 18 h. The reactions were cooled to R.T., and 10 µL (0.080 mmol) of TFT were added. The reactions were diluted with 2.0 mL of DCM, and allowed to stir for 5 min. An aliquot was removed and passed through a silica gel plug to remove the Pt, and then analyzed by 19F NMR for completion, yield, and selectivity.

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Experimental Procedures for Table 5-4:

Following General Procedure B, 0.025 g (0.10 mmol) of 5.8c was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.020 mmol of ligand and 0.004 g (0.010 mmol) of Pt(acac)$_2$ in 0.40 mL of DCB at 140 °C for 18 h, with or without 0.003 g (0.020 mmol) of CuCl$_2$. The reactions were cooled to R.T., and 10 µL (0.080 mmol) of
TFT were added. The reactions were diluted with 2.0 mL of DCM, and allowed to stir for 5 min. An aliquot was removed and passed through a silica gel plug to remove the Pt, and then analyzed by $^{19}$F NMR for completion, yield, and selectivity.

**Experimental Procedures for Table 5-5:**

![Chemical structures](image)

**Table 5-5:**

<table>
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<th>Conv.</th>
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<th>$5.10c$</th>
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<td>DCB</td>
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<td>DCB</td>
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<td>79</td>
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<td>Phenanthroline</td>
<td>DCB</td>
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<td>60</td>
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<td>Bathophenanthroline</td>
<td>DCB</td>
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</table>
Following General Procedure B, 0.025 g (0.10 mmol) of 5.8c was reacted with 0.052 g (0.30 mmol) of 4-bromophenol in the presence of 0.020 mmol of ligand and 0.020 mmol of copper salts in 0.40 mL of solvent at 120 °C for 18 h. The reactions were cooled to R.T., and 10 µL (0.080 mmol) of TFT were added. The reactions were diluted with 2.0 mL of DCM, and allowed to stir for 5 min. An aliquot was removed and passed through a silica gel plug to remove the Pt, and then analyzed by $^{19}$F NMR for completion, yield, and selectivity.

**Characterization of Compounds in Table 5-3, 5-4, and 5-5:**

![Chemical Structure](image)

2-(4-bromophenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-one (5.4):

$^{1}H$ NMR (500 MHz, CDCl$_3$): $\delta$ 7.47 (s, 2 H), 7.24–7.20 (m, 4 H), 3.98 (s, 3 H), 3.93 (s, 6 H)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –73.86 (s, 2 F)
2-(4-bromophenoxy)-1-(dibenzo[b,d]thiophen-4-yl)-2,2-difluoroethan-1-one (5.10c):

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.51 (dd, $J = 7.74$, 1.05 Hz, 1 H), 8.50–8.48 (m, 1 H), 8.25–8.23 (m, 1 H), 7.99–7.97 (m, 1 H), 7.67 (t, $J = 7.76$ Hz, 1 H), 7.58–7.50 (m, 4 H), 7.21 (d, $J = 8.97$ Hz, 2 H)

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –73.26 (s, 2 F)