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

By

Douglas Leo Orsi

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Chair: Ryan A. Altman

Paul R. Hanson

Michael D. Clift

Michael Rafferty

Mark P. Farrell

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The dissertation committee for Douglas Leo Orsi certifies that this is the approved version of the following dissertation:

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Chairperson: Ryan A. Altman

Date Approved: 16 May 2019

Abstract

Douglas L. Orsi

Department of Medicinal Chemistry, May 2019

The University of Kansas

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 β,β-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 O_2 to provide β-phenoxy-β,β-difluorobenzyl alcohols. This reaction proceeds by an unusual radical reaction pathway in which superoxide oxidizes phenol to phenoxyl 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_2O: di-*tert*-butyl decarbonate

^{n}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_3N: Triethylamine

EtOAc: Ethyl Acetate

Et_2O: 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_2CO_3: Potassium carbonate

KHMDS: Potassium Hexamethyldisilazide

$KMnO_4$: Potassium permanganate

K_3PO_4: Potassium phosphate, tribasic

LAH: Lithium aluminum hydride

MeCN: Acetonitrile

MeOH: Methanol

$MgSO_4$: Magnesium Sulfate

MHz: Megahertz

mmu: milli mass unit

m.p.: Melting point

MsOH: Methanesulfonate

mT: Millitesla

$NaBH_4$: Sodium borohydride

Na_2CO_3: Sodium Carbonate

NaOH: Sodium Hydroxide

Na_2SO_4: Sodium sulfate

$Na_2S_2O_5$: Sodium metabisulfite

$Na_2S_2O_8$: Sodium persulfate

NaH: Sodium Hydride

NH_4Cl: Ammonium Chloride

NMO: 4-methylmorpholine N-oxide

NMP: N-Methylpyrrolidone

NMR: Nuclear Magnetic Resonance

Nu^-: Nucleophile

Oct.: Octane

Ox. Addn.: Oxidative Addition

PCy_3: Tricyclohexylphosphine

PD: Pharmacodynamics

Pdt: Product

P_2Et: Tetramethyl(tris(dimethylamino)phosphoranylidene)phosphorictriamid-Et-imin

PGP: P-Glycoprotein

PhMe: Toluene

$PhNO_2$: Nitrobenzene

PK: Pharmacokinetics

PLP: Pyridoxal Phosphate

PMB: *Para*-methoxybenzyl

$POCl_3$: Phosphorus(V) oxychloride

PPh_3: Triphenylphosphine

ppm: Parts per million

PTFE: Polytetrafluoroethylene

PTSA-H_2O: *Para*-toluene sulfonic acid monohydrate

2-Pym: 2-Pyrimidine

Red. Elim.: Reductive Elimination

R.T.: Room Temperature

SDS: sodium dodecyl sulfate

$SOCl_2$: 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_2O: Trifluoromethylsulfonic anhydride

TFA: Trifluoroacetic acid

TFT: α,α,α-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.

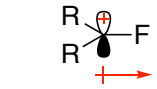
These fluorine-induced perturbations arise due to the unique biophysical properties of fluorine. Electronically, fluorine is the most electronegative element, significantly more so than the other halogens or similarly sized atoms (**Figure 1-1a**),[1a] allowing fluorine to easily adopt or stabilize a 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

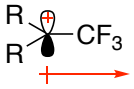
X	Electronegativity	Polarizability Å^3	Ionization Potential (kcal/mol)
H	2.2	0.667	314
F	4.0	0.557	402
Cl	3.2	2.18	299
Br	3.0	3.04	272
I	2.7	4.7	241
C	2.5	0.82	240
N	3.0	1.10	335
O	3.5	1.76	314

b) Effects of Fluorination on Reactive Intermediates

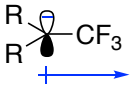


σ-Induction Destabilizes
Electron-Deficient Carbocation

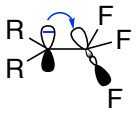
σ-Induction Stabilizes
Electron-Rich Carbanion



σ-Induction Destabilizes
Electron-Deficient Carbocation



σ-Induction Stabilizes
Electron-Rich Carbanion

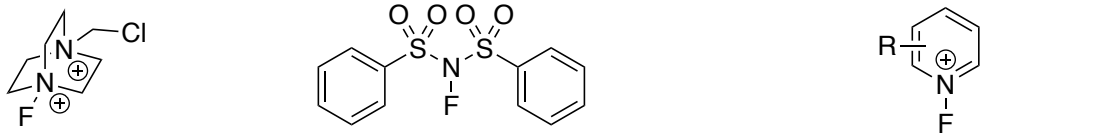


Hyperconjugation Stabilizes
Electron-Rich Carbanion

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

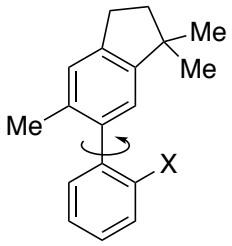
Fluorination of bioactive compounds affects a molecule's pharmacodynamic (PD), pharmacokinetic (PK), distribution, and metabolic profiles both *in vitro* and *in vivo*.[1a-h] Thus, many fluorinated bioisosteres exist to replace a wide variety of functional groups, providing a diverse toolkit of fluorinated functionalities to predictably modulate biophysical

properties.[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).[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.[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 *t*Bu group than a methyl group (**Figure 1-3**).

Figure 1-3: Steric Parameters of Fluorine

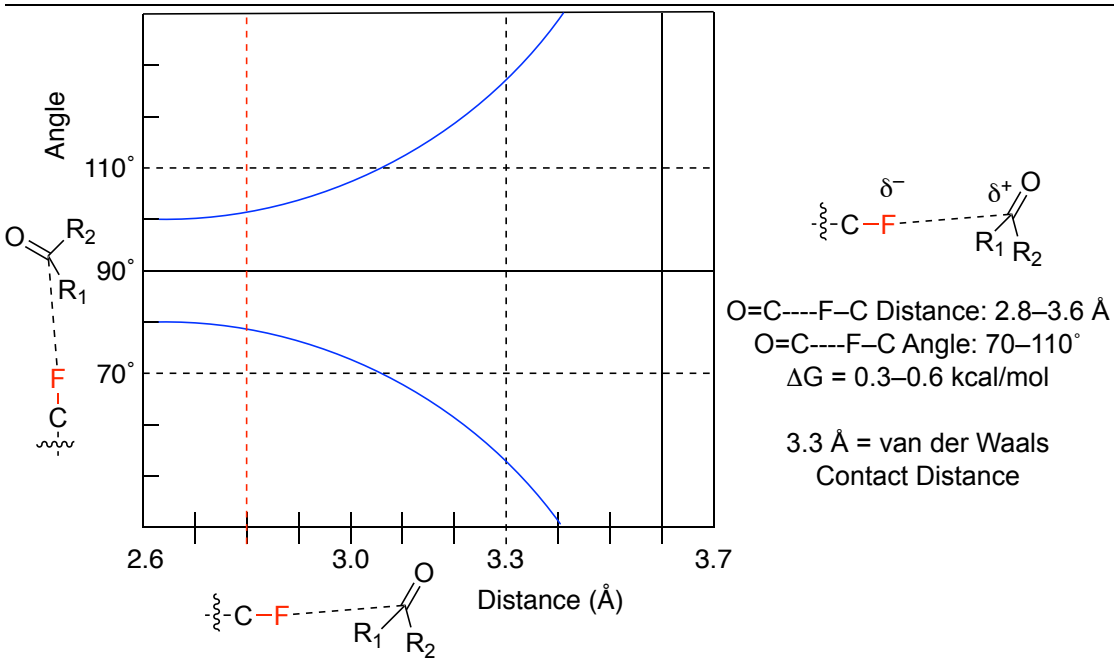


X	Atomic Radius Å	Taft E°_s	Axial Rotation Barrier ΔG (kcal/mol)	C–X Bond Length Å
H	1.20	0	10.6	1.09
F	1.47	–0.46	14.2	1.47
C	1.70	–	–	1.54
N	1.55		–	1.55
O	1.52	–0.55	–	1.52
Me	–	–1.24	19.3	–
CF_3	–	–2.40	22.2	–
^{i}Pr	–	–1.76	22.2	–
^{t}Bu	–	–2.78	–	–

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.[6] 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**).[6b, 7] 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_{α} 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[7c]

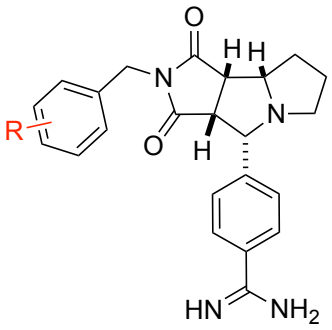


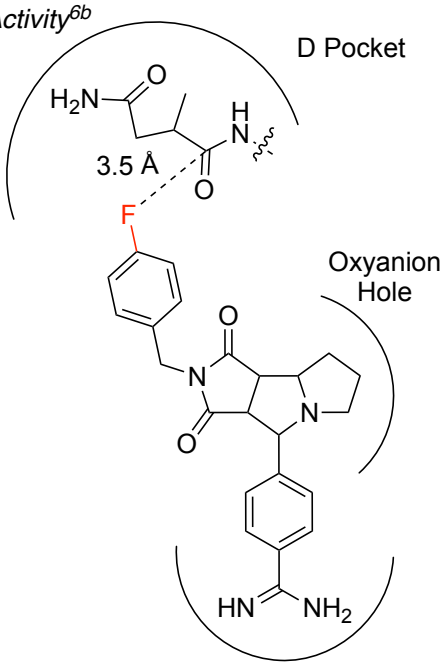
According to a matched molecular pair analysis conducted by Pfizer,[7c] multipolar interactions of fluorine with carbonyl carbons occur when separated by 2.8–3.6 Å. Closer than 2.8 Å steric repulsion dominates, while beyond 3.3 Å (the van der Waals contact distance), the strength of the interaction falls rapidly. Further, the C–F bond must be oriented within 70–110˚ of the carbonyl carbon (**Figure 1-4**).[7c] 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.[7c] Computational predictions of when a fluorine multipolar interaction might occur are improving, enabling the purposeful incorporation of multipolar interactions.[7e]

Multipolar interactions help explain the increased potency of a 4-fluorinated aryl ring in a series of thrombin inhibitors (**Figure 1-5a**).[6b] Multipolar interactions also help explain the increased potency of Lipitor relative to non-fluorinated analogs,[6a] and more recently were observed in an HIV-1 gp120 inhibitor (PDB: 4DKO, **Figure 1-5b**)[8] and a Procaspase-6 inhibitor (PDB: 4NBL; **Figure 1-5c**).[9]

Figure 1-5: Beneficial Multipolar Interactions in Medicinal Chemistry

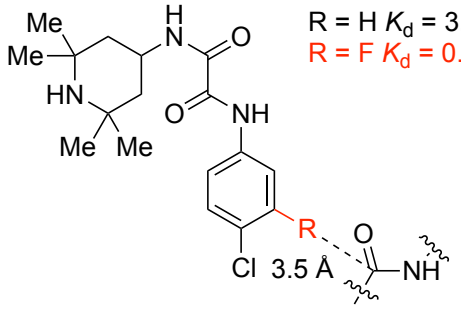
a) Multipolar Interactions Improve Thrombin Inhibitor Activity[6b]



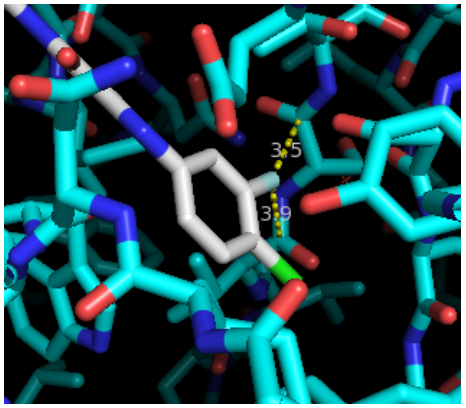


R	Thrombin K_i [μM]	Selectivity
–	0.31	15
2-F	0.50	10
3-F	0.36	26
4-F	**0.057**	**67**
2,6-F_2	0.61	9
3,5-F_2	0.59	25
1,2,3,4,5-F_5	0.27	44

b) Multipolar Interactions in an HIV-1 gp120 inhibitor[8]

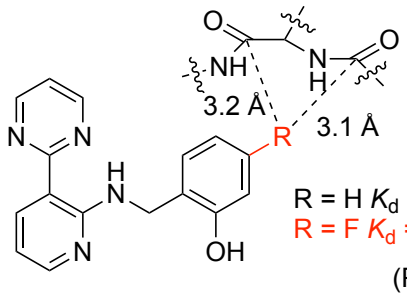


R = H K_d = 3.7 μM
R = F K_d = 0.76 μM



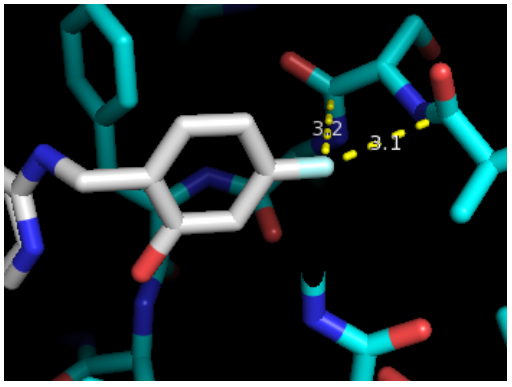
(PDB: 4DKO)

c) Multipolar Interactions in a Procaspase-6 Inhibitor[9]



R = H K_d = 2.9 μM
R = F K_d = 0.47 μM

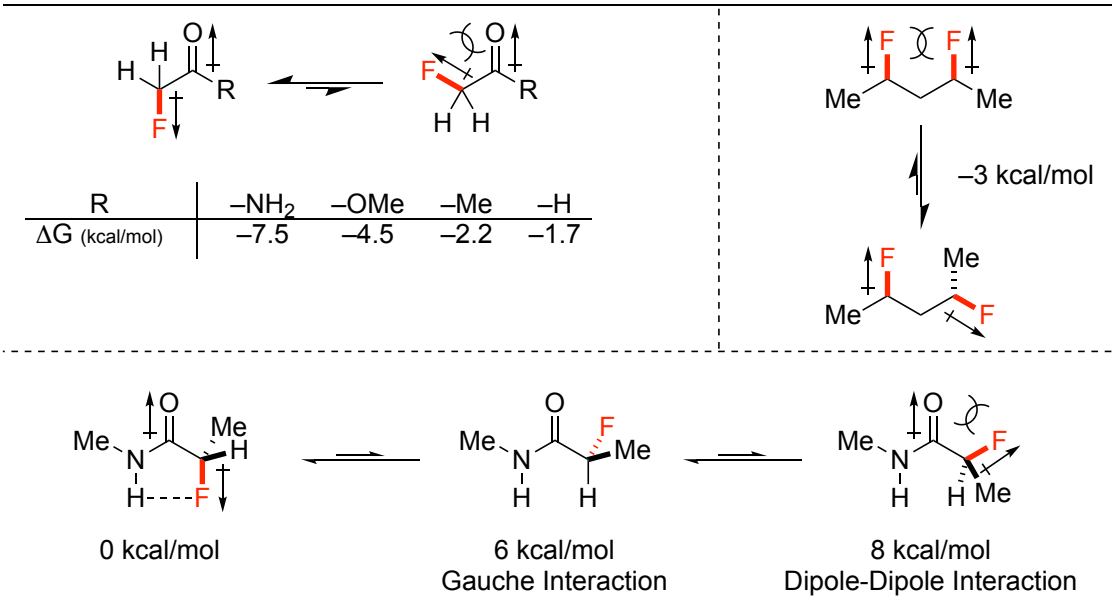
(PDB 4NBL)



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 α-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]

Figure 1-6: Dipole-Dipole Interactions of Fluorine Enforce Anti-Alignment of Dipoles[11]

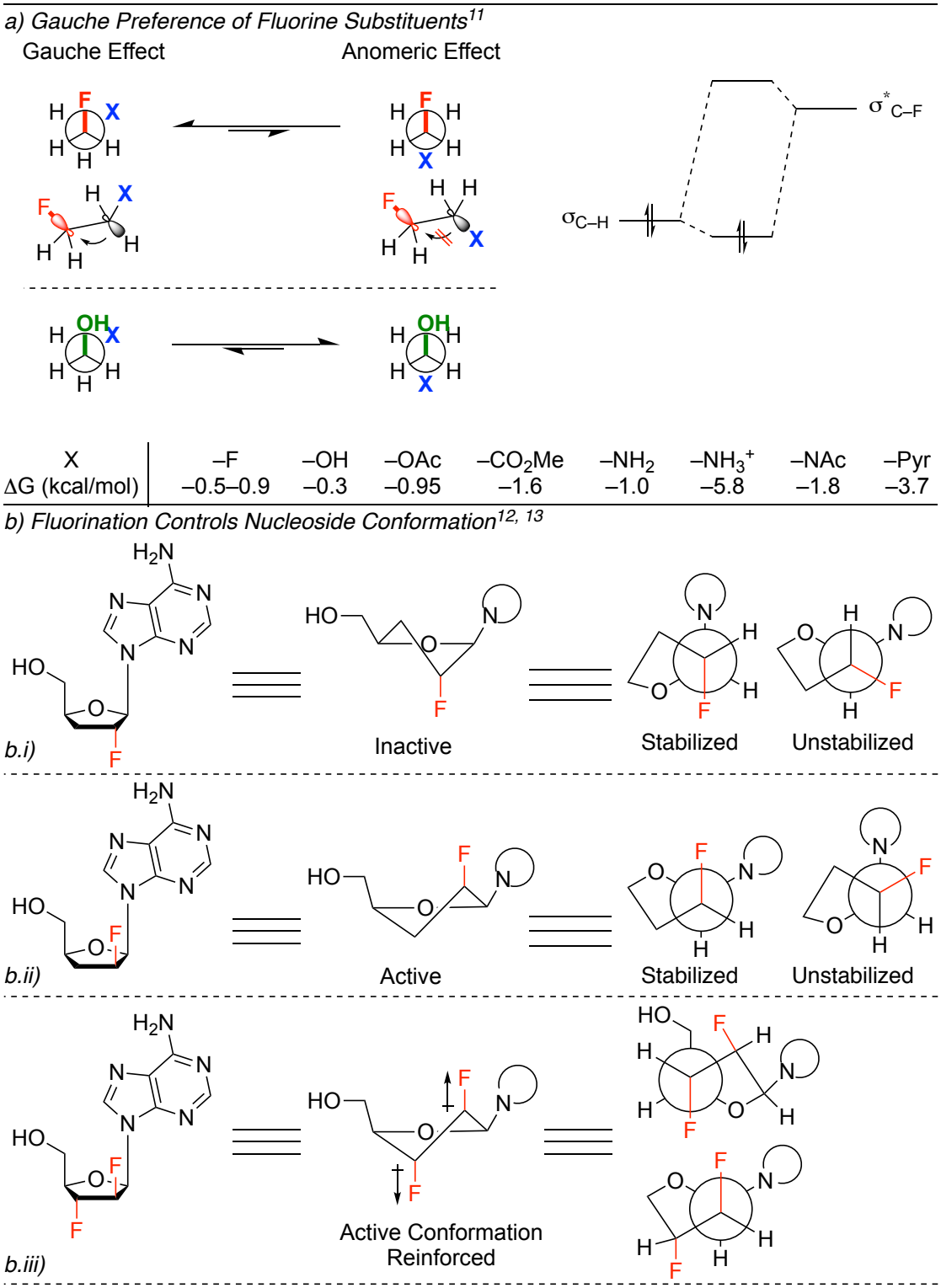


In addition to dipole alignment, fluorine can also control conformation by other means. In non-fluorinated alkanes, the large substituents prefer an anti-alignment to one another. This alignment keeps the larger substituents as far apart as possible to minimize unfavorable steric overlaps. Alternately, 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 σ* orbital of the other substituent. The anomeric effect requires an anti-orientation for proper orbital overlap.[11a]

In contrast, fluorine prefers gauche orientations with non-hydrogen substituents, especially heteroatoms. This gauche preference arises as the low-lying σ* C–F orbital is stabilized by hyperconjugation with C–H σ-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

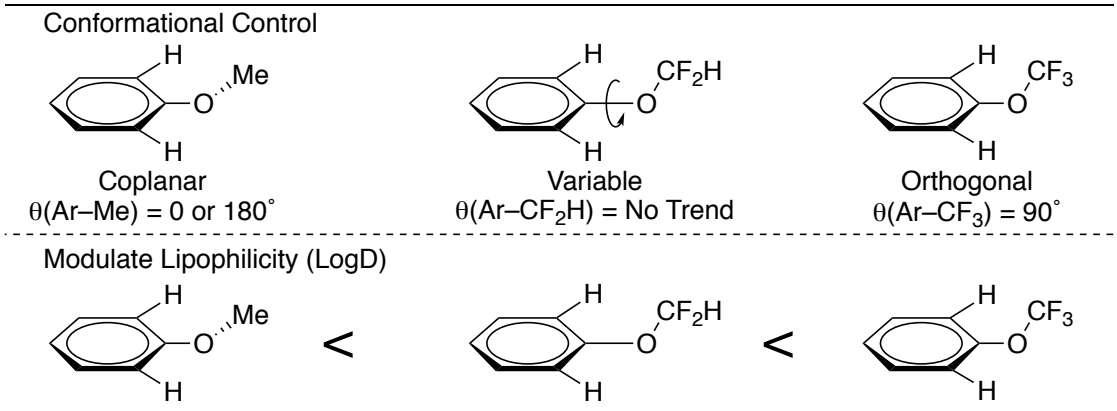
substituent. As such, when positioned vicinal to an ammonium group the gauche preference increases to –5.8 kcal/mol (**Figure 1-7a**). Further, the gauche effect is additive, thus the more substituents fluorine can orient gauche to the stronger the effect.[11] The gauche preference of fluorine helps stabilize the active conformation of nucleoside HIV viral replication inhibitors (**Figure 1-7b**).[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[12a, 12b] or by analysis of 1- and 2-D NMR spectra.[11a, 12c, 13] In a monofluorinated system, the gauche preference of fluorine drives conformational rigidity. In the inactive conformer, an α-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**).[13] In the active conformer, the α-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.[13] However, a β-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 β-2', α-3' difluorinated nucleoside possesses two stabilizing gauche interactions through the β-2' fluorine, a stabilizing anti-alignment of the fluorine dipoles of the β-2' and α-3' fluorine, and an additional stabilizing gauche orientation between the α-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



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 π-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 σ*.[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 π-system, instead interacting with the C–F σ*, 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]

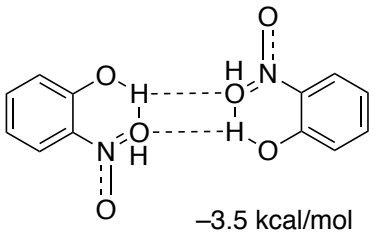


One specific fluorinated substructure, the difluoromethyl group, acts as an H-bond donor. Specifically, the σ-withdrawing effects of fluorine weakens the C–H bond, making the C–H bond act like a heteroatom–H bond. Thus, difluoromethyl groups are lipophilic H-bond donors, improving permeability and PGP efflux activity.[16] In analogous systems,

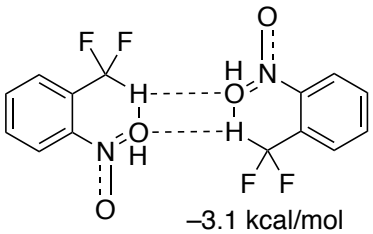
the difluoromethyl group formed H-bonds with nearly the same strength as H-bond to a hydroxyl group (–3.1 vs –3.5 kcal/mol),[16] and a recently developed HCV NS3 protease inhibitor exploits a difluoromethyl group to strengthen binding to the protease (**Figure 1-9**).[17]

Figure 1-9: CF_2H Donates Lipophilic H-Bonds

a) CF_2H H-Bond Strength[16]

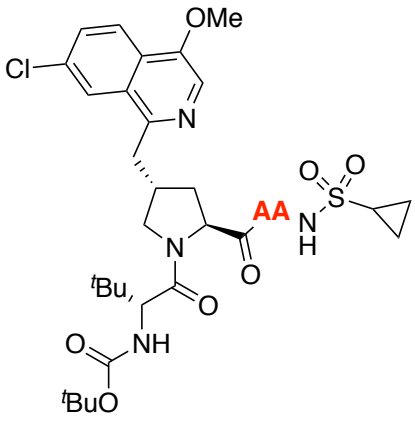


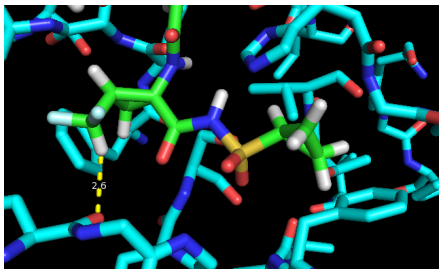
–3.5 kcal/mol



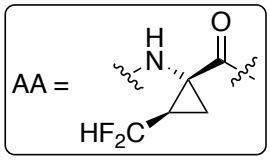
–3.1 kcal/mol

b) CF_2H as an H-Bond Donor in an HCV NS3 Protease Inhibitor[17]

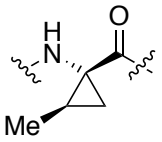
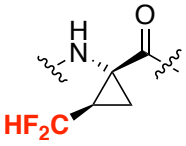
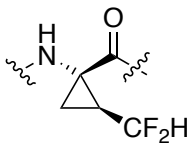
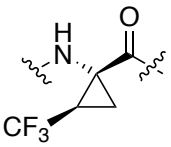
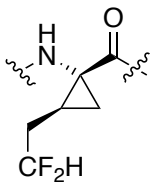




PDB: 6BQK



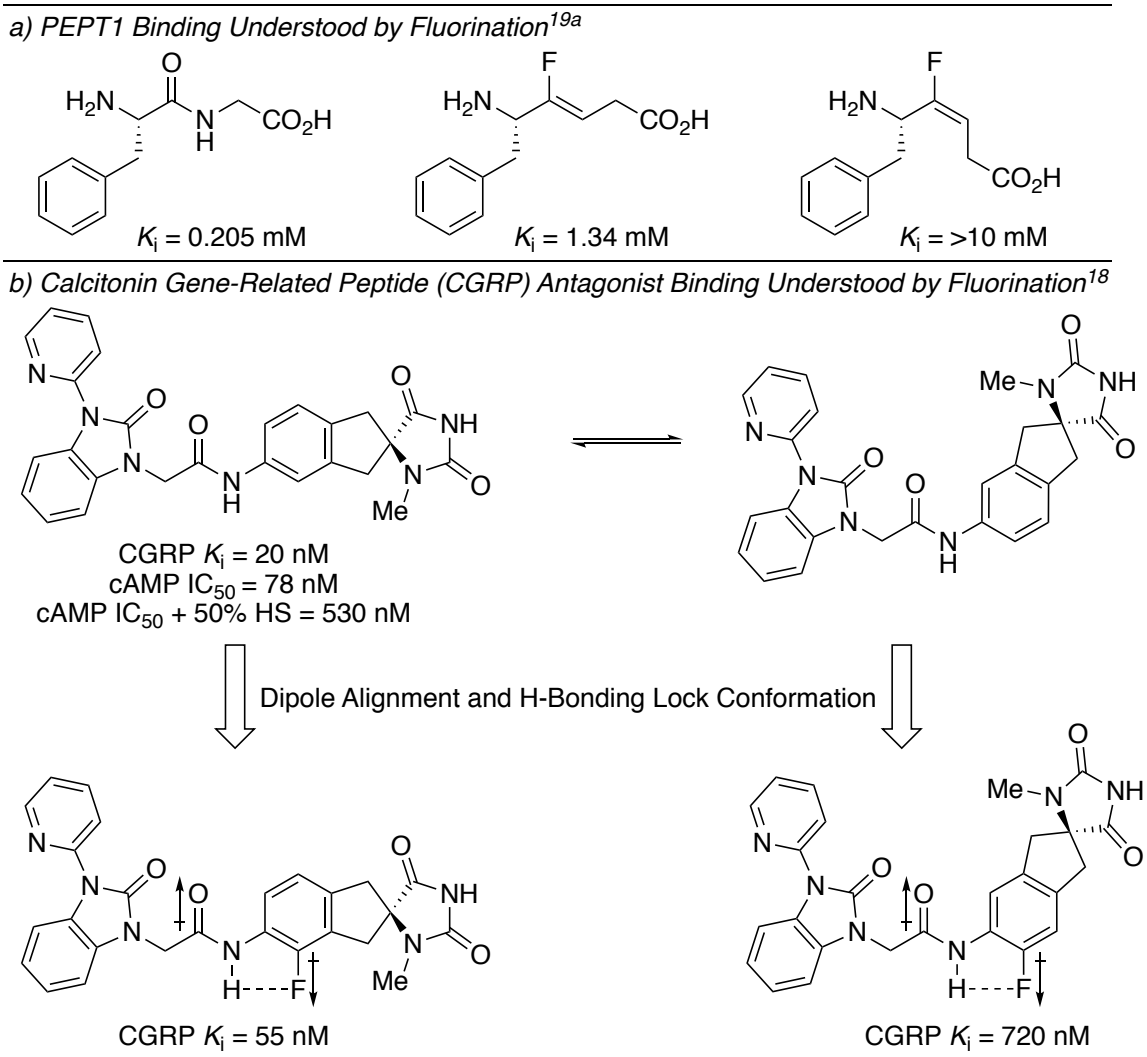
HCV NS3 Protease Inhibition GT-1b Replicon

AA	IC_{50} (nM)	EC_{50} (nM)
	13	64
	1	7.6
	12	58.9
	17	125
	14	31

The conformational effects of fluorine enable the investigation of the active conformers of bioactive compounds.[18] 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.[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.[19a] In another example, intramolecular H-bonding of fluorine has been exploited to enforce γ-turns structures in investigational therapeutics.[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**).[18]

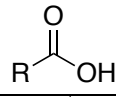
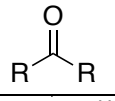
Figure 1-10: Determination of Active Conformer Through Fluorination



Fluorination also alters pK_a and hydrogen bonding, as fluorine affects the polarization and ionization of functional groups, disrupting solvation networks and partitioning characteristics.[1a] 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]

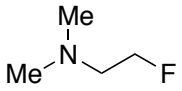
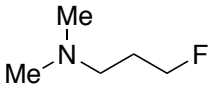
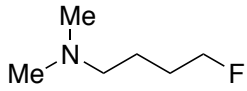
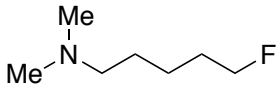
		R–OH						$R–NH_2$		
R	pK_a	R	pK_a	α_2^H	β_2^H	R	β_2^H	R	pK_a	β_2^H
$–CH_3$	4.76	$–CH_2CH_3$	15.9	0.33	0.44	$–CH_3$	0.48	$–CH_2CH_3$	10.7	0.70
$–CH_2F$	2.6	$–CH_2CF_3$	12.4	0.57	0.18	$–CF_3$	0.24	$–CH_2CF_3$	5.9	0.36
$–CF_2H$	1.3	$–C(CH_3)_3$	19.0	0.32	0.49			$–C_6H_5$	4.3	0.38
$–CF_3$	0.5	$–C(CF_3)_3$	5.4	0.86	–			$–C_6F_5$	0.36	–
$–C_6H_5$	4.21	$–C_6H_5$	10.0	0.60	0.22					
$–C_6F_5$	1.75	$–C_6F_5$	5.5	0.76	0.02					

α_2^H = H-Bond Donating Ability; β_2^H = H-Bond Accepting Ability

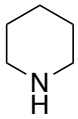
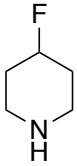
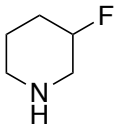
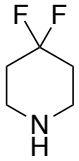
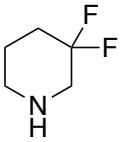
The perturbations in acidity due to fluorine can control the tissue selectivity of bioactive compounds by selectively modulating the binding interactions with molecular targets through tissue pH. For example, the opioid fentanyl is constitutively active throughout the body. μ-Opioid receptor activation 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 μ-opioid receptors in non-acidic tissues. Damaged tissue is acidic, thus the fluorinated Fentanyl derivative activates the μ-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: pK_a Modulation of Amines *via* Fluorination

a) Fluorination Affect on pK_a Decreases as Distance Increases[21b,c]

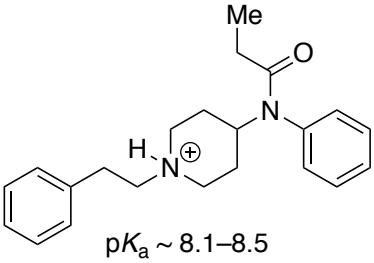
Amine				
ΔpK_a	–1.7	–0.7	–0.3	–0.1

b) Predictable Affect of Fluorination Affect on amine pK_a[21a]

Amine					
ΔpK_a Predicted	0	–1.4	–2.0	–2.8	–4.0
ΔpK_a Observed	0	–1.7	–1.8	–2.6	–3.7

c) Fluorination Controls Fentanyl pK_a and Tissue Selective Activity[22]

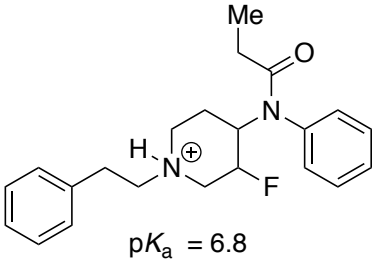
Fentanyl: Constituatively Active



pK_a ~ 8.1–8.5

Tissue pH	Ki, μOR [nm]
5.5	0.9 +/- 0.3
6.5	1.4 +/- 0.2
7.4	1.1 +/- 0.2

Fentanyl: Active in Acidic (Injured) Tissue



pK_a = 6.8

Tissue pH	Ki, μOR [nm]
5.5	7.3 +/- 2.6
6.5	3.7 +/- 0.7
7.4	17.9 +/- 4.8

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**).[1a] 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 increases less, 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[1a]

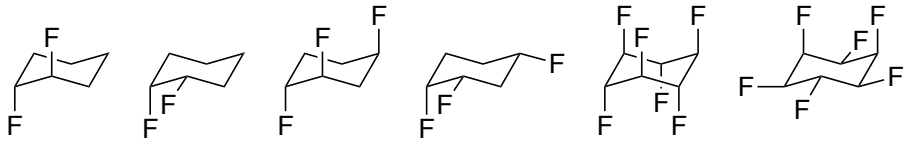
Parent Compound	LogP	Fluorinated Compound	LogP	ΔLogP
CH_3–CH_3	1.81	CH_3–CHF_2	0.75	–1.06
CH_3CH_2OH	0.32	CF_3CH_2OH	0.36	+0.04
$CH_3(CH_2)_2OH$	0.34	$CF_3(CH_2)_2OH$	0.39	+0.05
$CH_3(CH_2)_5OH$	1.64	$CF_3(CH_2)_5OH$	1.36	–0.28

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**).[23] 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.[23] For an all-cis tetrafluorinated cyclohexane, the logP decreases by 2.41 log units relative to the non-fluorinated cyclohexane (**Figure 1-14b**).[23a] Recently, the Müller group recently systematically explored the effect of many fluorination patterns on polarity, logP, solubility, and metabolism.[15b, 24] 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**).[23]

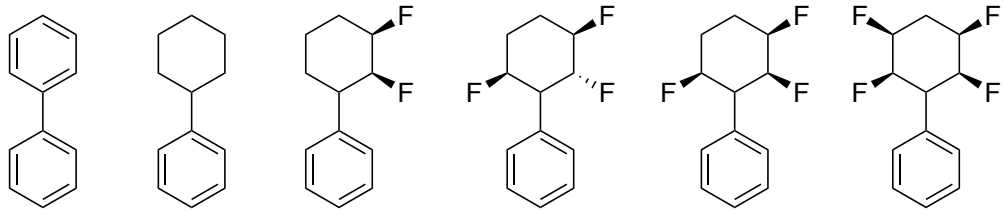
Figure 1-14: Fluorination Patterning Increases the Effect of Fluorination on Biological Properties

a) Fluorination Patterning of Cyclohexane Rings Controls Polarity[23b]



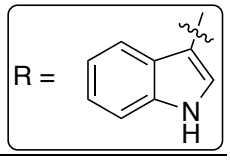
Dipole Moment (Debye):	0.80	3.39	1.93	3.57	0.00	4.72

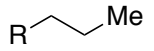
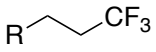
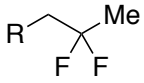
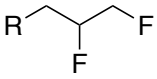
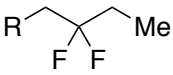
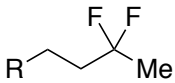
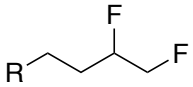
b) Fluorination Patterning of Cyclohexane Rings Lowers LogP[23a]

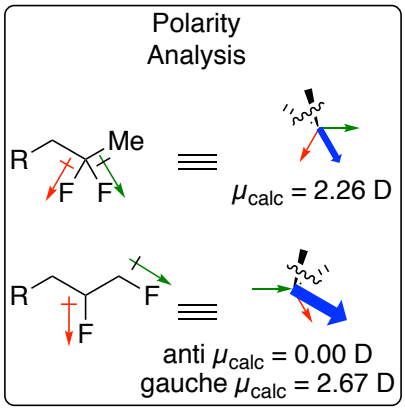


LogP:	3.76	4.99	3.30	2.79	2.64	2.58

c) Fluorination Patterning Perturbs PK Properties[24]

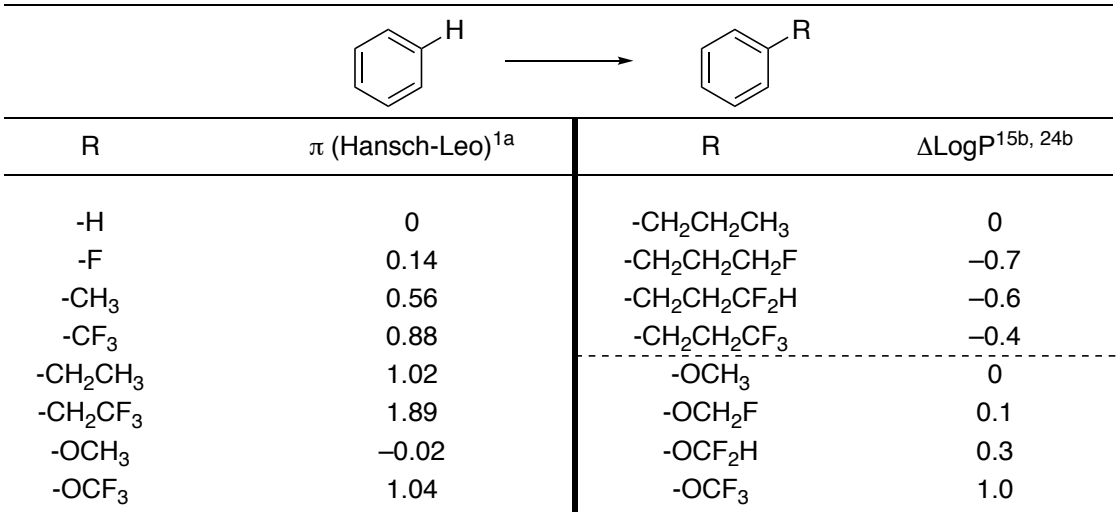


Alkyl Fluoride	LogP	Solubility μmol/L	Clearance μg/L
	3.3	200	513
	3.1	30	30
	2.8	820	508
	2.5	>1700	212
	3.1	182	644
	3.0	115	321
	2.8	277	245



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 π-system, resulting in a small increase in logP for each fluorine substituent.[1a] Such an effect is maintained for perfluoroalkyl groups. Partially fluorinated aryl substituents, such as difluoromethylene groups, reduce logP through the previously discussed polarity vector addition (**Figure 1-15**).[14b, 23] The effect is especially pronounced for fluorinated alkyl chains with vicinal rather than germinal fluorination.[15b, 24]

Figure 1-15: Effect of Aromatic Fluorination on Lipophilicity



R	π (Hansch-Leo)[1a]	R	ΔLogP[15b, 24b]
-H	0	$-CH_2CH_2CH_3$	0
-F	0.14	$-CH_2CH_2CH_2F$	–0.7
$-CH_3$	0.56	$-CH_2CH_2CF_2H$	–0.6
$-CF_3$	0.88	$-CH_2CH_2CF_3$	–0.4
$-CH_2CH_3$	1.02	$-OCH_3$	0
$-CH_2CF_3$	1.89	$-OCH_2F$	0.1
$-OCH_3$	–0.02	$-OCF_2H$	0.3
$-OCF_3$	1.04	$-OCF_3$	1.0

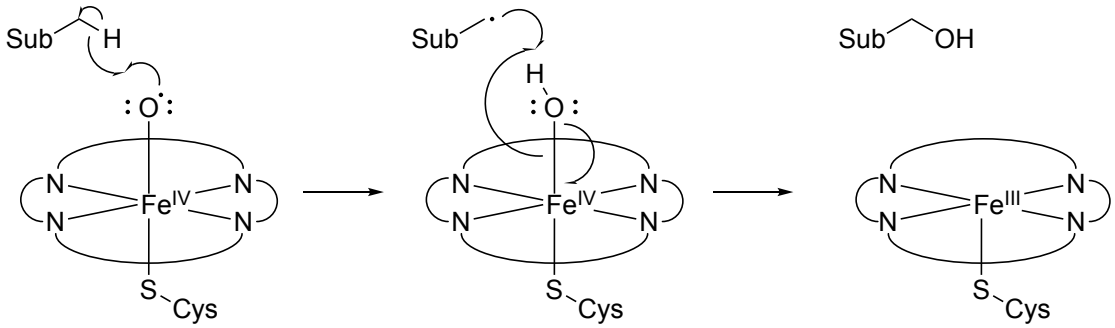
Mostly, fluorine is used to block metabolism, or shift the site of metabolism. Multiple effects, including the strength of C–F bonds relative to C–H bonds, and the electronic character of fluorine, drive these shifts in metabolism. First, at aliphatic metabolic sites, fluorination precludes metabolism 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.

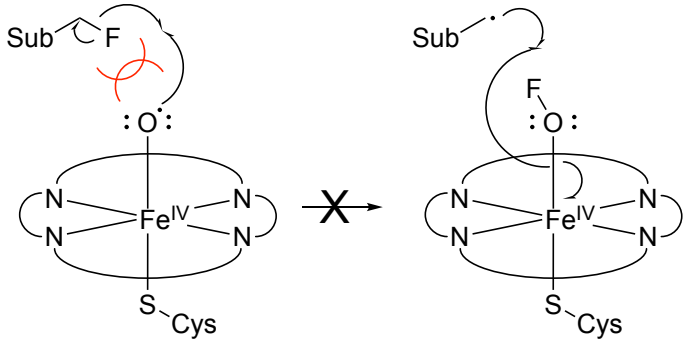
When F replaces H, several changes prevent the oxidative cleavage of the C–F bond. First, the C–F bond is generally 5–8 kcal/mol stronger than the analogous C–H bond, making homolytic bond cleavage more difficult.[2] Second, the C–F bond possesses partial negative charge on the fluorine atom, which repels the electron rich oxygen of the iron-oxo species and raises the transition state energy of CYP_{450} 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 Bosentan[25] and Begacestat[26] (**Figure 1-16c**, **Figure 1-17**).

Figure 1-16: Fluorination Prevents CYP_{450} Mediated Oxidation

a) Oxidative Metabolism of C–H Bond by CYP_{450}

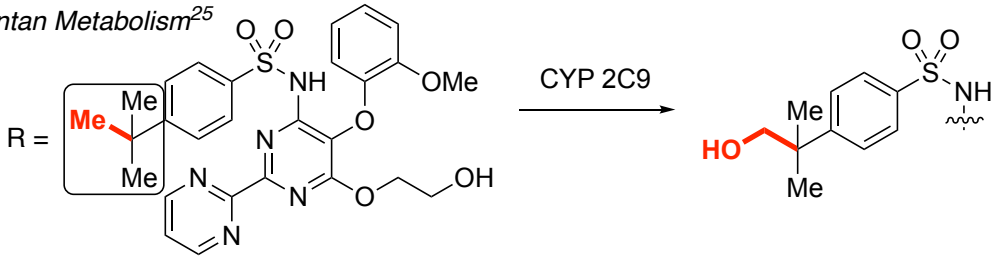


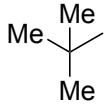
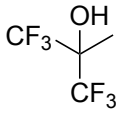
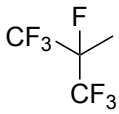
b) Oxidative Metabolism of Analogous C–F Bond by CYP_{450}



Bond Strength[2] (kcal/mol)	
C–H	104
C–F	110
C–O	90
O–H	102
O–F	53

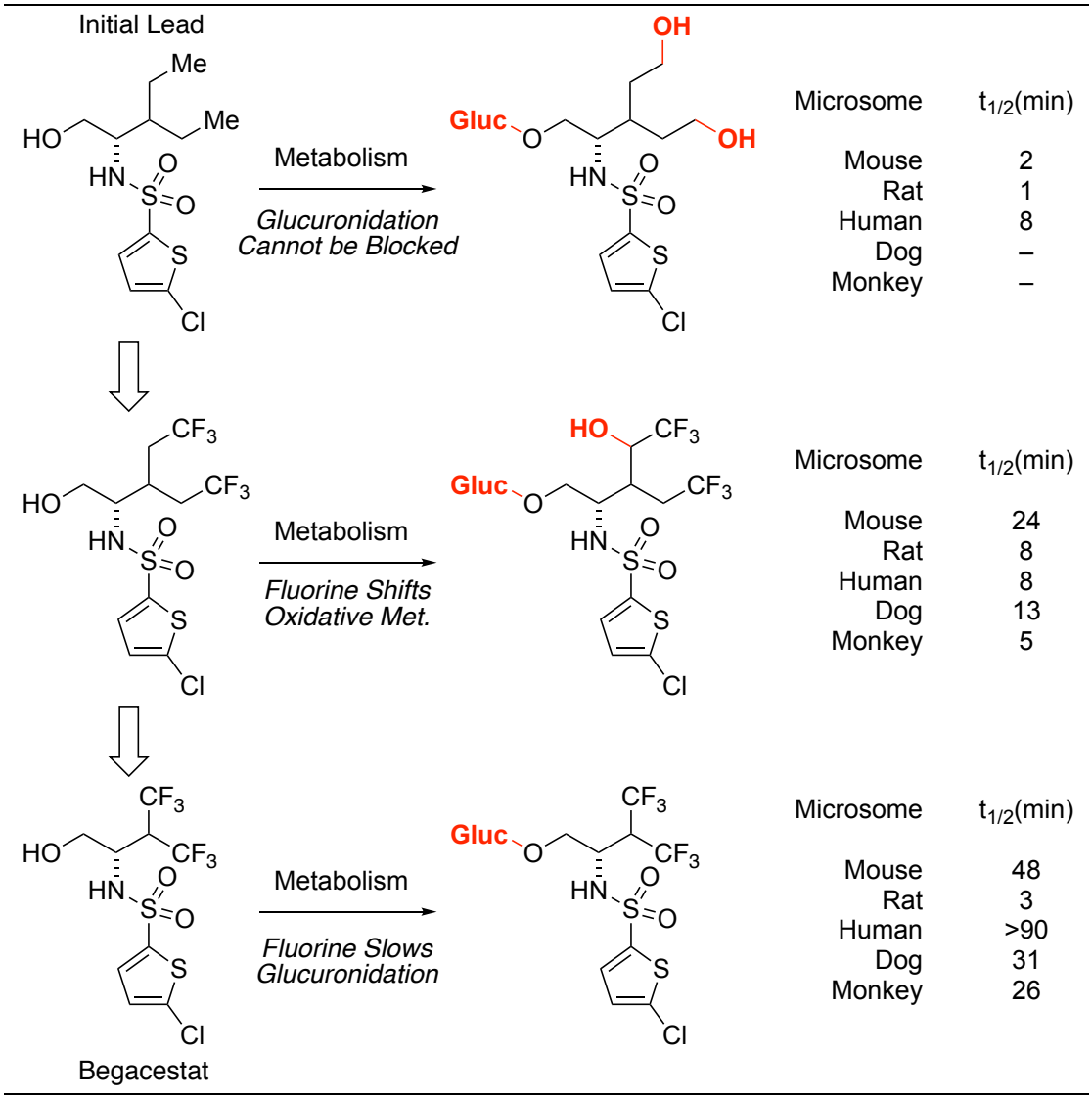
c) Bosentan Metabolism[25]



R =	HLM, 30 min Incubation % Remaining	CYP2C9, 30 min Incubation % Remaining
	91.6%	75.8%
	90.1%	100%
	99%	100%

Another example of fluorination inhibiting the oxidative activation of C–H bonds by CYP_{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**).[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[26]



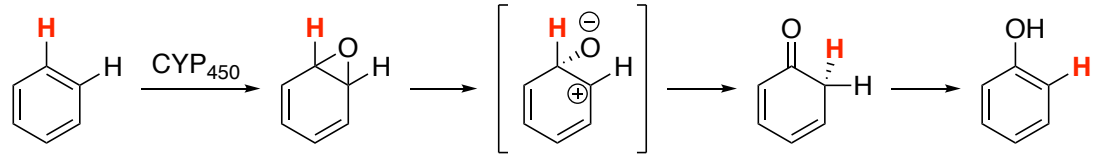
In aromatic systems, fluorination alters the "NIH" hydride shift that occurs upon CYP_{450}-mediated aromatic oxidation reactions.[27] CYP_{450} mediated aromatic metabolism generally requires electron-rich aromatic rings, as aromatic metabolism initiates *via* an epoxidation where the π-system of the aromatic ring acts as a nucleophile to react with the CYP_{450} 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.

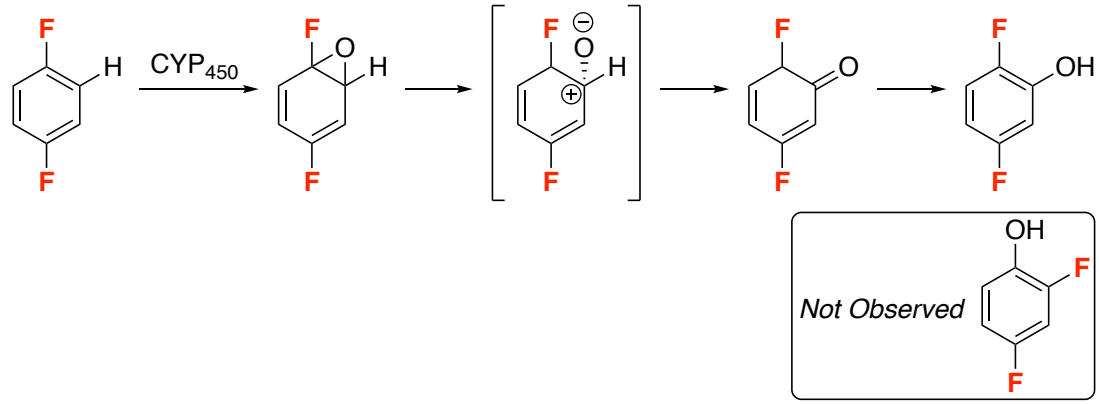
First, fluorine perturbs the distribution of electron density of an aromatic ring, which might decrease metabolism by slowing the initial reaction of the nucleophilic arene π-system on the CYP_{450} Fe–O species. Second, the dearomatized C–F bond is strong, and does not readily undergo 1,2-fluoride shifts, 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**).[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**).[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.

Figure 1-18: Fluorination of Aryl Rings Perturbs Metabolism

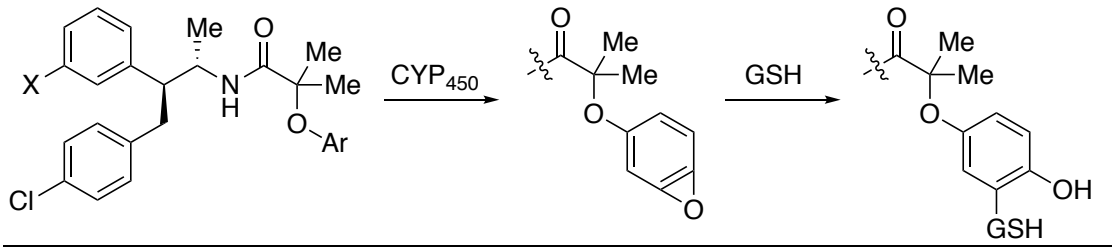
a) Oxidative Metabolism of Aryl Rings: NIH Shift[26]



b) Oxidative Metabolism of Fluorinated Aryl Rings[26]



c) Taranabant Metabolism[27]



X	Ar	*In Vitro* GSH Adducts	Covalent Binding HLM (pM-eq/mg protein)
H	Ph	+++++	3870 +/- 303
H	3,5-F_2-(C_6H_3)	+++++	1690 +/- 215
H	2-Pyridine	++++	911 +/- 109
H	5-Cl-2-Pyridine	++	303 +/- 81
H	5-CF_3-2-Pyridine	+	88 +/- 4
CN	5-CF_3-2-Pyridine	–	27 +/- 2

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

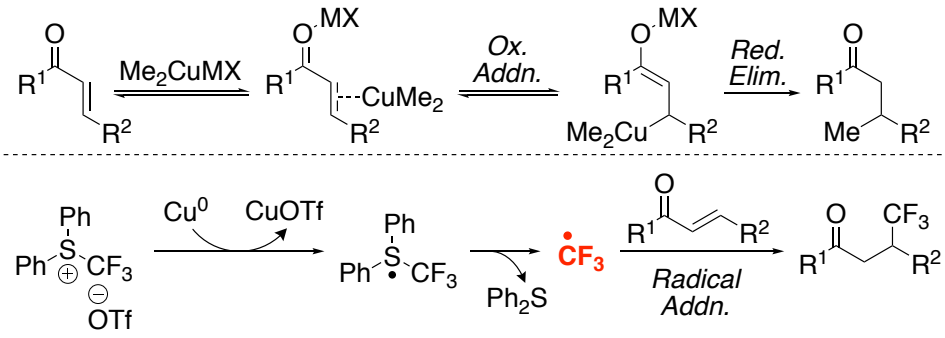
chemists.[29] However, fluorination of a substrate can present distinct reactivity patterns in organic chemistry, making many synthetic transformations challenging to extrapolate to fluorinated systems. Often, standard organic reactions do not work in the presence of fluorinated reagents or with fluorinated 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,[30] compatible with a broad spectrum of organic nucleophiles, including simple methyl groups.[31] While the first examples of the Cu-mediated 1,4-addition of a methyl group date back at least to 1941,[32] the first examples of 1,4-addition of $^{-}CF_3$ were only reported in 1988[33] and 1989,[34] with the first general strategy reported in 2003.[35]

In the non-fluorinated case, the reaction proceeds with catalytic quantities of Cu(I) at 0 ˚C or lower,[36] 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**).[37] In contrast, similar reaction conditions do not promote conjugate addition reactions of $^{-}CF_3$. Instead, reactions to generate a new C(β)–CF_3 bond require super-stoichiometric quantities of Cu

at 60 °C, and proceed by a distinct mechanism involving addition of "free •CF_3" 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 Nucleophiles[36-38]

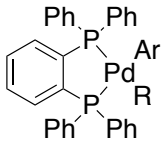


As a second example, Pd-catalyzed cross-coupling reactions to generate C(aryl)–CF_3 bonds have proven challenging. The Pd–CF_3 bond resists reductive elimination, because the high electronegativity of the trifluoromethyl group[39] imparts strong ionic bond character to the Pd–C bond (**Figure 1-20a**).[40] This reductive elimination step requires ~22 kcal/mol to reach the transition state, with most of the energy required to break the Pd–CF_3 bond (**Figure 1-20b**).[41] Since reductive elimination of the L_n(Ar)Pd–CF_3 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)–CF_3 bond, the Ruppert-Prakash reagent (TMS–CF_3), the most common $^-CF_3$ source, decomposes to :CF_2 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)–

CF_3 bond, which instead requires specialized ligands or higher oxidation states of Pd to promote reductive elimination.[41, 42b, 43]

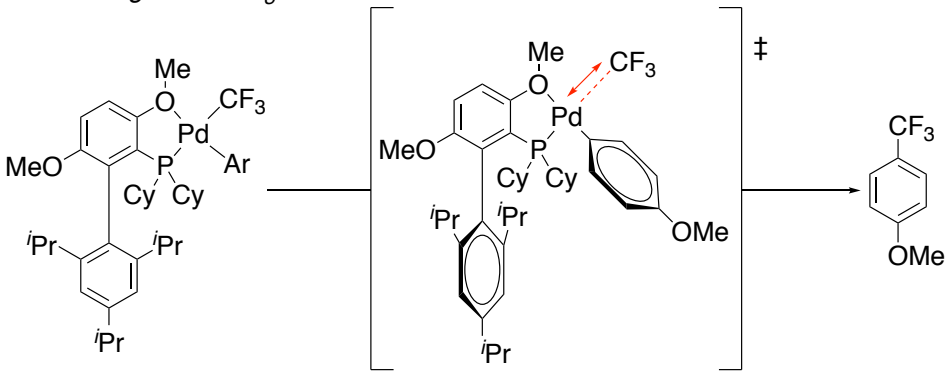
Figure 1-20: Challenging Reductive Elimination of Pd–CF_3

a) High electronegativity of CF_3 group resists red. elim. of Ar–R bond[39]



R	σ*	Red. Elim. k_{rel} @ 110 °C	Red. Elim. $t_{1/2}$ (min)
Me	**0.00**	**>600**	**<5 (90 °C)**
CH_2Ph	0.22	>250	<5 (90 °C)
$CH_2C(O)Ar$	0.60	31	39 (90 °C)
CH_2CF_3	0.92	1.7	~720 (110 °C)
CH_2CN	1.30	1	~1,200 (110 °C)
CF_3	**2.60**	**No Rxn**	**No Rxn (>130 °C)**

b) High energy at TS for reductive elimination derives from lengthening and breaking of Pd–CF_3 bond[40]



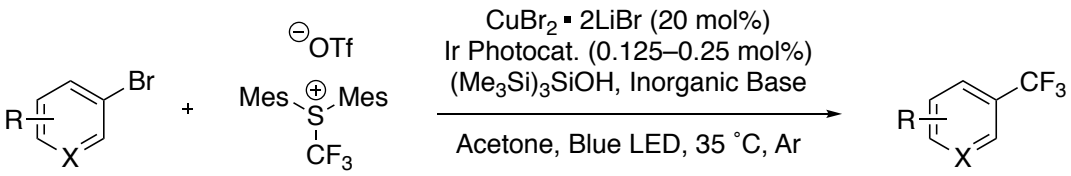
$\Delta G^{\ddagger}$ ~ 22 kcal/mol

The challenging reductive elimination from Pd can be avoided by employing other metal catalysts. For example, reductive elimination of CF_3 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 CF_3 addition to Cu(II) enables access to the Ar–Cu(III)–CF_3 complex that can undergo a more facile reductive elimination (**Scheme 1-1a**).[44] This strategy exploits a variety of •CF_3 precursors, from photocatalytic activation of an S–CF_3 reagent[44] or the direct one electron

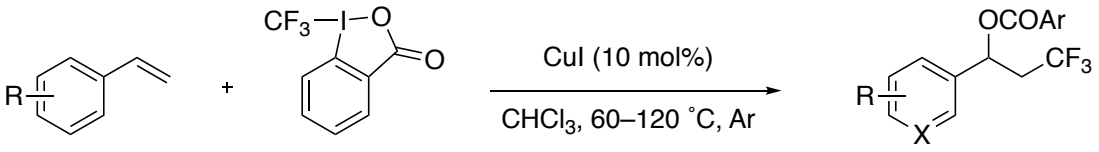
transfer of •CF_3 to a Cu(I) catalyst from Togni or Umemoto's reagent (**Scheme 1-1b**).[45] Reductive elimination of Ar–CF_3 from Cu(III) is so facile that it is possible even at room temperature (**Scheme 1-1c**).[46]

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

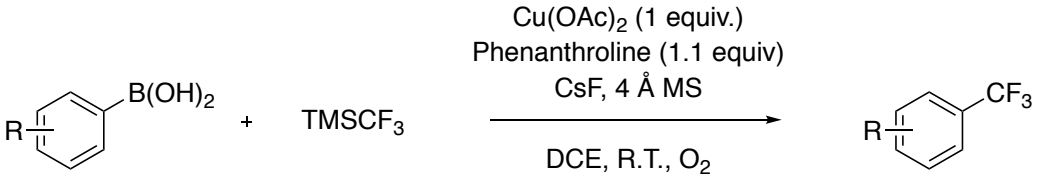
a) Co-catalytic Photocatalysis Enables Facile CF_3 reductive elimination from Cu[43]



b) Trifluoromethylation Reagents Enable CF_3 reductive elimination from Cu[44]



c) Oxidative Trifluoromethylation of Boronic Acids Mediated by Cu[45]

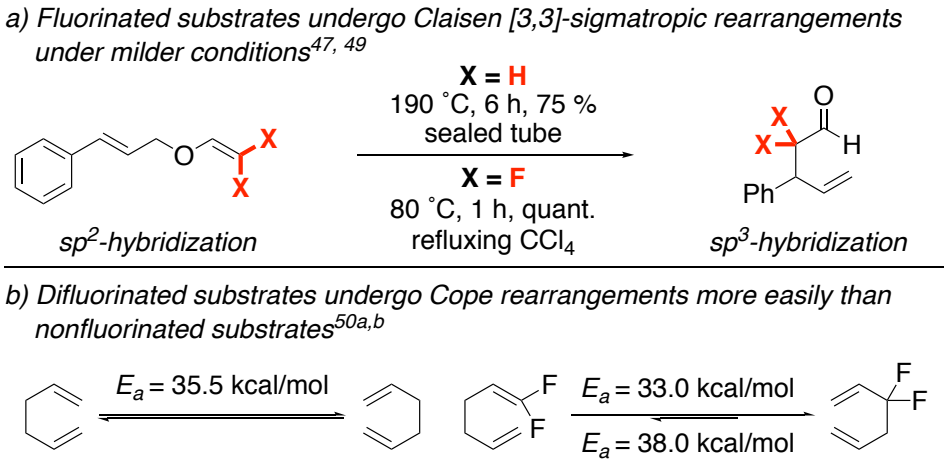


These two examples in which fluorinated reagents pose unique challenges relative to reactions of non-fluorinated reagents demonstrate why so much effort from the synthetic community has been devoted to finding new strategies for incorporating fluorinated substituents into organic molecules.[29, 47]

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.[48] 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.[49] However, when fluorinated at the α-position of the enol ether, the Claisen reaction occurs under more mild conditions (80 °C, 1 h).[50] In this case, the *gem*-difluorinated carbon prefers an sp^3-hybridized state rather than the sp^2-hybrized state, thus providing a thermodynamic driving force that disfavors the reverse reaction (**Figure 1-21a**).[51] 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**).[51a, 51b]

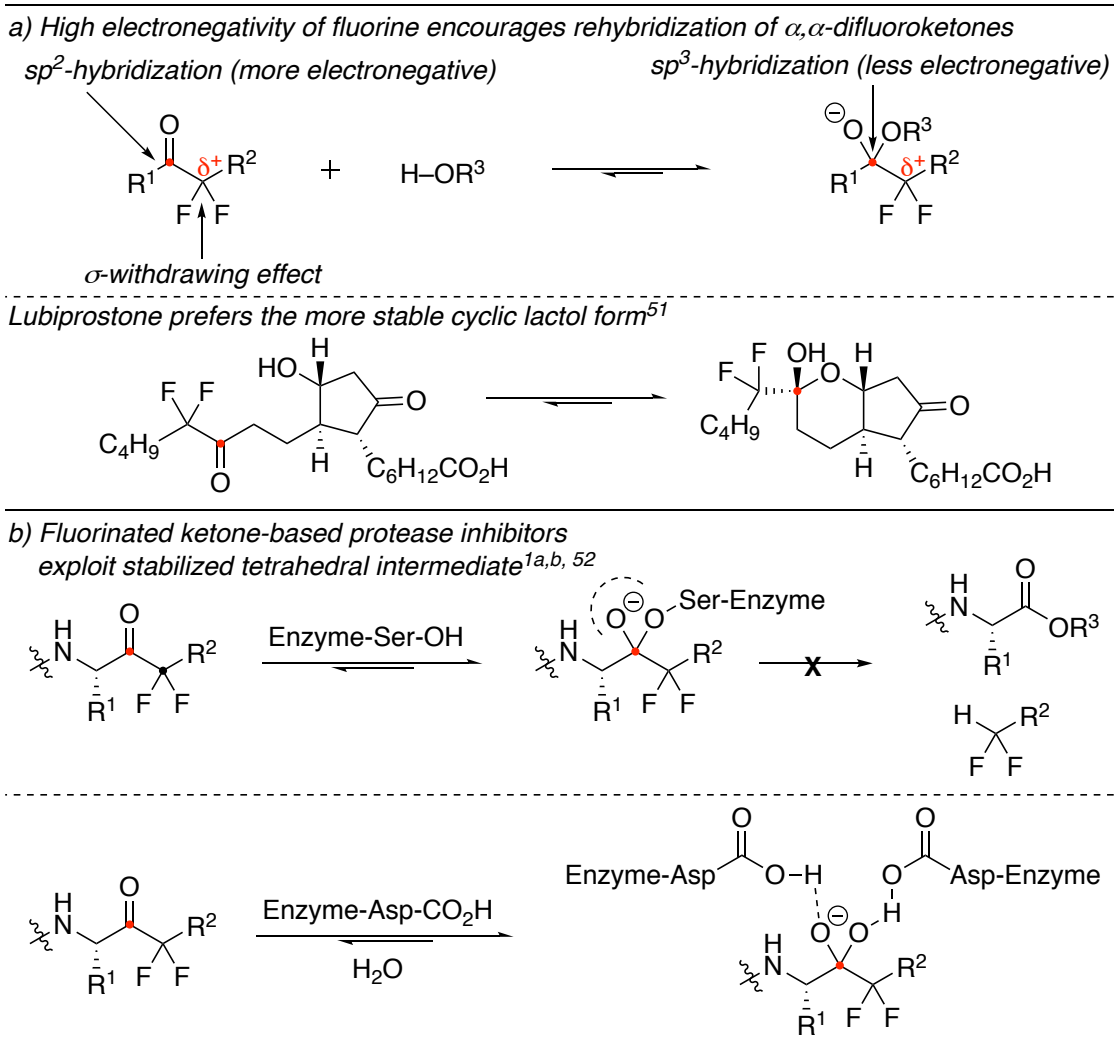
Figure 1-21: The Presence of Fluorinate Facilitates [3,3]–Sigmatropic Rearrangements



Fluorination also affects the reactivity of carbonyl and other sp^2 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, α-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 α-carbon and the carbonyl oxygen (**Figure 1-22a**). This property has been exploited for developing therapeutically relevant agents, such as Lubiprostone, in which the α,α-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 α,α-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, α,α-difluoroketones prefer sp^3-hybridization at the carbonyl carbon, thus stabilizing the tetrahedral intermediate and acting as a mechanism-based inhibitor.

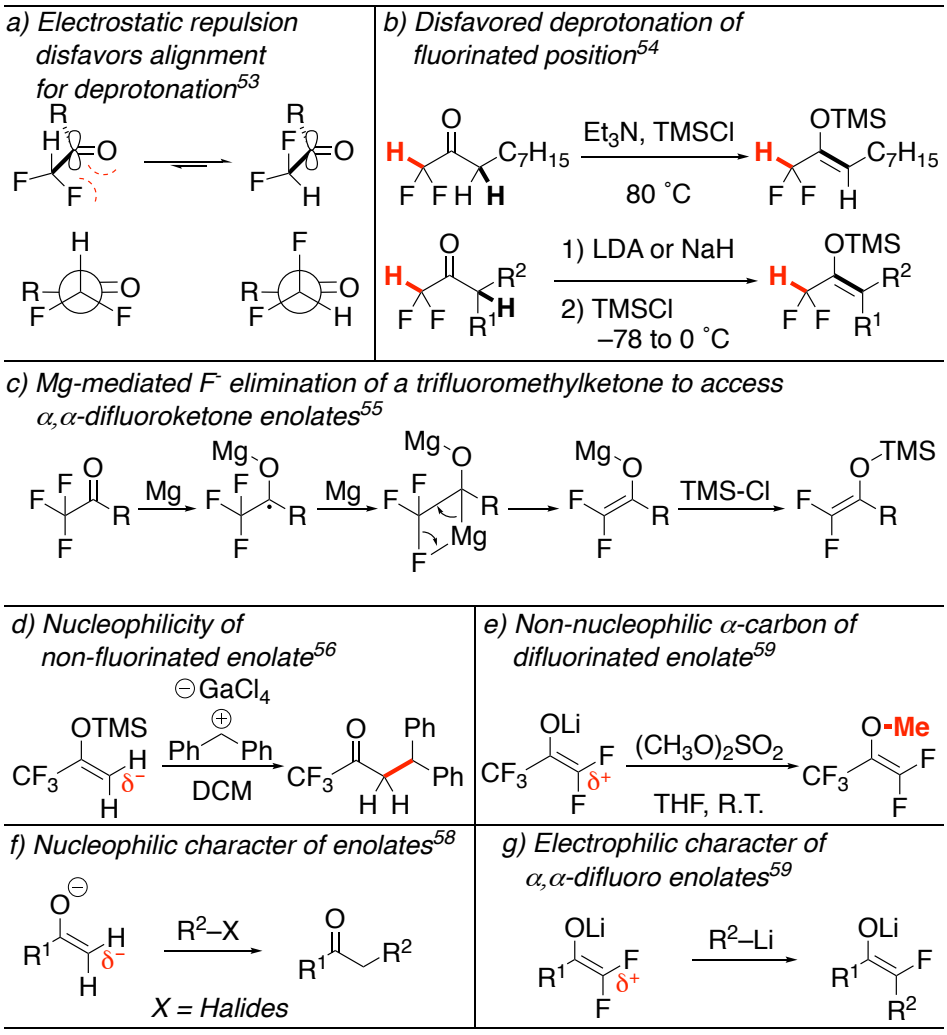
Figure 1-22: α,α-Difluoroketones Prefer sp^3-Hybridization



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 carbonyls or nitro groups, increase acidity through π-

withdrawing effects that weaken the C–H bond, while deprotonation requires overlap between the α-H and the π-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 α-H atom orthogonal to the π system, which disfavors deprotonation (**Figure 1-23a**). As such, ketones bearing an α,α-difluoromethyl group and a simple alkyl group will preferentially generate the non-fluorinated enolate under both kinetic and thermodynamic conditions (**Figure 1-23b**).[55] Thus, alternate strategies, such as Mg^0-mediated F^- elimination from a trifluoromethyl ketone and subsequent trapping with TMS (**Figure 1-23c**),[56] are required to access α,α-difluoroketone enolate derivatives.

Figure 1-23: α,α-Difluoroketones Perturb Traditional Enolate Reactivity

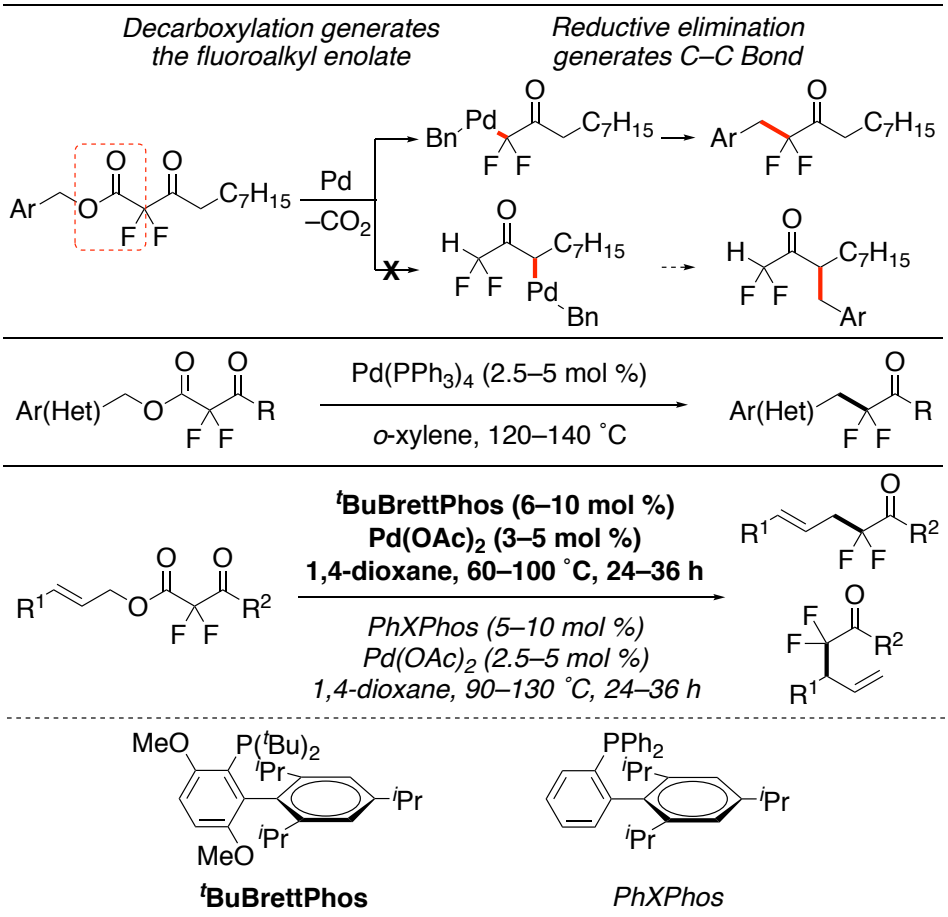


Enolates typically exhibit strong nucleophilicity at the α-carbon, providing a functional handle for C–C bond formation *via* an S_N2 reaction between a ketone enolate and an sp^3-hybridized electrophile (**Figure 1-23d**),[57] and are frequently exploited in complex molecule synthesis. Fluorinated enolates 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**).[60]

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**).[61]

Scheme 1-2: Metal Catalyzed Reactions Enable Nucleophilic Enolate Reactivity for α,α-Difluoroketones[61]



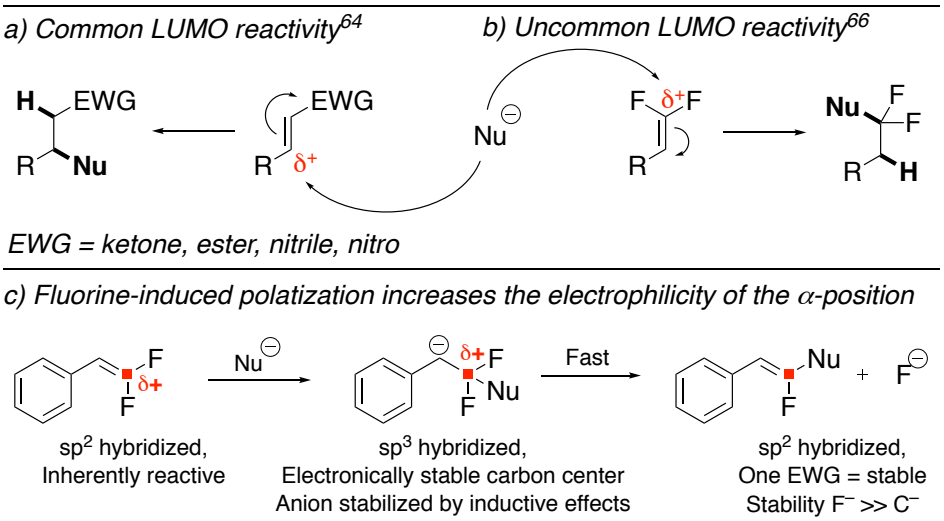
1.4. Fluorine-Induced Perturbations of Alkene Reactivity

Similar to the cases of α,α-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 π-HOMO orbitals,[30, 62] while also reacting with nucleophiles through the π*-LUMO. To react with the π* orbital, non-fluorinated alkenes require activation, typically

through incorporation of carbonyl, nitrile, and nitro groups that lower the LUMO through resonance effects.[62] This activation restricts nucleophilic attack to the electrophilic β-carbon (**Figure 1-24a**),[63] while functional groups that facilitate attack at the α-carbon are less common.

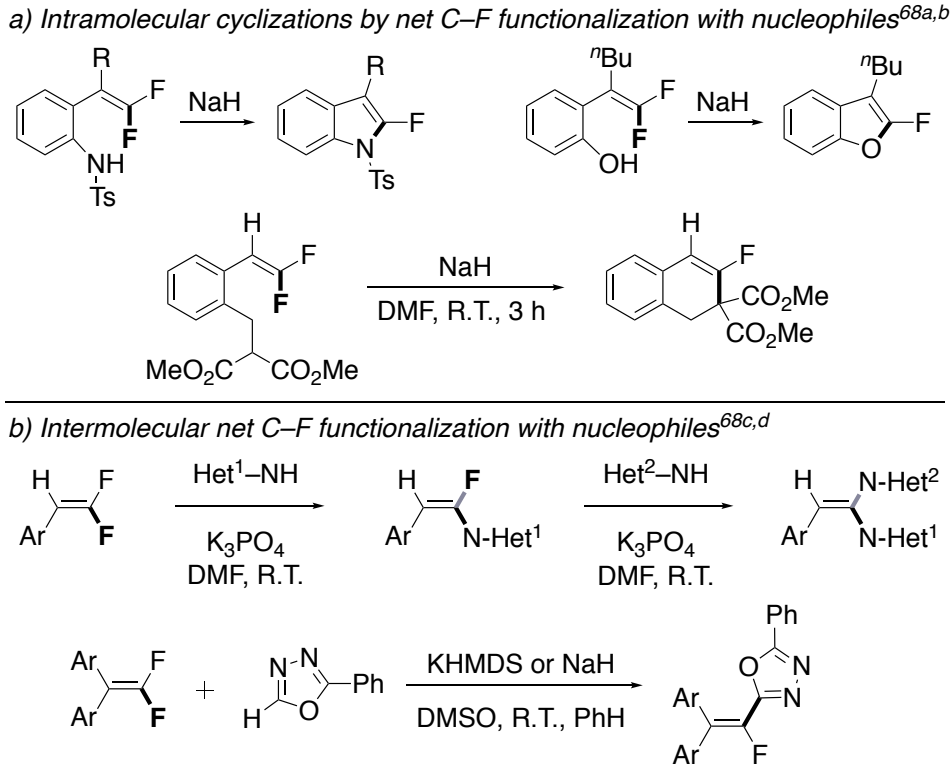
In contrast, fluorination of alkenes allows an alternate mode of reactivity,[64] thus providing a distinct subset of products relative to classical 1,4-addition reactions (**Figure 1-24a**).[65] For fluorinated alkenes, the inductive, σ-withdrawing effect of fluorine atoms activates the geminal carbon, while the resonance effect of fluorine disfavors attack of the β-position (**Figure 1-24b**).[58b] 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 sp^2 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**).[66] Combined with the extreme electron deficiency of a difluorinated carbon, difluoroalkenes are exceptionally electrophilic at the difluorinated carbon,[67] 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,[67] due to the formation of the β-anionic intermediate enabling an addition / elimination mechanism (**Figure 1-24c**).[64, 67-68] 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**).[64, 69] 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.

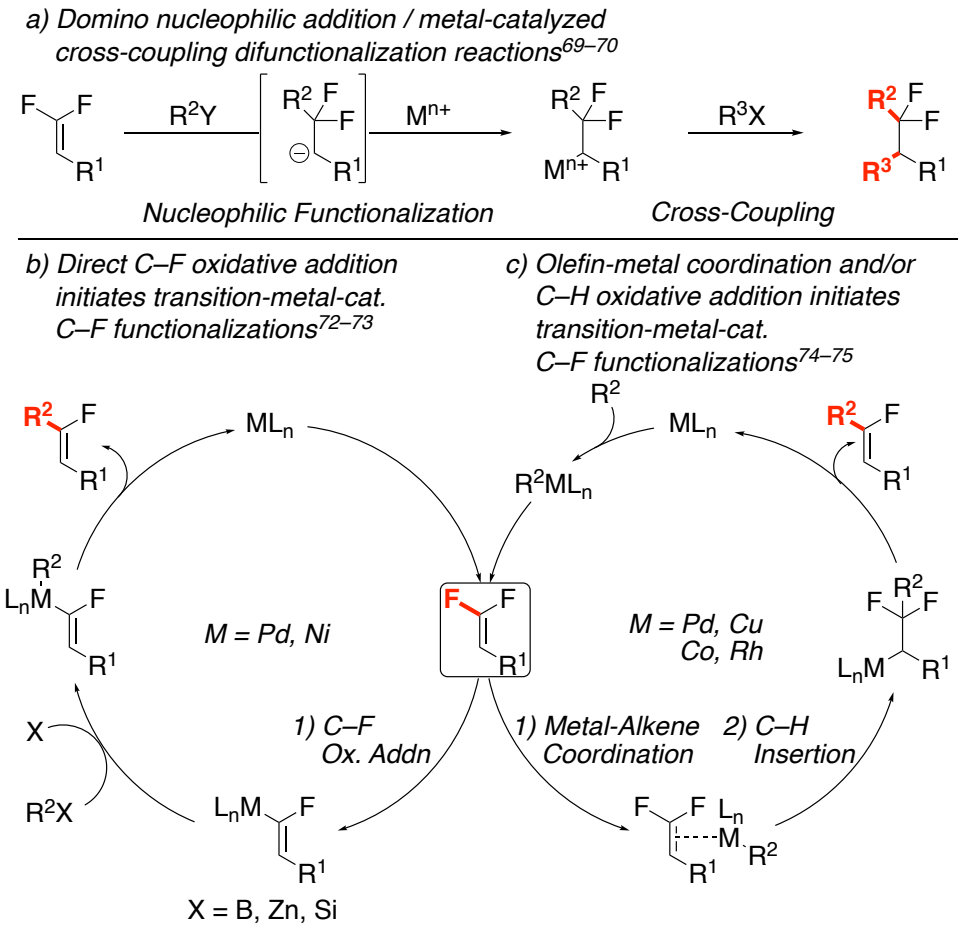
Scheme 1-3: C–F Functionalization Reactions of *gem*-Difluoroalkenes with Nucleophiles Involve Nucleophilic Addition / F^- Elimination Mechanisms



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 Loh[70] and Hu[71] 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[73] and Ni-based[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[75] or C–H oxidative addition[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 *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 *gem*-difluoroalkenes is addressed in Chapter 4 and Chapter 5.

Figure 1-25: Metal-Catalyzed Paradigms for Functionalization of *gem*-Difluoroalkenes



Exploiting the reactivity of *gem*-difluoroalkenes is a valuable goal, as *gem*-difluoroalkenes are easily-accessible[64, 77] synthetic building blocks. These α,α-difluoroalkene substrates can be generated by a variety of methods,[64] including cross coupling reactions of aryl halides[77g] and aryl boronic acids,[77f] and olefination reactions of diazo compounds,[77e] ketones, and aldehydes (Wittig[77b] and Julia-Kocienski[77d] 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

1. (a) Bégué, J.-P.; Bonnet-Delpon, D., *Bioorganic and Medicinal Chemistry of Fluorine*. Wiley-VCH:Weinheim: 2008; (b) Ojima, I., *Fluorine in Medicinal Chemistry and Chemical Biology*. Wiley-Blackwell: West Sussex, UK, 2009; (c) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*. Imperial College Press: London, 2012; (d) O'Hagan, D., Understanding organofluorine chemistry. An introduction to the C-F bond. *Chem. Soc. Rev.* **2008,** *37* (2), 308-19; (e) Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M., Fluorine in medicinal chemistry. *Chembiochem* **2004,** *5* (5), 637-43; (f) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V., Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008,** *37* (2), 320-30; (g) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H., Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016,** *116* (2), 422-518; (h) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H., Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001-2011). *Chem. Rev.* **2014,** *114* (4), 2432-506; (i) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015,** *58* (21), 8315-59.

2. Dean, J. A.; Lange, N. A., *Lange's Handbook of Chemistry*. 15 ed.; McGraw-Hill: 1999; p 1538.

3. Yang, J. D.; Wang, Y.; Xue, X. S.; Cheng, J. P., A Systematic Evaluation of the N-F Bond Strength of Electrophilic N-F Reagents: Hints for Atomic Fluorine Donating Ability. *J. Org. Chem.* **2017,** *82* (8), 4129-4135.

4. (a) Ravindra, M.; Wilson, M. R.; Tong, N.; O'Connor, C.; Karim, M.; Polin, L.; Wallace-Povirk, A.; White, K.; Kushner, J.; Hou, Z.; Matherly, L. H.; Gangjee, A., Fluorine-Substituted Pyrrolo[2,3- d]Pyrimidine Analogues with Tumor Targeting via Cellular Uptake by Folate Receptor alpha and the Proton-Coupled Folate Transporter and Inhibition of de Novo Purine Nucleotide Biosynthesis. *J. Med. Chem.* **2018,** *61* (9), 4228-4248; (b) Steffel, L. R.; Cashman, T. J.; Reutershan, M. H.; Linton, B. R., Deuterium exchange as an indicator of hydrogen bond donors and acceptors. *J. Am. Chem. Soc.* **2007,** *129* (43), 12956-7; (c) Manjunatha Reddy, G. N.; Vasantha Kumar, M. V.; Guru Row, T. N.; Suryaprakash, N., N-H...F hydrogen bonds in fluorinated benzanilides: NMR and DFT study. *Phys. Chem. Chem. Phys.* **2010,** *12* (40), 13232-7; (d) Divya, K.; Hebbar, S.; Suryaprakash, N., Intra-molecular hydrogen bonding with organic fluorine in the solution state: Deriving evidence by a two dimensional NMR experiment. *Chem. Phys. Lett.* **2012,** *525-526*, 129-133; (e) Chaudhari, S. R.; Mogurampelly, S.; Suryaprakash, N., Engagement of CF3 group in N-H...F-C hydrogen bond in the solution state: NMR spectroscopy and MD simulation studies. *J. Phys. Chem. B* **2013,** *117* (4), 1123-9; (f) Paquin, J.-F.; Champagne, P.; Desroches, J., Organic Fluorine as a Hydrogen-Bond Acceptor: Recent Examples and Applications. *Synthesis* **2014,** *47* (03), 306-322.

5. Meanwell, N. A., Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**.

6. (a) Istvan, E. S.; Deisenhofer, J., Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* **2001,** *292* (5519), 1160-4; (b) Olsen, J. A.; Banner, D. W.; Seiler, P.; Obst Sander, U.; D'Arcy, A.; Stihle, M.; Muller, K.; Diederich, F., A fluorine scan of thrombin inhibitors to map the fluorophilicity/fluorophobicity of an enzyme active site: evidence for C-F...C=O interactions. *Angew. Chem. Int. Ed. Engl.* **2003,** *42* (22), 2507-11.

7. (a) Muller, K.; Faeh, C.; Diederich, F., Fluorine in pharmaceuticals: looking beyond intuition. *Science* **2007,** *317* (5846), 1881-6; (b) Paulini, R.; Muller, K.; Diederich, F., Orthogonal multipolar interactions in structural chemistry and biology. *Angew. Chem. Int. Ed. Engl.* **2005,** *44* (12), 1788-805; (c) Xing, L.; Keefer, C.; Brown, M. E., Fluorine multipolar interaction: Toward elucidating its energetics in binding recognition. *J. Fluorine Chem.* **2017,** *198*, 47-53; (d) Bauer, M. R.; Jones, R. N.; Baud, M. G.; Wilcken, R.; Boeckler, F. M.; Fersht, A. R.; Joerger, A. C.; Spencer, J., Harnessing Fluorine-Sulfur Contacts and Multipolar Interactions for the Design of p53 Mutant Y220C Rescue Drugs. *ACS Chem Biol* **2016,** *11* (8), 2265-74; (e) Pollock, J.; Borkin, D.; Lund, G.; Purohit, T.; Dyguda-Kazimierowicz, E.; Grembecka, J.; Cierpicki, T., Rational Design of Orthogonal Multipolar Interactions with Fluorine in Protein-Ligand Complexes. *J. Med. Chem.* **2015,** *58* (18), 7465-74.

8. LaLonde, J. M.; Kwon, Y. D.; Jones, D. M.; Sun, A. W.; Courter, J. R.; Soeta, T.; Kobayashi, T.; Princiotto, A. M.; Wu, X.; Schon, A.; Freire, E.; Kwong, P. D.; Mascola, J. R.; Sodroski, J.; Madani, N.; Smith, A. B., 3rd, Structure-based design, synthesis, and

characterization of dual hotspot small-molecule HIV-1 entry inhibitors. *J. Med. Chem.* **2012,** *55* (9), 4382-96.

9. Murray, J.; Giannetti, A. M.; Steffek, M.; Gibbons, P.; Hearn, B. R.; Cohen, F.; Tam, C.; Pozniak, C.; Bravo, B.; Lewcock, J.; Jaishankar, P.; Ly, C. Q.; Zhao, X.; Tang, Y.; Chugha, P.; Arkin, M. R.; Flygare, J.; Renslo, A. R., Tailoring small molecules for an allosteric site on procaspase-6. *ChemMedChem* **2014,** *9* (1), 73-7, 2.

10. Lovering, F.; Bikker, J.; Humblet, C., Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009,** *52* (21), 6752-6.

11. (a) Thiehoff, C.; Rey, Y. P.; Gilmour, R., The Fluorine Gauche Effect: A Brief History. *Isr. J. Chem.* **2017,** *57* (1-2), 92-100; (b) Hunter, L., The C-F bond as a conformational tool in organic and biological chemistry. *Beilstein J Org Chem* **2010,** *6*, 38.

12. (a) Barchi, J. J., Jr.; Karki, R. G.; Nicklaus, M. C.; Siddiqui, M. A.; George, C.; Mikhailopulo, I. A.; Marquez, V. E., Comprehensive structural studies of 2',3'-difluorinated nucleosides: comparison of theory, solution, and solid state. *J. Am. Chem. Soc.* **2008,** *130* (28), 9048-57; (b) Van Roey, P.; Salerno, J. M.; Chu, C. K.; Schinazi, R. F., Correlation between preferred sugar ring conformation and activity of nucleoside analogues against human immunodeficiency virus. *Proc. Natl. Acad. Sci. U. S. A.* **1989,** *86* (11), 3929-3933; (c) Mikhailopulo, I. A.; Pricota, T. I.; Sivets, G. G.; Altona, C., 2'-chloro-2',3'-dideoxy-3'-fluoro-d-ribonucleosides: synthesis, stereospecificity, some chemical transformations, and conformational analysis. *J. Org. Chem.* **2003,** *68* (15), 5897-908.

13. Ford, H.; Dai, F.; Mu, L.; Siddiqui, M. A.; Nicklaus, M. C.; Anderson, L.; Marquez, V. E.; Barchi, J. J., Adenosine Deaminase Prefers a Distinct Sugar Ring Conformation for Binding and Catalysis: Kinetic and Structural Studies. *Biochemistry* **2000,** *39* (10), 2581-2592.

14. Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R., New trends in the chemistry of α-fluorinated ethers, thioethers, amines and phosphines. *J. Fluorine Chem.* **2010,** *131* (2), 140-158.

15. (a) Xing, L.; Blakemore, D. C.; Narayanan, A.; Unwalla, R.; Lovering, F.; Denny, R. A.; Zhou, H.; Bunnage, M. E., Fluorine in drug design: a case study with fluoroanisoles. *ChemMedChem* **2015,** *10* (4), 715-26; (b) 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.

16. Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J., CF2H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017,** *139* (27), 9325-9332.

17. Zheng, B.; D'Andrea, S. V.; Sun, L. Q.; Wang, A. X.; Chen, Y.; Hrnciar, P.; Friborg, J.; Falk, P.; Hernandez, D.; Yu, F.; Sheaffer, A. K.; Knipe, J. O.; Mosure, K.; Rajamani, R.; Good, A. C.; Kish, K.; Tredup, J.; Klei, H. E.; Paruchuri, M.; Ng, A.; Gao, Q.; Rampulla, R. A.; Mathur, A.; Meanwell, N. A.; McPhee, F.; Scola, P. M., Potent Inhibitors of Hepatitis C Virus NS3 Protease: Employment of a Difluoromethyl Group as a Hydrogen-Bond Donor. *ACS Med Chem Lett* **2018,** *9* (2), 143-148.

18. Stump, C. A.; Bell, I. M.; Bednar, R. A.; Fay, J. F.; Gallicchio, S. N.; Hershey, J. C.; Jelley, R.; Kreatsoulas, C.; Moore, E. L.; Mosser, S. D.; Quigley, A. G.; Roller, S. A.; Salvatore, C. A.; Sharik, S. S.; Theberge, C. R.; Zartman, C. B.; Kane, S. A.; Graham, S. L.; Selnick, H. G.; Vacca, J. P.; Williams, T. M., Identification of potent, highly constrained CGRP receptor antagonists. *Bioorg. Med. Chem. Lett.* **2010,** *20* (8), 2572-6.

19. (a) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.; Fujii, N., Unequivocal synthesis of (Z)-alkene and (E)-fluoroalkene dipeptide isosteres to probe structural requirements of the peptide transporter PEPT1. *Org. Lett.* **2006,** *8* (4), 613-6; (b) Allmendinger, T.; Felder, E.; Hungarbühler, E., Fluoroolefin dipeptide isosteres -II. *Tetrahedron Lett.* **1990,** *31* (50), 7301-7304; (c) Lin, J.; Toscano, P. J.; Welch, J. T., Inhibition of dipeptidyl peptidase IV by fluoroolefin-containing N-peptidyl-O-hydroxylamine peptidomimetics. *Proc Natl Acad Sci U S A* **1998,** *95* (24), 14020-4.

20. Chang, W.; Mosley, R. T.; Bansal, S.; Keilman, M.; Lam, A. M.; Furman, P. A.; Otto, M. J.; Sofia, M. J., Inhibition of hepatitis C virus NS5A by fluoro-olefin based gamma-turn mimetics. *Bioorg. Med. Chem. Lett.* **2012,** *22* (8), 2938-42.

21. (a) Morgenthaler, M.; Schweizer, E.; Hoffmann-Roder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Muller, K., Predicting and tuning physicochemical properties in lead optimization: amine basicities. *ChemMedChem* **2007,** *2* (8), 1100-15; (b) Sani, M.; Volonterio, A.; Zanda, M., The Trifluoroethylamine Function as Peptide Bond Replacement. *ChemMedChem* **2007,** *2* (12), 1693-1700; (c) Jagodzinska, M.; Huguenot,

F.; Candiani, G.; Zanda, M., Assessing the bioisosterism of the trifluoromethyl group with a protease probe. *ChemMedChem* **2009,** *4* (1), 49-51.

22. Spahn, V.; Del Vecchio, G.; Labuz, D.; Rodriguez-Gaztelumendi, A.; Massaly, N.; Temp, J.; Durmaz, V.; Sabri, P.; Reidelbach, M.; Machelska, H.; Weber, M.; Stein, C., A nontoxic pain killer designed by modeling of pathological receptor conformations. *Science* **2017,** *355* (6328), 966-969.

23. (a) Rodil, A.; Bosisio, S.; Ayoup, M. S.; Quinn, L.; Cordes, D. B.; Slawin, A. M. Z.; Murphy, C. D.; Michel, J.; O'Hagan, D., Metabolism and hydrophilicity of the polarised 'Janus face' all-cis tetrafluorocyclohexyl ring, a candidate motif for drug discovery. *Chem Sci* **2018,** *9* (11), 3023-3028; (b) Luo, Q.; Randall, K. R.; Schaefer, H. F., Easy chairs: the conformational preferences of polyfluorocyclohexanes. *Rsc Adv* **2013,** *3* (18).

24. (a) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Muller, K., Fluorination Patterning: A Study of Structural Motifs That Impact Physicochemical Properties of Relevance to Drug Discovery. *J. Med. Chem.* **2015,** *58* (22), 9041-60; (b) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Muller, K., On the polarity of partially fluorinated methyl groups. *J. Fluorine Chem.* **2013,** *152*, 119-128.

25. Lepri, S.; Goracci, L.; Valeri, A.; Cruciani, G., Metabolism study and biological evaluation of bosentan derivatives. *Eur. J. Med. Chem.* **2016,** *121*, 658-670.

26. Mayer, S. C.; Kreft, A. F.; Harrison, B.; Abou-Gharbia, M.; Antane, M.; Aschmies, S.; Atchison, K.; Chlenov, M.; Cole, D. C.; Comery, T.; Diamantidis, G.; Ellingboe, J.; Fan,

K.; Galante, R.; Gonzales, C.; Ho, D. M.; Hoke, M. E.; Hu, Y.; Huryn, D.; Jain, U.; Jin, M.; Kremer, K.; Kubrak, D.; Lin, M.; Lu, P.; Magolda, R.; Martone, R.; Moore, W.; Oganesian, A.; Pangalos, M. N.; Porte, A.; Reinhart, P.; Resnick, L.; Riddell, D. R.; Sonnenberg-Reines, J.; Stock, J. R.; Sun, S. C.; Wagner, E.; Wang, T.; Woller, K.; Xu, Z.; Zaleska, M. M.; Zeldis, J.; Zhang, M.; Zhou, H.; Jacobsen, J. S., Discovery of begacestat, a Notch-1-sparing gamma-secretase inhibitor for the treatment of Alzheimer's disease. *J. Med. Chem.* **2008,** *51* (23), 7348-51.

27. Koerts, J.; Soffers, A. E.; Vervoort, J.; De Jager, A.; Rietjens, I. M., Occurrence of the NIH shift upon the cytochrome P450-catalyzed in vivo and in vitro aromatic ring hydroxylation of fluorobenzenes. *Chem. Res. Toxicol.* **1998,** *11* (5), 503-12.

28. Hagmann, W. K., The discovery of taranabant, a selective cannabinoid-1 receptor inverse agonist for the treatment of obesity. *Arch Pharm (Weinheim)* **2008,** *341* (7), 405-11.

29. Yerien, D. E.; Bonesi, S.; Postigo, A., Fluorination methods in drug discovery. *Org Biomol Chem* **2016,** *14* (36), 8398-427.

30. Carey, F. A.; Sundberg, R. J., *Advanced Organic Chemistry Part B: Reactions and Synthesis*. 5 ed.; Springer Science & Business Media: New York, 2007.

31. (a) House, H. O.; Respess, W. L.; Whitesides, G. M., The Chemistry of Carbanions. XII. The Role of Copper in the Conjugate Addition of Organometallic Reagents. *J. Org. Chem.* **1966,** *31*, 3128-41; (b) Marshall, J. A.; Cohen, G. M., The Stereoselective Total Synthesis of Racemic Fukinone. *J. Org. Chem.* **1970,** *36* (7), 877-82.

32. Kharasch, M. S.; Tawney, P. O., Factors determining the course and mechanisms of Grignard reactions. II. The effect of metallic compounds on the reaction between isophorone and methylmagnesium bromide. *J. Am. Chem. Soc.* **1941,** *63*, 2308-2315.

33. Alekseenko, A. N.; Nazaretyan, V. P.; Il'chenko, A. Y.; Yagulpol'skii, L. M., (Polyfluoroalkyl)succinic acids. *Zh. Org. Khim.* **1988,** *24* (11), 2362-7.

34. Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A., Synthetic Methods and Reactions .141. Fluoride-Induced Trifluoromethylation of Carbonyl-Compounds with Trifluoromethyltrimethylsilane (Tms-Cf3) - a Trifluoromethide Equivalent. *J. Am. Chem. Soc.* **1989,** *111* (1), 393-395.

35. Sevenard, D. V.; Sosnovskikh, V. Y.; Kolomeitsev, A. A.; Königsmann, M. H.; Röschenthaler, G.-V., Regioselective 1,4-trifluoromethylation of α,β-enones using 'protect-in-situ' methodology. *Tetrahedron Lett.* **2003,** *44* (41), 7623-7627.

36. (a) Palais, L.; Babel, L.; Quintarf, A.; Belot, S.; Alexakis, A., Copper-Catalyzed Enantioselective 1,4-Addition to a,b-Unsaturated Aldehydes. *Org. Lett.* **2010,** *12* (9), 1988-91; (b) Alexakis, A.; Goncalves-Contal, S.; Gremaud, L.; Palais, L.; Babel, L., Copper-Catalyzed Enantioselective Conjugate Addition to α,β-Unsaturated Aldehydes with Various Organometallic Reagents. *Synthesis* **2016,** *48* (19), 3301-3308; (c) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L., Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents to Acyclic Enones. *J. Am. Chem. Soc.* **2004,** *126* (40), 12784-5.

37. (a) Woodward, S., Decoding the 'black box' reactivity that is organocuprate conjugate addition chemistry. *Chem. Soc. Rev.* **2000,** *29* (6), 393-401; (b) Nakamura, E.; Mori, S., Wherefore Art Thou Copper? Structures and Reaction Mechanisms of Organocuprate Clusters in Organic Chemistry. *Angew. Chem. Int. Ed. Engl.* **2000,** *39* (21), 3750-3771; (c) Krause, N.; Gerold, A., Regio- and stereoselective syntheses with organocopper reagents. *Angew. Chem. Int. Ed.* **1997,** *36* (3), 187-204; (d) Mori, S.; Nakamura, E., Modern Organocopper Chemistry. Krause, N., Ed. Wiley-VCH Verlag GmbH: Weinheim, 2002; (e) Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L., On the Mechanism of the Copper-Catalyzed Enantioselective 1,4-Addition of Grignard Reagents to a,b-Unsaturated Carbonyl Compounds. *J. Am. Chem. Soc.* **2006,** *128*, 9103-18.

38. Okusu, S.; Sugita, Y.; Tokunaga, E.; Shibata, N., Regioselective 1,4-trifluoromethylation of alpha,beta-unsaturated ketones via a S-(trifluoromethyl)diphenylsulfonium salts/copper system. *Beilstein J Org Chem* **2013,** *9*, 2189-93.

39. Culkin, D. A.; Hartwig, J. F., Carbon-carbon bond-forming reductive elimination from arylpalladium complexes containing functionalized alkyl groups. Influence of ligand steric and electronic properties on structure, stability, and reactivity. *Organometallics* **2004,** *23* (14), 3398-3416.

40. Hartwig, J. F., Electronic effects on reductive elimination to form carbon-carbon and carbon-heteroatom bonds from palladium(II) complexes. *Inorg. Chem.* **2007,** *46* (6), 1936-47.

41. Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L., The palladium-catalyzed trifluoromethylation of aryl chlorides. *Science* **2010,** *328* (5986), 1679-81.

42. (a) Grushin, V. V.; Marshall, W. J., Unexpected H2O-induced Ar-X activation with trifluoromethylpalladium(II) aryls. *J. Am. Chem. Soc.* **2006,** *128* (14), 4632-41; (b) Ball, N. D.; Kampf, J. W.; Sanford, M. S., Aryl-CF3 Bond-Forming Reductive Elimination from Palladium(IV). *J. Am. Chem. Soc.* **2010,** *132* (9), 2878-+.

43. Grushin, V. V.; Marshall, W. J., FAcile Ar-CF3 Bond Formation at Pd. Strikingly Different Outcomes of Reductive Elimination from [(Ph3P)2Pd(CF3)Ph] and [(Xantphos)Pd(CF3)Ph]. *J. Am. Chem. Soc.* **2006,** *128* (39), 12644-5.

44. Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C., A radical approach to the copper oxidative addition problem: Trifluoromethylation of bromoarenes. *Science* **2018,** *360* (6392), 1010-1014.

45. Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabo, K. J., Electrophilic trifluoromethylation by copper-catalyzed addition of CF3-transfer reagents to alkenes and alkynes. *Org. Lett.* **2012,** *14* (11), 2882-5.

46. Senecal, T. D.; Parsons, A. T.; Buchwald, S. L., Room temperature aryl trifluoromethylation via copper-mediated oxidative cross-coupling. *J. Org. Chem.* **2011,** *76* (4), 1174-6.

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

fluorine and fluorine-containing functional groups. *Angew. Chem. Int. Ed. Engl.* **2013,** *52* (32), 8214-64.

48. Cresson, P., Application of the Claisen rearrangement in the synthesis of g,d-ethylenic aldehydes. II. *Bull. Soc. Chim. Fr.* **1964,** (10), 2929-35.

49. Ziegler, F. E., The Thermal, Aliphatic Claisen Rearrangement. *Chem. Rev.* **1988,** *88* (8), 1423-1452.

50. Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P., The synthesis of a,a-difluoroaldehydes and ketones via Claisen rearrangements. *Tetrahedron Lett.* **1985,** *26* (24), 2861-4.

51. (a) Dolbier, W. R.; Alty, A. C.; Phanstiel, O., Kinetic and Stereochemical Effect of a Fluorine Substituent on the Cope and the Homodienyl 1,5-Hydrogen Shift Rearrangements. *J. Am. Chem. Soc.* **1987,** *109* (10), 3046-3050; (b) Dolbier, W. R., Jr.; Medinger, K. S., The Thermodynamic Effect of Fluorine as a Substituent. *Tetrahedron* **1982,** *38* (15), 2415–20; (c) Lam, Y. H.; Stanway, S. J.; Gouverneur, V., Recent progress in the use of fluoroorganic compounds in pericyclic reactions. *Tetrahedron* **2009,** *65* (48), 9905-9933.

52. Sorbera, L. A.; Castaner, J.; Mealy, N. E., Lubiprostone. Treatment of constipation, treatment of irritable bowel syndrome, treatment of postoperative ileus, CIC-2 channel activator. *Drugs of the Future* **2004,** *29* (4), 336-341.

53. (a) Dreyer, G. B.; Metcalf, B. W., a,a-Difluoroketone Inhibitors of HMG CoA Reductase. *Tetrahedron Lett.* **1988,** *29* (52), 6885-6888; (b) Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester,

J. A.; Hockerman, G. H.; Colby, D. A., Evaluation of difluoromethyl ketones as agonists of the gamma-aminobutyric acid type B (GABAB) receptor. *J. Med. Chem.* **2013,** *56* (6), 2456-65.

54. (a) Pollack, R. M., Stereoelectroninc Control in the Reactions of Ketones and Their Enol(ate)s. *Tetrahedron* **1989,** *45* (16), 4913–38; (b) Corey, E. J.; Sneen, R. A., Stereoelectronic Control in Enolization-Ketonization Reactions. *J. Am. Chem. Soc.* **1956,** *78* (24), 6269-6278.

55. (a) Yamana, M.; Ishihara, T.; Ando, T., A Convenient Synthesis of 2,2-Difluoro Enol Silyl Ethers from Chlorodifluoromethyl Ketones. *Tetrahedron Lett.* **1983,** *24* (5), 507-510; (b) Kuroboshi, M.; Ishihara, T., An Efficient and General Method for the Reformatsky-Type Reaction of Chlorodifluoromethyl Ketones with Carbonyl Compounds Giving a,a-Difluoro-b-hydroxy Ketones. *Bull. Chem. Soc. Jpn.* **1990,** *63* (2), 428-37; (c) Liu, Y. L.; Zhou, J., Organocatalytic asymmetric synthesis of 3-difluoroalkyl 3-hydroxyoxindoles. *Chem. Commun.* **2012,** *48* (13), 1919-21.

56. (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K., Mg0-promoted selective C–F bond cleavage of trifluoromethyl ketones: a convenient method for the synthesis of 2,2-difluoro enol silanes. *Chem. Commun.* **1999,** (14), 1323-1324; (b) Mae, M.; Amii, H.; Uneyama, K., First synthesis of 3,3-difluoroserine and cysteine derivatives via Mg(0)-promoted selective C-F bond cleavage of trifluoromethylimines. *Tetrahedron Lett.* **2000,** *41* (41), 7893-7896.

57. (a) Stolz, D.; Kazmaier, U., Metal Enolates as Synthons in Organic Chemistry. In *Chemistry of Metal Enolates*, Zabicky, J., Ed. John Wiley and Sons: London, 2009; pp

355–409; (b) Stoltz, B. M.; Bennett, N. B.; Duquette, D. C.; Goldberg, A. F. G.; Liu, Y.; Loewinger, M. B.; REeve, C. M., In *Comprehensive Organic Synthesis II*, Knochel, P.; Molander, G. A., Eds. Elsevier: Amsterdam, 2014; Vol. 3, pp 1-55.

58. (a) Qian, C. P.; Nakai, T.; Dixon, D. A.; Smart, B. E., Ketone perfluoro enolates: regioselective and stereoselective synthesis, unique reactivities, and electronic properties. *J. Am. Chem. Soc.* **1990,** *112* (11), 4602-4; (b) Uneyama, K., *Organofluorine Chemistry*. Blackwell Publishing Ltd: New Dehli, India, 2006.

59. Laub, H. A.; Gladow, D.; Reissig, H. U.; Mayr, H., The influence of perfluorinated substituents on the nucleophilic reactivities of silyl enol ethers. *Org. Lett.* **2012,** *14* (15), 3990-3.

60. Qian, C.-P.; Nakai, T., Perfluoro-enolate chemistry: Facile generation and unique reactivities of metal E-1-propen-2-olates. *Tetrahedron Lett.* **1988,** *29* (33), 4119-22.

61. (a) Yang, M. H.; Hunt, J. R.; Sharifi, N.; Altman, R. A., Palladium Catalysis Enables Benzylation of alpha,alpha-Difluoroketone Enolates. *Angew. Chem. Int. Ed. Engl.* **2016,** *55* (31), 9080-3; (b) Yang, M. H.; Orsi, D. L.; Altman, R. A., Ligand-controlled regiodivergent palladium-catalyzed decarboxylative allylation reaction to access alpha,alpha-difluoroketones. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (8), 2361-5.

62. Anslyn, E. V.; Dougherty, D. A., *Modern Physical Organic Chemistry*. University Science Books: 2006; p 545–568.

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.*

Fluorine Chem. **2015,** *178*, 40-46; (b) Phelan, J. P.; Ellman, J. A., Conjugate addition-enantioselective protonation reactions. *Beilstein J Org Chem* **2016,** *12*, 1203-28.

64. Zhang, X.; Cao, S., Recent advances in the synthesis and CF functionalization of gem-difluoroalkenes. *Tetrahedron Lett.* **2017,** *58* (5), 375-392.

65. (a) Zhu, L. G.; Li, Y.; Zhao, Y. C.; Hu, J. B., Nucleophilic (phenylsulfonyl)difluoromethylation of alkyl halides using PhSO2CF2SiMe3: preparation of gem-difluoroalkenes and trifluoromethyl compounds. *Tetrahedron Lett.* **2010,** *51* (47), 6150-6152; (b) Lee, C. C.; Lin, S. T., Study on the addition of hydrogen fluoride to 2,2 '-difluorostyrenes. *Journal of Chemical Research-S* **2000,** (3), 142-144; (c) Nguyen, B. V.; Burton, D. J., A new route for the preparation of substituted 2,2-difluorostyrenes and a convenient route to substituted (2,2,2-trifluoroethyl)benzenes. *J. Org. Chem.* **1997,** *62* (22), 7758-7764.

66. Bent, H. A., An Appraisal of Valence-bond Structures and Hybridization in Compounds of the First-row elements. *Chem. Rev.* **1961,** *61* (3), 275-311.

67. Amii, H.; Uneyama, K., C-F bond activation in organic synthesis. *Chem. Rev.* **2009,** *109* (5), 2119-83.

68. (a) Suda, M., Reactions of 1,1-Difluoro-1-Olefins with Electrophilic Reagents. *Tetrahedron Lett.* **1980,** *21* (26), 2555-2556; (b) Timperley, C. M.; Waters, M. J.; Greenall, J. A., Fluoroalkene chemistry Part 3. Reactions of arylthiols with perfluoroisobutene, perfluoropropene and chlorotrifluoroethene. *J. Fluorine Chem.* **2006,** *127* (2), 249-256; (c) Timperley, C. M., Fluoroalkene chemistry. *J. Fluorine Chem.* **2004,** *125* (5), 685-693;

(d) Kim, M. S.; Jeong, I. H., A highly stereoselective preparation of CF3-substituted 1-aryl-1,2-diphenylethenes: application to the synthesis of panomifene. *Tetrahedron Lett.* **2005,** *46* (20), 3545-3548.

69. (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T., 5-endo-trigonal cyclization of o-substituted gem-difluorostyrenes: Syntheses of 2-fluorinated indoles, benzo[b]furans and benzo[b]thiophenes. *Chem. Commun.* **1997,** (16), 1537-1538; (b) Saito, A.; Okada, M.; Nakamura, Y.; Kitagawa, O.; Horikawa, H.; Taguchi, T., Carbocyclization reactions of terminally difluorinated alkenyl active methine compounds mediated by SnCl4 and amine. *J. Fluorine Chem.* **2003,** *123* (1), 75-80; (c) Xiong, Y.; Zhang, X.; Huang, T.; Cao, S., Synthesis of N-(alpha-fluorovinyl)azoles by the reaction of difluoroalkenes with azoles. *J. Org. Chem.* **2014,** *79* (14), 6395-402; (d) Zhang, X. X.; Lin, Y. Y.; Zhang, J.; Cao, S., Base-mediated direct fluoroalkenylation of 2-phenyl-1,3,4-oxadiazole, benzothiazole and benzoxazole with *gem*-difluoroalkenes. *Rsc Adv* **2015,** *5* (11), 7905-7908.

70. Tian, P.; Wang, C. Q.; Cai, S. H.; Song, S.; Ye, L.; Feng, C.; Loh, T. P., F(-) Nucleophilic-Addition-Induced Allylic Alkylation. *J. Am. Chem. Soc.* **2016,** *138* (49), 15869-15872.

71. (a) Gao, B.; Zhao, Y.; Hu, J., AgF-mediated fluorinative cross-coupling of two olefins: facile access to alpha-CF3 alkenes and beta-CF3 ketones. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (2), 638-42; (b) Gao, B.; Zhao, Y.; Ni, C.; Hu, J., AgF-mediated fluorinative homocoupling of gem-difluoroalkenes. *Org. Lett.* **2014,** *16* (1), 102-5.

72. Vela, J.; Smith, J. M.; Yu, Y.; Ketterer, N. A.; Flaschenriem, C. J.; Lachicotte, R. J.; Holland, P. L., Synthesis and reactivity of low-coordinate iron(II) fluoride complexes

and their use in the catalytic hydrodefluorination of fluorocarbons. *J. Am. Chem. Soc.* **2005,** *127* (21), 7857-70.

73. (a) Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S., Base-Free Hiyama Coupling Reaction via a Group 10 Metal Fluoride Intermediate Generated by C-F Bond Activation. *Organometallics* **2014,** *33* (14), 3669-3672; (b) Ohashi, M.; Saijo, H.; Shibata, M.; Ogoshi, S., Palladium-Catalyzed Base-Free Suzuki-Miyaura Coupling Reactions of Fluorinated Alkenes and Arenes via a Palladium Fluoride Key Intermediate. *Eur. J. Org. Chem.* **2013,** *2013* (3), 443-447; (c) Ohashi, M.; Kambara, T.; Hatanaka, T.; Saijo, H.; Doi, R.; Ogoshi, S., Palladium-catalyzed coupling reactions of tetrafluoroethylene with arylzinc compounds. *J. Am. Chem. Soc.* **2011,** *133* (10), 3256-9; (d) Dai, W.; Xiao, J.; Jin, G.; Wu, J.; Cao, S., Palladium- and nickel-catalyzed Kumada cross-coupling reactions of gem-difluoroalkenes and monofluoroalkenes with Grignard reagents. *J. Org. Chem.* **2014,** *79* (21), 10537-46.

74. (a) Dai, W. P.; Zhang, X. X.; Zhang, J.; Lin, Y. Y.; Cao, S., Synthesis of Exocyclic Trisubstituted Alkenes via Nickel-Catalyzed Kumada-Type Cross-Coupling Reaction of gem-Difluoroalkenes with Di-Grignard Reagents. *Adv. Synth. Catal.* **2016,** *358* (2), 183-187; (b) Xiong, Y.; Huang, T.; Ji, X.; Wu, J.; Cao, S., Nickel-catalyzed Suzuki-Miyaura type cross-coupling reactions of (2,2-difluorovinyl)benzene derivatives with arylboronic acids. *Org Biomol Chem* **2015,** *13* (27), 7389-92.

75. (a) Yamada, S.; Shimoji, K.; Takahashi, T.; Konno, T.; Ishihara, T., An effective preparation of sulfonyl- or sulfinyl-substituted fluorinated alkenes and their stereoselective addition-elimination reactions with organocuprates. *Chem Asian J* **2010,**

5 (8), 1846-53; (b) Yamada, S.; Noma, M.; Hondo, K.; Konno, T.; Ishihara, T., Preparation and Addition–Elimination Reactions of Benzyl a,b,b-Trifluoroacrylate. A New Stereoselective Approach to (*Z*)-b-Substituted a,b-Difluoroacrylates. *J. Org. Chem.* **2008,** *73*, 522–8; (c) Yamada, S.; Noma, M.; Konno, T.; Ishihara, T.; Yamanaka, H., Novel synthesis of (Z)-difluoroacrylates via a highly stereoselective addition-elimination reaction. *Org. Lett.* **2006,** *8* (5), 843-5; (d) Dai, W.; Shi, H.; Zhao, X.; Cao, S., Sterically Controlled Cu-Catalyzed or Transition-Metal-Free Cross-Coupling of gem-Difluoroalkenes with Tertiary, Secondary, and Primary Alkyl Grignard Reagents. *Org. Lett.* **2016,** *18* (17), 4284-7; (e) Zhang, X.; Dai, W.; Wu, W.; Cao, S., Copper-Catalyzed Coupling Cyclization of gem-Difluoroalkenes with Activated Methylene Carbonyl Compounds: Facile Domino Access to Polysubstituted Furans. *Org. Lett.* **2015,** *17* (11), 2708-11.

76. (a) Kikushima, K.; Sakaguchi, H.; Saijo, H.; Ohashi, M.; Ogoshi, S., Copper-mediated One-pot Synthesis of Trifluorostyrene Derivatives from Tetrafluoroethylene and Arylboronate. *Chem. Lett.* **2015,** *44* (7), 1019-1021; (b) Tian, P.; Feng, C.; Loh, T. P., Rhodium-catalysed C(sp(2))-C(sp(2)) bond formation via C-H/C-F activation. *Nat Commun* **2015,** *6*, 7472; (c) Thornbury, R. T.; Toste, F. D., Palladium-Catalyzed Defluorinative Coupling of 1-Aryl-2,2-Difluoroalkenes and Boronic Acids: Stereoselective Synthesis of Monofluorostilbenes. *Angew. Chem. Int. Ed. Engl.* **2016,** *55* (38), 11629-32; (d) Kong, L.; Zhou, X.; Li, X., Cobalt(III)-Catalyzed Regio- and Stereoselective alpha-Fluoroalkenylation of Arenes with gem-Difluorostyrenes. *Org. Lett.* **2016,** *18* (24), 6320-6323.

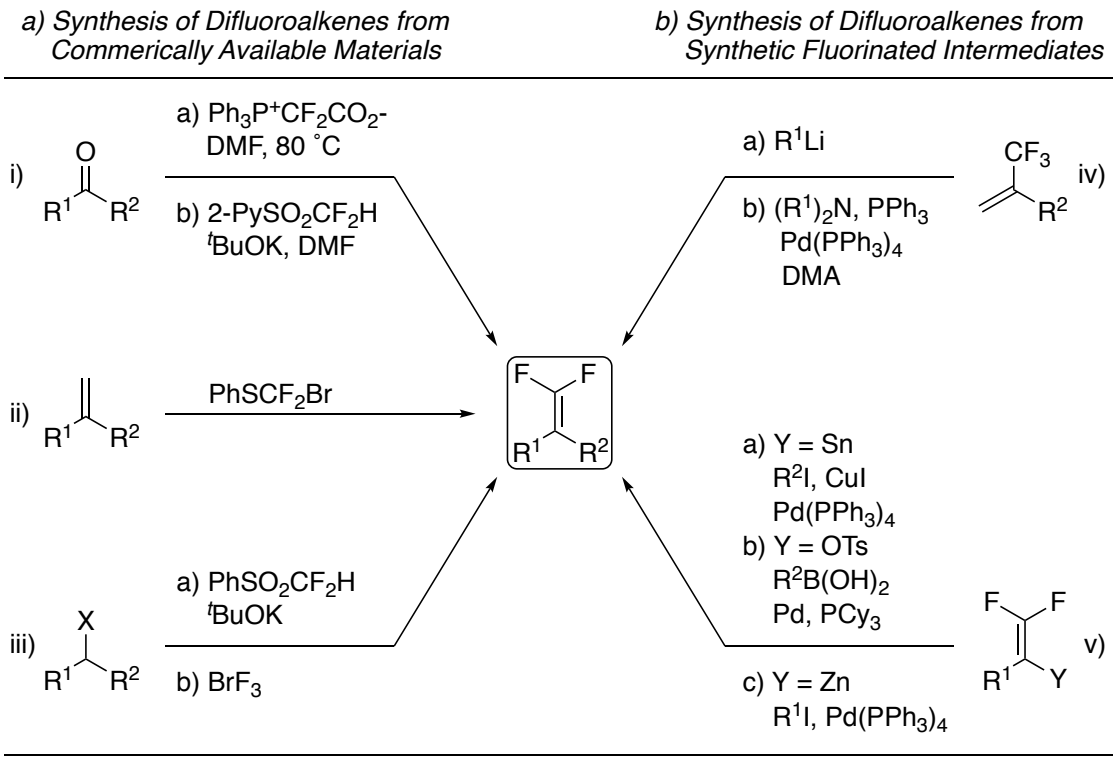
77. (a) Zheng, J.; Lin, J. H.; Cai, J.; Xiao, J. C., Conversion between difluorocarbene and difluoromethylene ylide. *Chemistry* **2013,** *19* (45), 15261-6; (b) Zheng, J.; Cai, J.; Lin, J. H.; Guo, Y.; Xiao, J. C., Synthesis and decarboxylative Wittig reaction of difluoromethylene phosphobetaine. *Chem. Commun.* **2013,** *49* (68), 7513-5; (c) Krishnamoorthy, S.; Kothandaraman, J.; Saldana, J.; Prakash, G. K. S., Direct Difluoromethylenation of Carbonyl Compounds by Using TMSCF3: The Right Conditions. *Eur. J. Org. Chem.* **2016,** *2016* (29), 4965-4969; (d) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J., gem-Difluoroolefination of diaryl ketones and enolizable aldehydes with difluoromethyl 2-pyridyl sulfone: new insights into the Julia-Kocienski reaction. *Chemistry* **2014,** *20* (25), 7803-10; (e) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J., gem-Difluoroolefination of Diazo Compounds with TMSCF3 or TMSCF2Br: Transition-Metal-Free Cross-Coupling of Two Carbene Precursors. *J. Am. Chem. Soc.* **2015,** *137* (45), 14496-501; (f) Gogsis, T. M.; Sobjerg, L. S.; Lindhardt, A. T.; Jensen, K. L.; Skrydstrup, T., Direct Vinylation and Difluorovinylation of Arylboronic Acids Using Vinyl- and 2,2-Difluorovinyl Tosylates via the Suzuki-Miyaura Cross Coupling. *J. Org. Chem.* **2008,** *73*, 3404–10; (g) Ichitsuka, T.; Takanohashi, T.; Fujita, T.; Ichikawa, J., A versatile difluorovinylation method: Cross-coupling reactions of the 2,2-difluorovinylzinc-TMEDA complex with alkenyl, alkynyl, allyl, and benzyl halides. *J. Fluorine Chem.* **2015,** *170*, 29-37.

Chapter 2 – Organocatalytic Reactions of Thiols with *gem*-Difluoroalkenes

2.1. Metal-Free Reactions of gem*-Difluoroalkenes*

Gem-difluoroalkenes are an easily accessed[1] 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[1a-f, 1n-p] or Julia-Kocienski[1j, 1q, 1r] olefinations (**Scheme 2-1i**), alkenes through radical functionalization (**Scheme 2-1ii**),[1s] and alkyl halides *via* nucleophilic addition reactions (**Scheme 2-1iii**).[1t-v] Other methods to access *gem*-difluoroalkenes require synthesis of fluorinated intermediates, such as S_N2' reactions with vinyl trifluoromethanes (**Scheme 2-1iv**),[1w-ac] or cross coupling with difluoroethylene derived compounds, such as difluorovinyl organo-zinc compounds,[1g, 1af] difluorovinyl stannanes,[1ad] and difluorovinyl tosylates (**Scheme 2-1v**).[1ae] Due to the wide variety of methods and starting materials to access *gem*-difluoroalkenes, many functionalization reactions of this moiety have been developed.

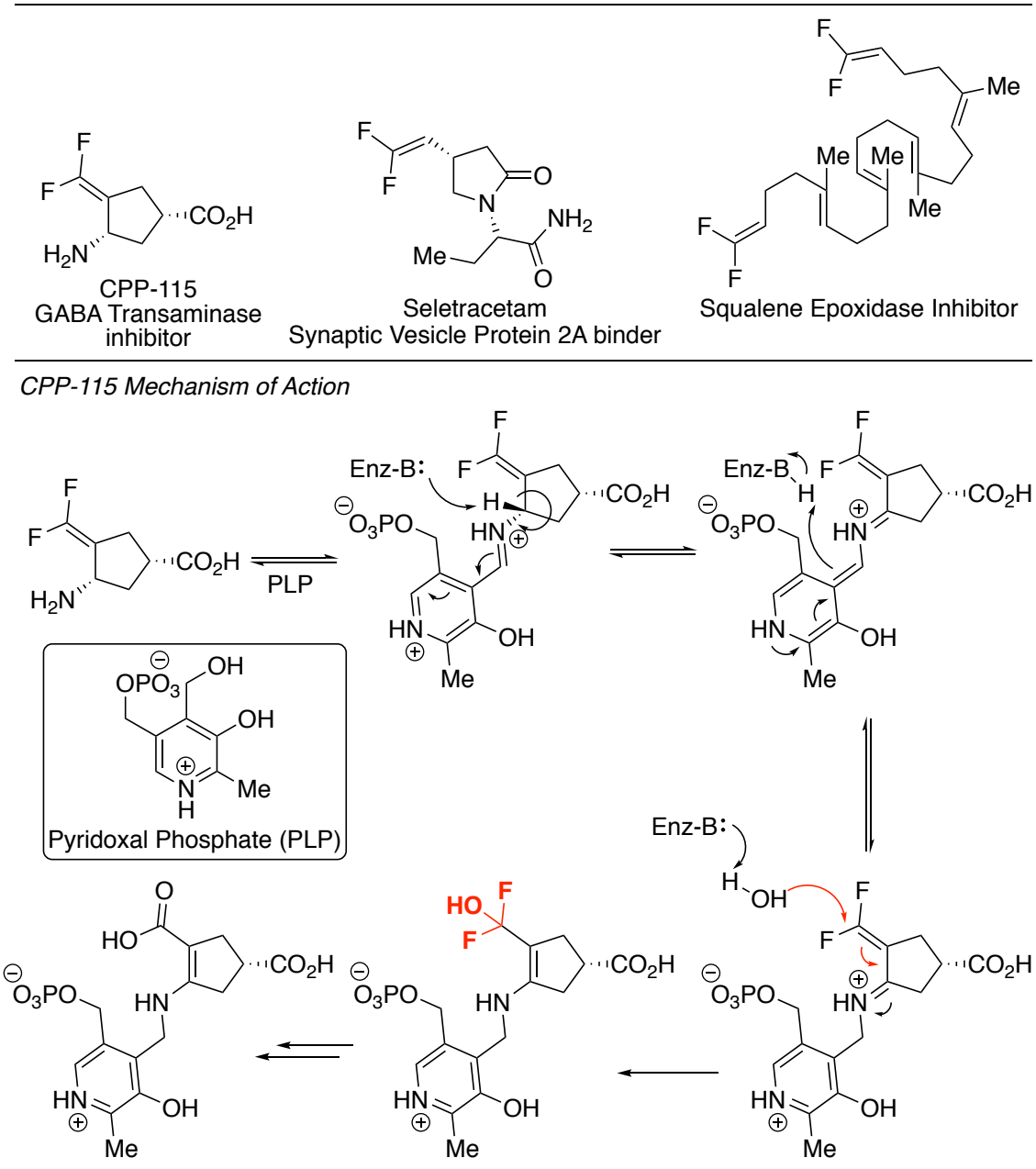
Scheme 2-1: Methods to Synthesize *gem*-Difluoroalkenes



The incorporation of fluorine in *gem*-difluoroalkenes perturbs physicochemical properties thus enabling new reactivity that contrasts the reactivity of the non-fluorinated alkene.[1h, 2] The σ-withdrawing effects of the fluorine substituents activate the difluorinated position for regioselective nucleophilic attack under both transition metal-catalyzed and non-catalyzed conditions (**Figure 2-2**).[1h, 1x] The difluorinated carbon of the alkene is electrophilic, which activates *gem*-difluoroalkenes for regioselective attack at the α-position. This activation delivers a distinct regioselectivity from common alkene activating groups, such as carbonyls and nitro groups, which react at the β–position relative to the activating group. Combined, these physicochemical characteristics allow *gem*-

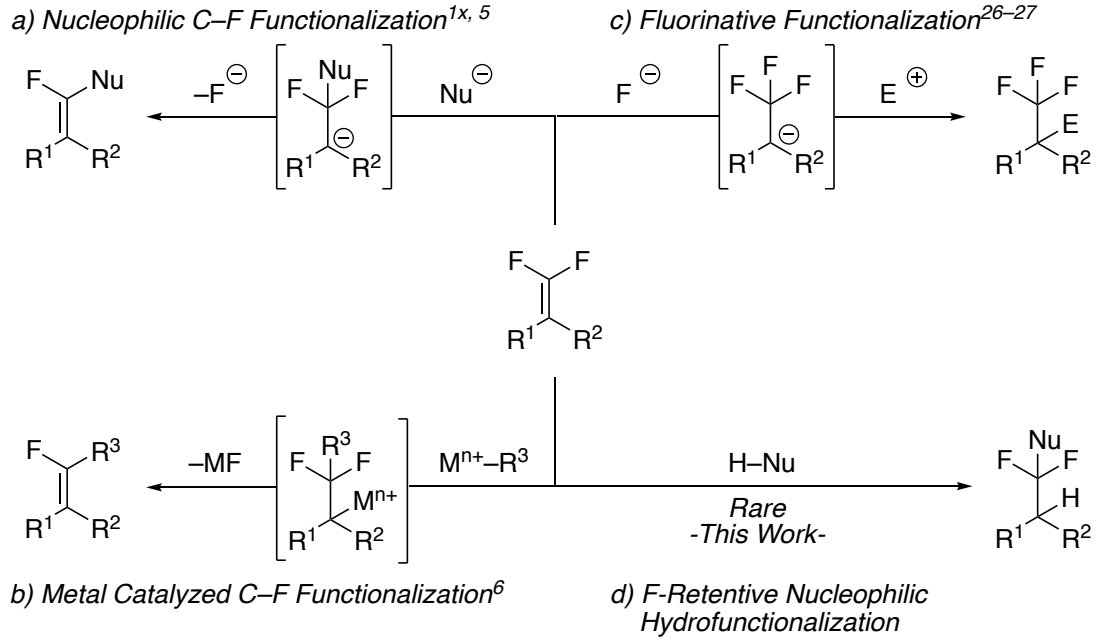
difluoroalkenes to serve as mechanism-based inhibitors of enzymes with nucleophilic residues in the active sites (**Figure 2-1**).[3]

Figure 2-1: Mechanism Based Inhibitors Containing *gem*-Difluoroalkenes[3b, 4]



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

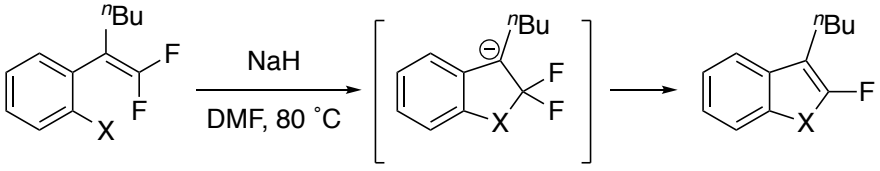


The fluoroalkene products are lipophilic, conformationally locked mimics of peptide amide bonds,[7] found in a variety of bioactive compounds. Typical fluoroalkene synthesis proceeds through the direct fluorination of non-fluorinated starting materials, including Shapiro fluorination,[8] olefination reactions with mono-fluorinated ylides,[9] or the electrophilic fluorination of alkenyl-metal species.[10] Alternate methods of fluoroalkene

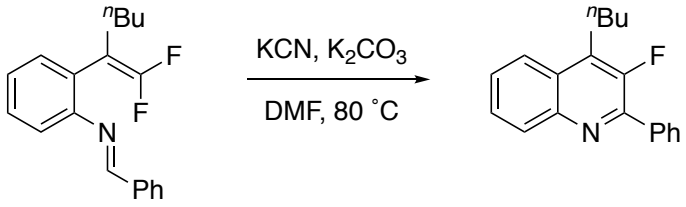
synthesis require fluorinated starting materials, such as elimination reactions of fluoroalkanes,[11] S_N2' reactions of allylic *gem*-difluorides,[12] or transition-metal catalyzed cross-coupling reactions.[1ae, 13] Fluoroalkene synthesis from *gem*-difluoroalkenes occurs *via* an orthogonal process, 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 Funtionalization of gem*-Difluoroalkenes: Synthesis of 2-F Substituted Five Member Heterocycles*[14]



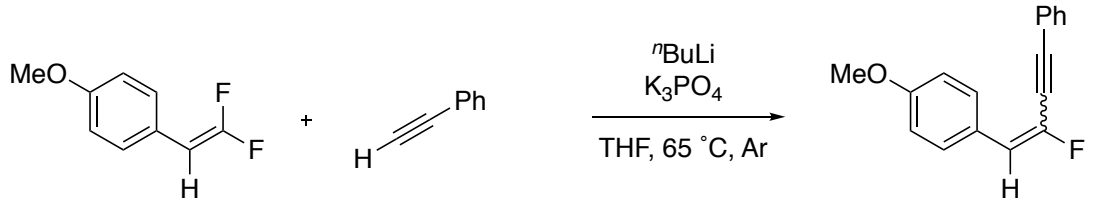
b) Representative C–F Funtionalization of gem*-Difluoroalkenes: Synthesis of Six Member Heterocycles*[15]



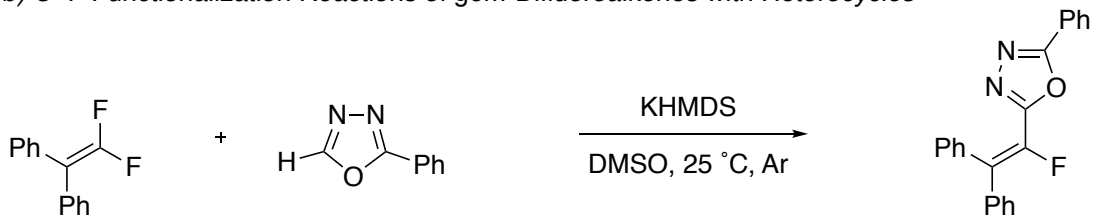
Intermolecular nucleophilic addition reactions to *gem*-difluoroalkenes exploit the same reactivity. However, the intermolecular attack of C-based nucleophiles to *gem*-difluoroalkenes requires strong bases, such as organolithium species.[16] Aryl and alkyl lithium species efficiently react with TMS-containing *gem*-difluoroalkenes,[16] while alkynyl lithium nucleophiles react with β,β-difluorostyrenes to generate β-fluoroenynes (**Scheme 2-3a**).[17] More acidic, activated C-based nucleophiles, such as heterocycles[18] (**Scheme 2-3b**) or malonates,[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.[20] Grignard reagents react without base, and preferentially react with *gem*-difluoroalkenes over carbonyls in an α,β-unsaturated system (**Scheme 2-3c**),[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_3PO_4, providing fluorovinyl aryl ethers *via* a three component reaction from a boronic acid nucleophile and O_2 (**Scheme 2-3d**).[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 *gem*-Difluoroalkenes

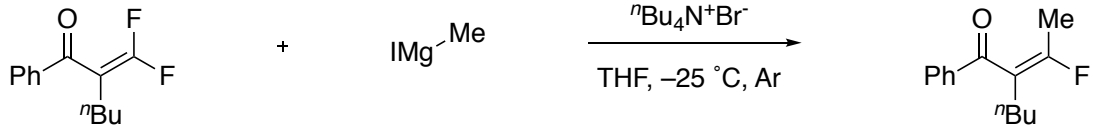
a) C–F Functionalization Reactions of gem*-Difluoroalkenes with Alkynyl Lithium Nucleophiles*[17]



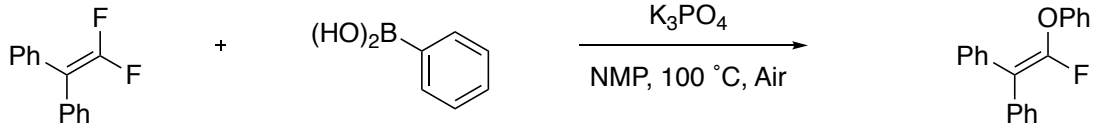
b) C–F Functionalization Reactions of gem*-Difluoroalkenes with Heterocycles*[18]



c) C–F Functionalization Reactions of gem*-Difluoroalkenes with Grignard Reagents*[21]



d) Three Component C–F Functionalization Reaction of gem*-Difluoroalkenes*[22]

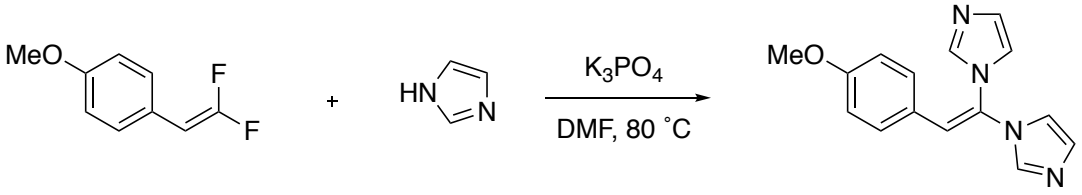


For intermolecular reactions of N- or S-based nucleophiles with *gem*-difluoroalkenes sequential nucleophilic addition / fluoride elimination reactions are facile, resulting in non-fluorinated products (**Scheme 2-4a**).[23] For these nucleophiles, achieving a single nucleophilic addition / fluoride elimination reaction requires control of nucleophile equivalents and reaction time (**Scheme 2-4b**).[24] However, mono-addition of a basic N-derived nucleophile results in a non-fluorinated product. When a basic nitrogen sits α to a C–F bond, the lone pair electrons of N eliminate fluoride to generate imines (**Scheme**

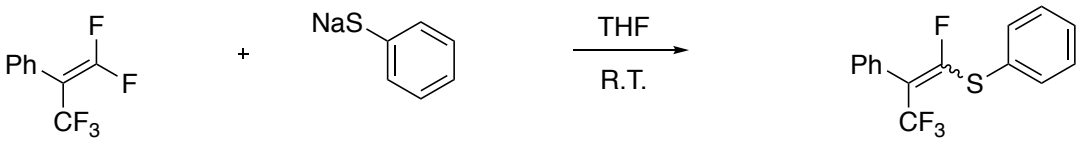
2-4c).[25] This elimination makes the fluorine-retentive intermolecular functionalization of *gem*-difluoroalkenes with N-based nucleophiles to generate basic-nitrogen containing products an immense challenge.

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

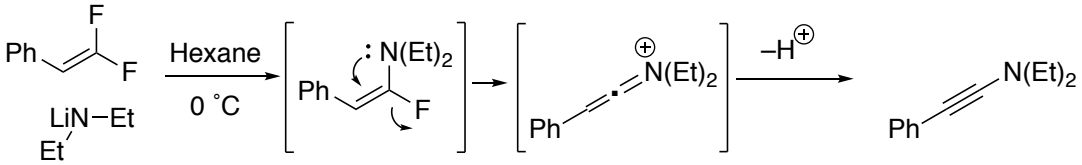
a) Representative Double C–F Functionalization Reactions of gem*-Difluoroalkenes*[23]



b) Representative Mono C–F Functionalization Reactions of gem*-Difluoroalkenes*[24]



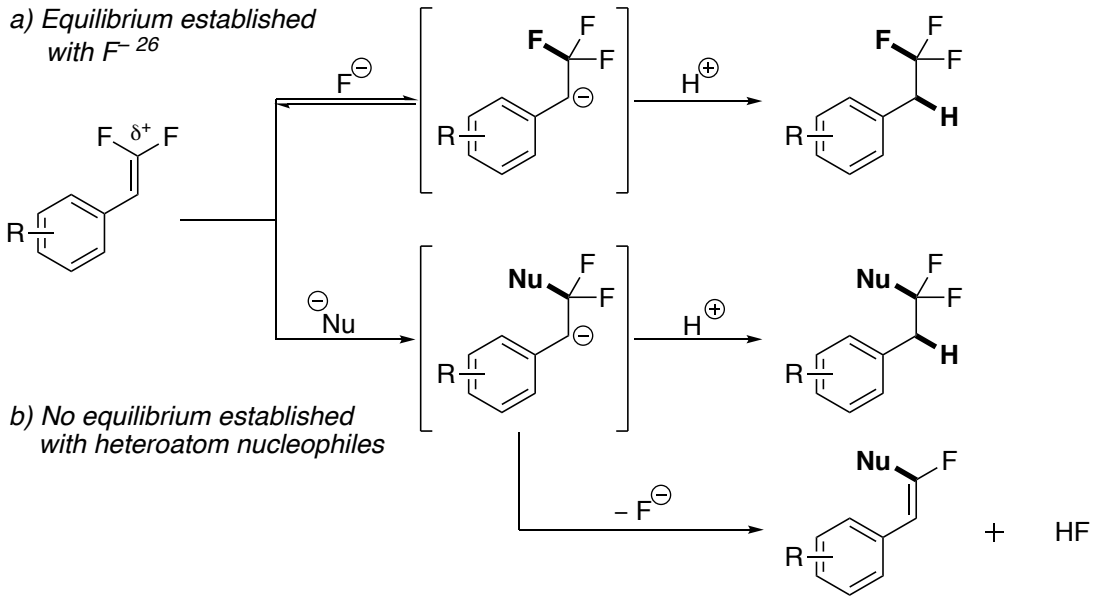
c) Reactions of Amines with gem*-Difluoroalkenes Provide Non-Fluorinated Products*[25]



Uniquely, the addition of F^- to *gem*-difluoroalkenes to form trifluoromethanes[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 α-trifluoromethyl anion that is trapped with residual H_2O (**Figure 2-3a**). Initially, these reactions required the use of crown ethers and the explicit preparation, isolation, and purification of the *gem*-difluoroalkene.[1t] 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.[26] Other reactions exploit this equilibrium process to intercept the β-fluoroanion with transition metals and further functionalizing *gem*-difluoroalkenes.[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 (**Figure 2-3b**). Thus, general examples of such "fluorine-retentive" nucleophilic hydro-functionalization of *gem*-difluoroalkenes remain elusive (**Figure 2-2d**).

Figure 2-3: Fluorinated Alkenes React *via* Nucleophilic Addition / Protonation.

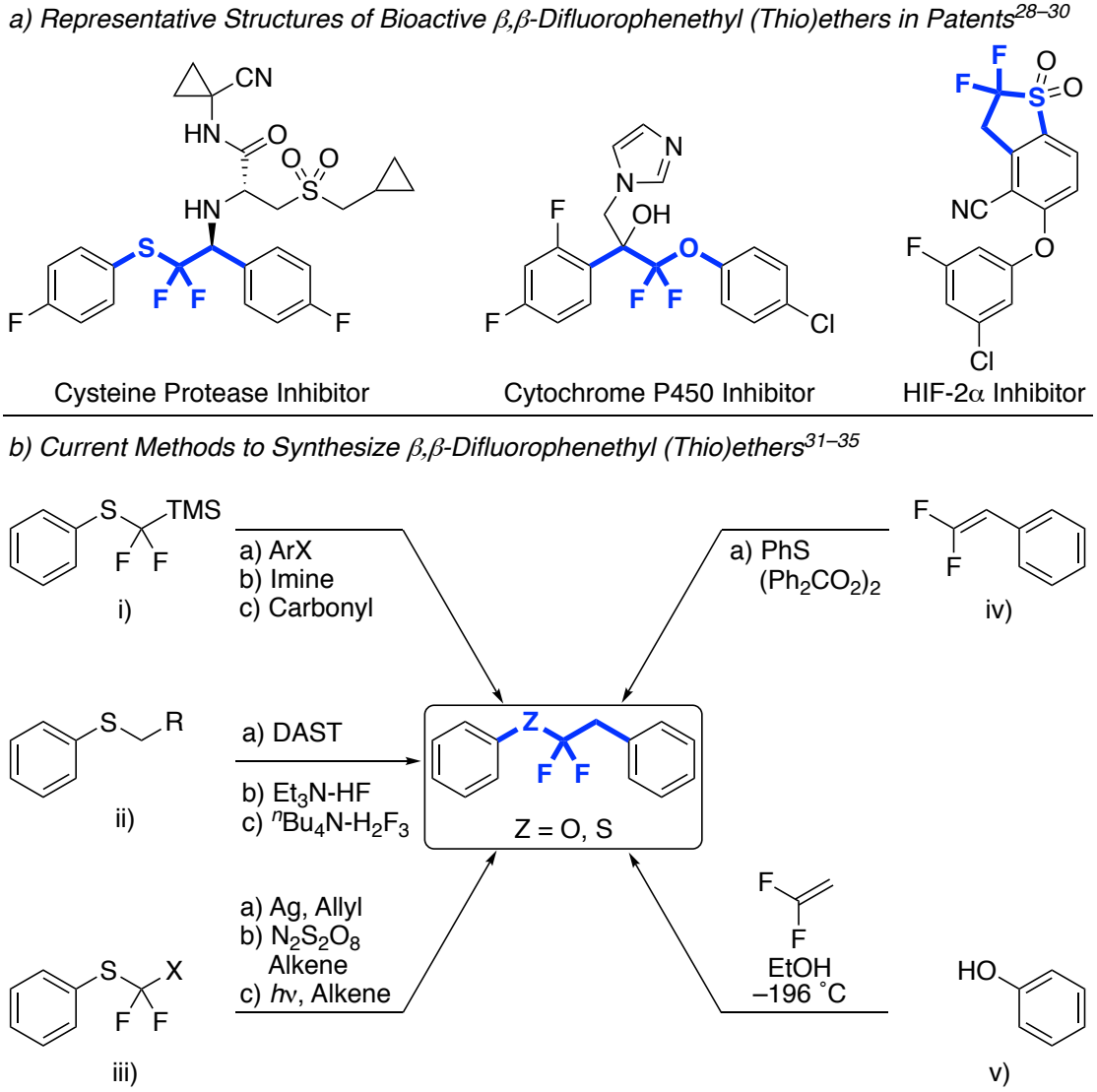


Such an undeveloped general intermolecular "fluorine-retentive" nucleophilic functionalization of *gem*-difluoroalkenes would allow access to underexplored fluorinated functional groups. Specifically, fluorine-retentive reactions with thiols would provide access to α,α-difluoroalkylthioethers from common, 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[28] and anti-inflammatory[29] agents and agrichemicals (**Figure 2-4a**).[30] Only a few suboptimal strategies exist to form α,α-difluoroalkylthioethers, leaving most of the potentially bioactive α,α-difluoroalkylthioethers prophetic in patents. Of these strategies, nucleophilic substitution reactions of silylated[31] or halogenated (**Figure 2-4bi**)[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 α,α-difluoroalkylthioethers are more direct; however, the existing radical methods use a limited set of starting materials (**Figure 2-4biii**).[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**).[34] In a non-convergent method, oxidative methods that utilize harsh fluorinating reagents enable direct access to the desired α,α-difluoroalkylthioether substructure (**Figure 2-4bii**).[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 α,α-difluoroalkylthioethers *via* the base-catalyzed hydrofunctionalization of *gem*-difluoroalkenes with thiols, exploiting a nucleophilic addition / protonation mechanism,

complements existing methods to access α,α-difluoroalkylthioethers, and should facilitate access to valuable, underexplored bioactive compounds.

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



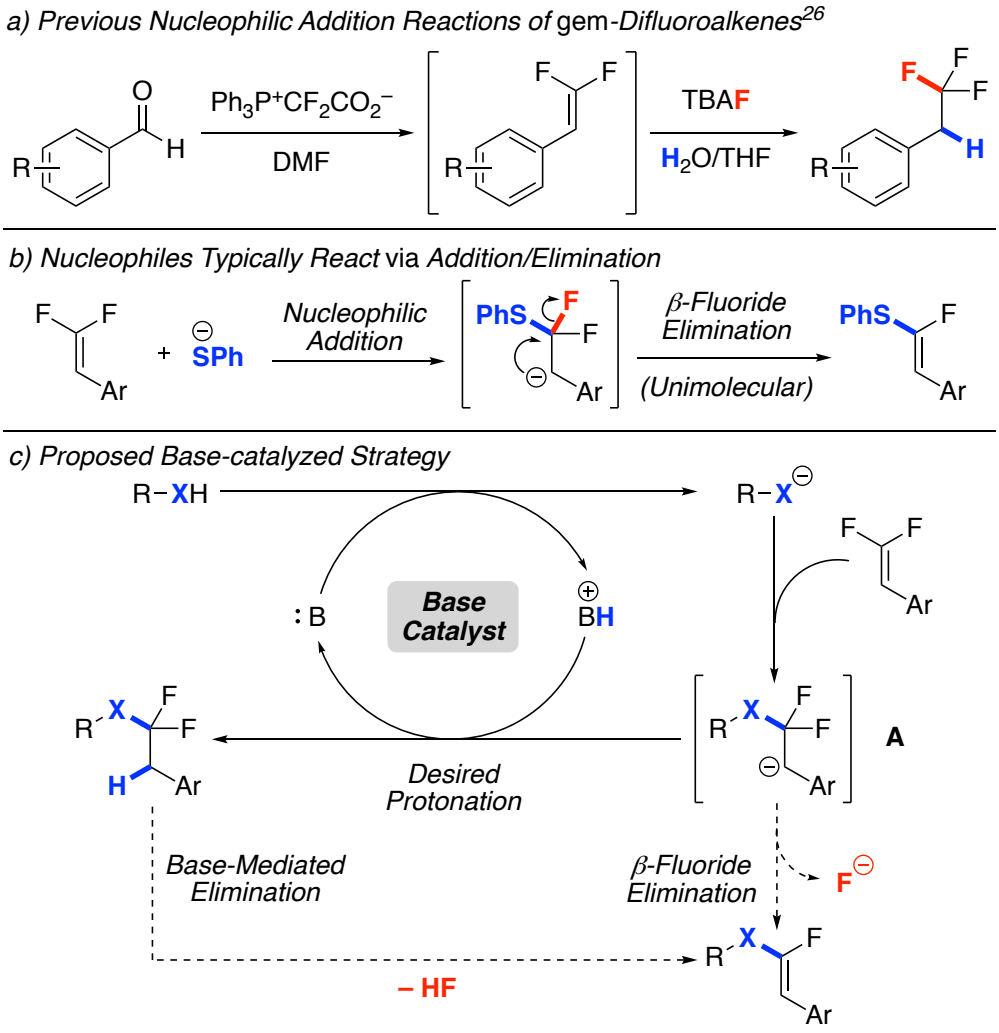
2.2. Base Catalysis Enables Access to β,β-Difluorophenethyl Arylthioethers

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 β-fluoride elimination.

Once the unstable β-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 β,β-difluorophenethyl thioether product is significantly less acidic than either the protonated catalyst or thiol, proton transfer might occur faster than β–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.

Scheme 2-5: Base Catalyst Enables Nucleophilic Addition to *gem*-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),[23b, 23c] 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

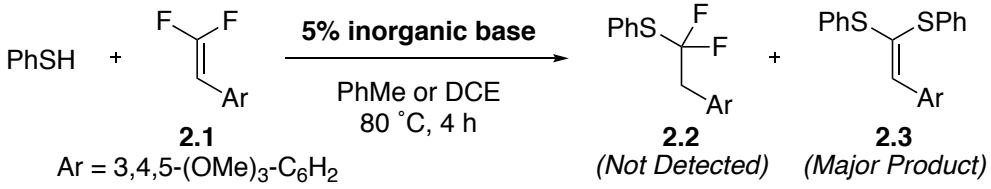
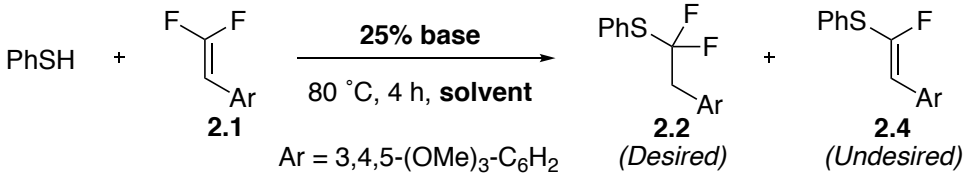
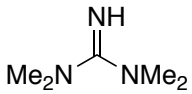


Table 2-1: Optimization of the Reaction Conditions[a]

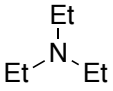


entry	base	solvent	conv/yield [%][b]	**2.2:2.4**[b]
1	TMG	DCE	>99/96	>25:1
2	Et_3N	DCE	>99/82	>25:1
3	DMAP	DCE	>99/67	>25:1[e]
4	TBD	DCE	>99/77	>25:1
5[c]	PhSNa	DCE	15/<1	N/A
6	TMG	$PhNO_2$	94/60	4:1
7	TMG	DMF	>99/36	1:1.2
8	TMG	PhMe	56/8	>25:1

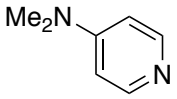
9	TMG	MeCN	83/15	1:3.5
10[d]	TMG	DCM	>99/88	>25:1
11[c]	TMG	DCE	>99/91	>25:1



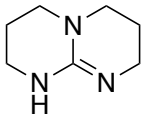
TMG



Et_3N



DMAP



TBD

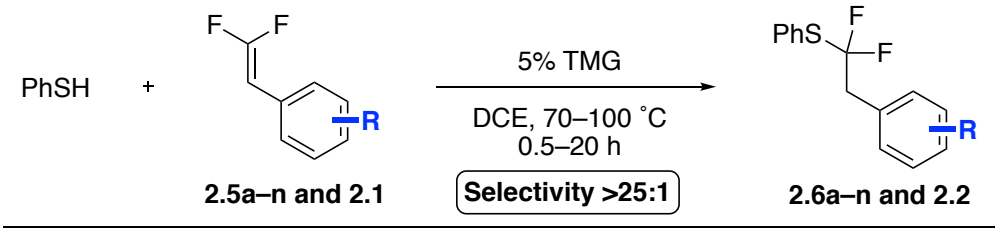
[a] Standard conditions: **2.1** (1.0 equiv.), PhSH (2.0 equiv.), solvent (0.50 M), base (25 mol %), 80 ˚C, 4 h. [b] Determined by ^{19}F NMR standardized with $PhCF_3$ (1.0 equiv.). [c] Solvent (0.25 M), base (5.0 mol %), 70 ˚C, 0.5 h. [d] 40 ˚C. [e] Reaction generated a sulfoxide side product. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

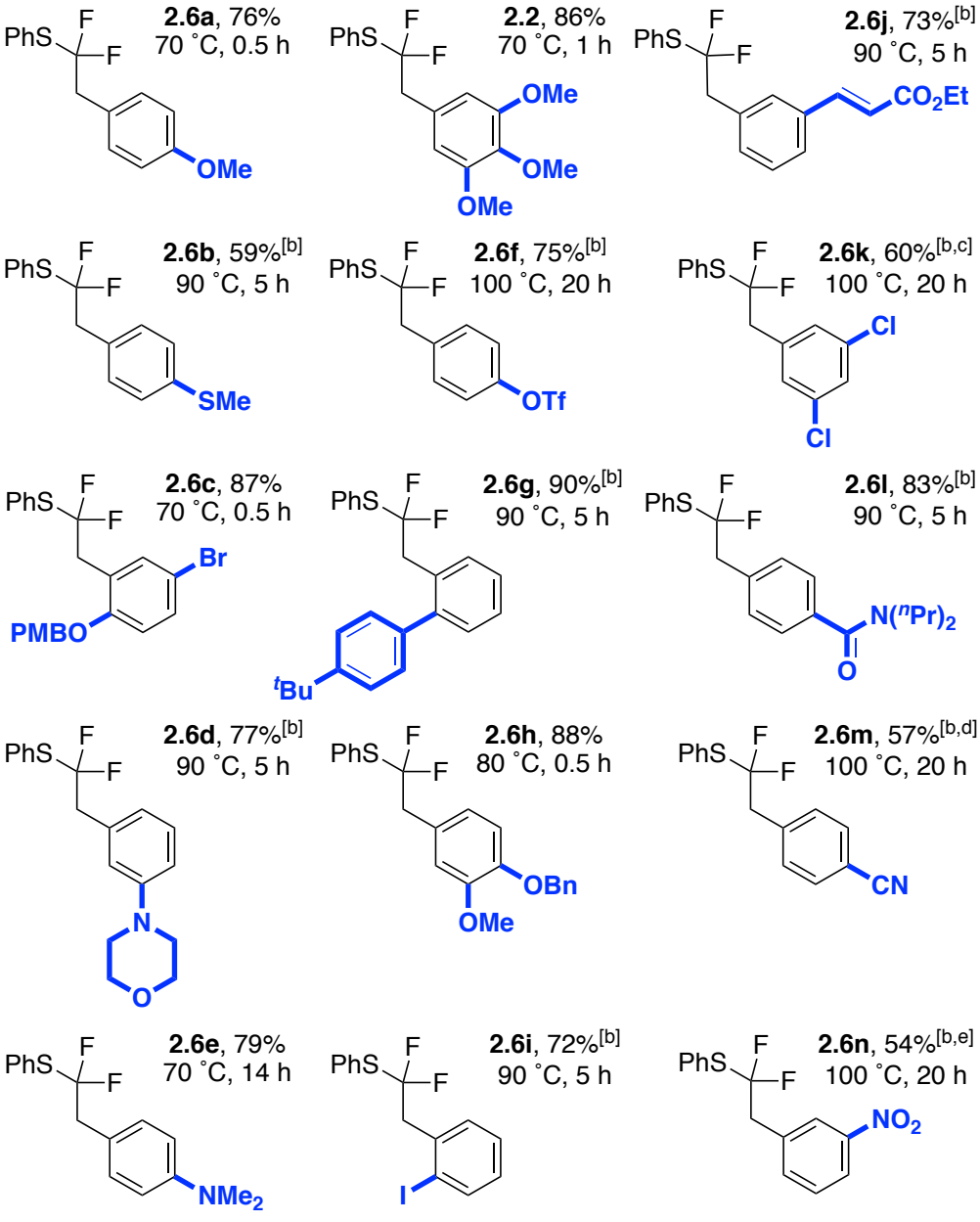
Of note, as the scale of the reaction increased, the optimized reaction conditions (5% TMG, 1.5 equiv. thiophenol, 70 ˚C, 0.5–4 h) showed reduced efficiency. Specifically, when the scale increase from a 0.1 mmol exploratory scale to a 0.5 mmol preparative scale, the reaction quickly approached completion (~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, 2.6l–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–fluorovinylthioether side product (6.6:1–13:1).

Scheme 2-7: Scope of Distinct β,β-Difluorostyrenes[a]

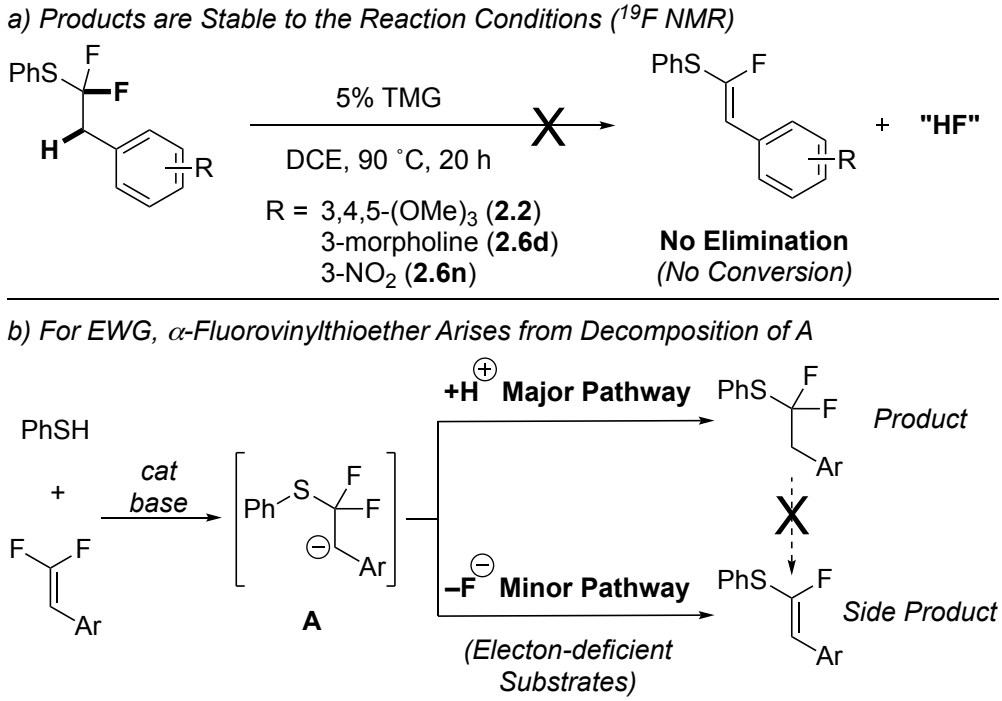




[a] Standard conditions: **2.5a–n** (1.0 equiv.), PhSH (2.0 equiv.), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by ^{19}F NMR analysis of the reaction mixture, unless otherwise indicated. Yields represent an average of two runs. [b] PhSH (3.0 equiv.).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

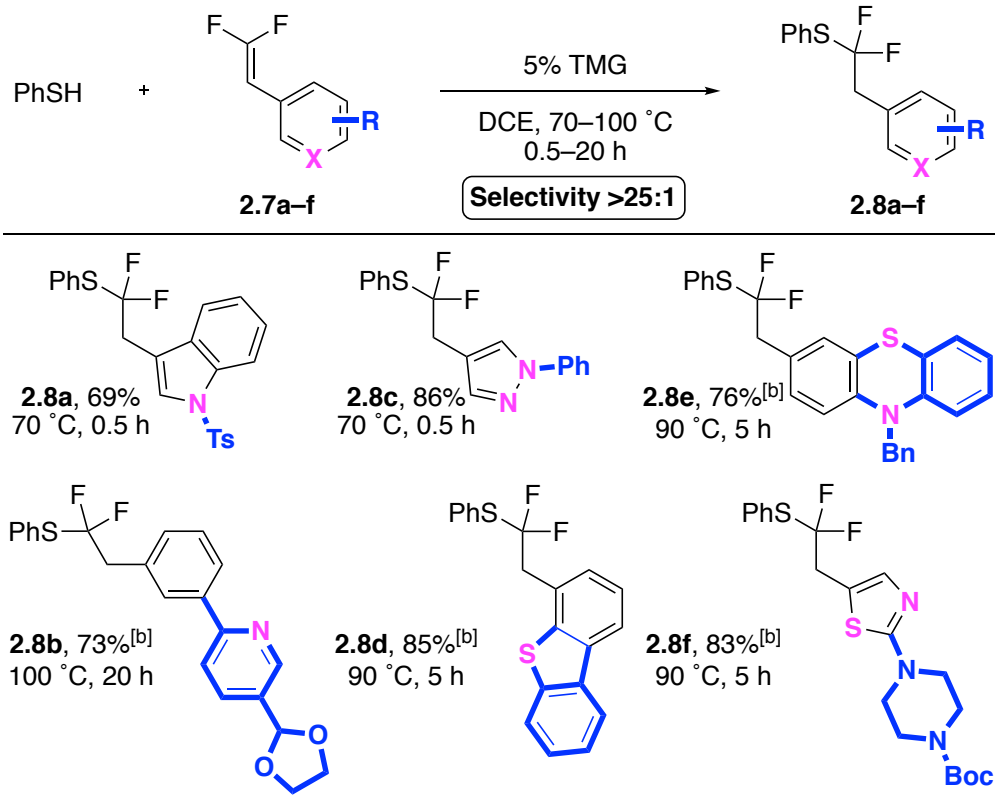
To determine whether the reduced selectivity arose from the instability of the product or of anionic intermediate **A** (**Scheme 2-5c**), purified products **2.2**, **2.6d**, and **2.6n** were re-subjected to the reaction conditions (**Scheme 2-8a**). ^{19}F NMR analysis of the reaction mixtures showed 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 (benzothiophene **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 β,β-Difluorostyrenes[a]

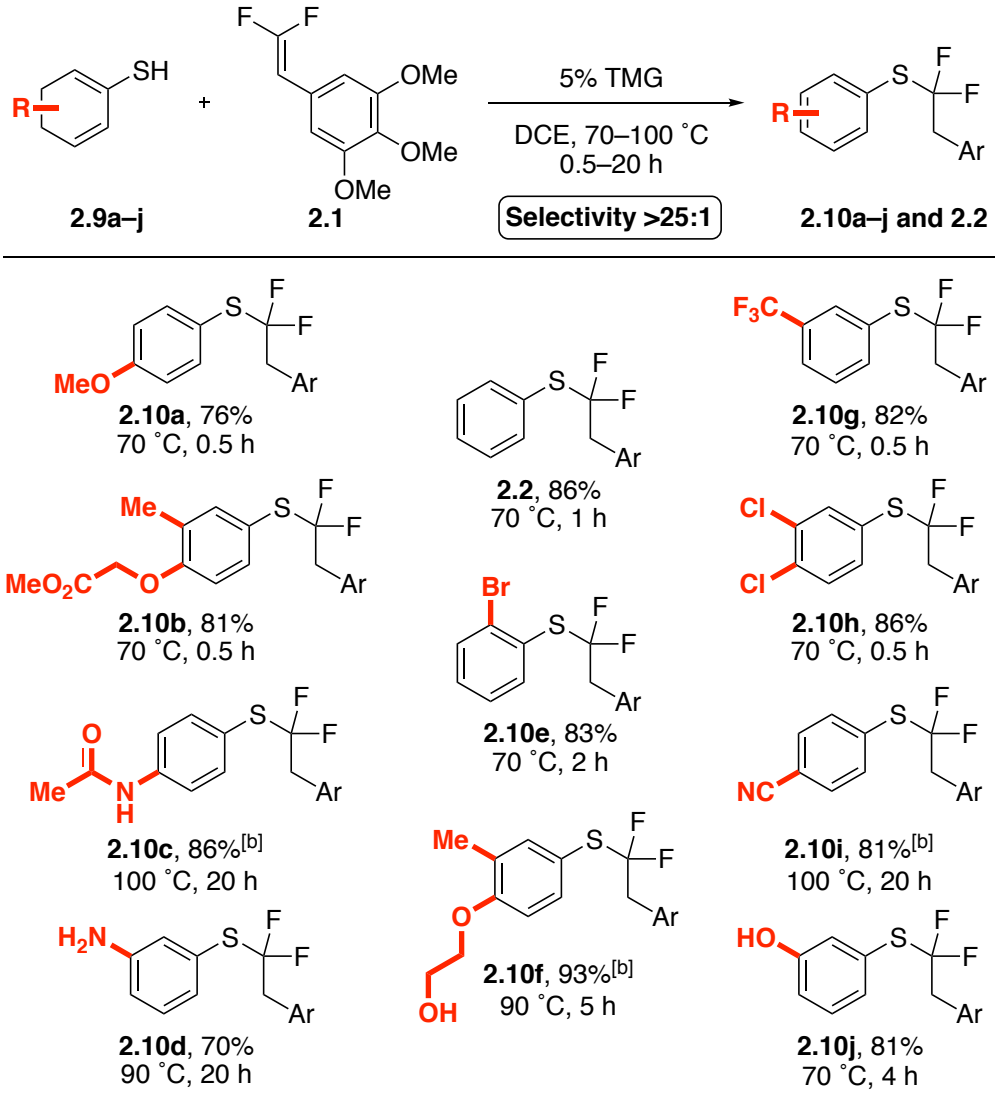


[a] Standard conditions: **2.7a–n** (1.0 equiv.), PhSH (2.0 equiv.), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by ^{19}F NMR analysis of the reaction mixture. Yields represent an average of two runs. [b] PhSH (3.0 equiv.). Ts = 4-toluenesulfonyl.

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 α,α-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[a]



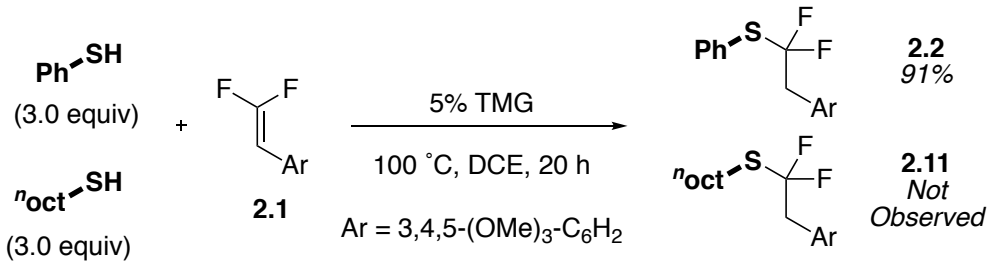
[a] Standard conditions: **2.1** (1.0 equiv.), ArSH **2.9a–j** (2.0 equiv.), TMG (5.0 mol %), DCE (0.25 M), temperature and time as indicated. Selectivity >25:1 as determined by ^{19}F

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*-methoxylbenzyl-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



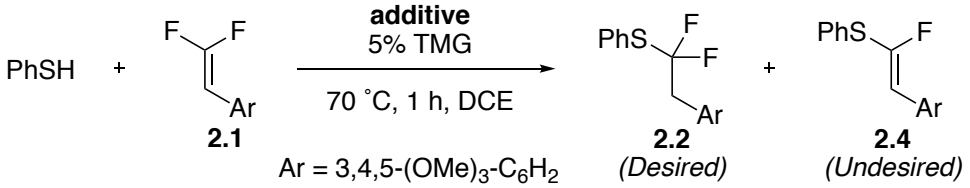
2.3. Mechanistic Considerations

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.

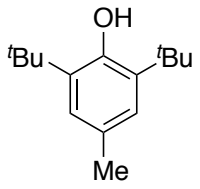
Several experiments support the proposed addition / protonation pathway over a mechanism involving S-based radicals. First, the reaction ran smoothly in the absence of light and O_2, which are known radical initiators of thiols (**Table 2-2**, entry 1–3). Second, although the reaction utilizes TMG (which can have inorganic impurities that can oxidize a thiolate),[37] other amine bases that lack such impurities (e.g. distilled Et_3N) are competent base catalysts (**Table 2-1**, entry 2). Third, when running the reaction in CD_2Cl_2 (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.

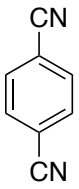
Table 2-2: Experiments for Mechanistic Determination[a]



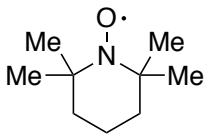
entry	additive	conv/yield [%][b]	**2.2:2.4**[b]
1[c]	O_2	>99/90	>25:1
2[c]	Dark	>99/90	>25:1
3[c]	O_2 and Dark	>99/95	>25:1
4[d]	DCM-D_2	>99/86	>25:1
5	1,4-$(CN)_2$-C_6H_4	>99/88	>25:1
6	BHT	>99/82	>25:1
7	TEMPO	>0/0	N/A



BHT



1,4-$(CN)_2$-C_6H_4



TEMPO

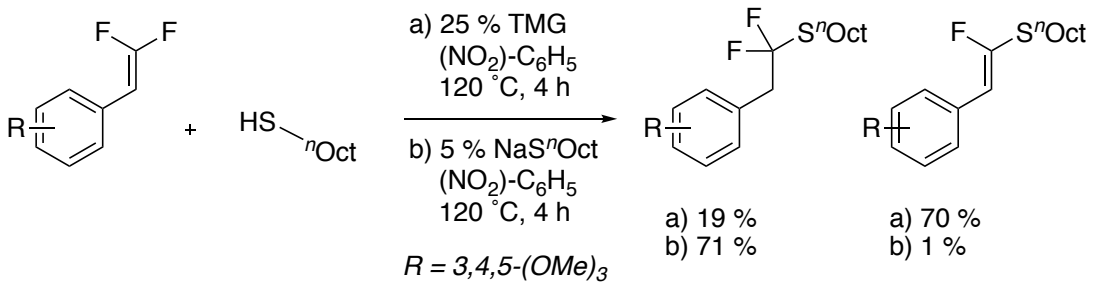
[a] Standard conditions: **2.1** (1.0 equiv.), PhSH (2.0 equiv.), additive (2.0 equiv.), DCE (0.50 M), TMG (5 mol %), 70 ˚C, 1 h. [b] Determined by ^{19}F NMR standardized with $PhCF_3$ (1.0 equiv.). [c] Run at 80 ˚C. [d] Run in DCM-D_2 instead of DCE for 4 h at 40 ˚C. BHT = Butylated Hydroxy Toluene.

2.4. Organocatalysis to Access β,β–Difluorophenethyl Alkylthioethers

As evidenced in **Scheme 2-11**, alkyl thiols are less competent nucleophiles than aryl thiols in the TMG catalyzed hydrothiolation of *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 α-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 β-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 α-monofluorovinyl thioether when using aryl thiols, the desired β,β-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 β-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]

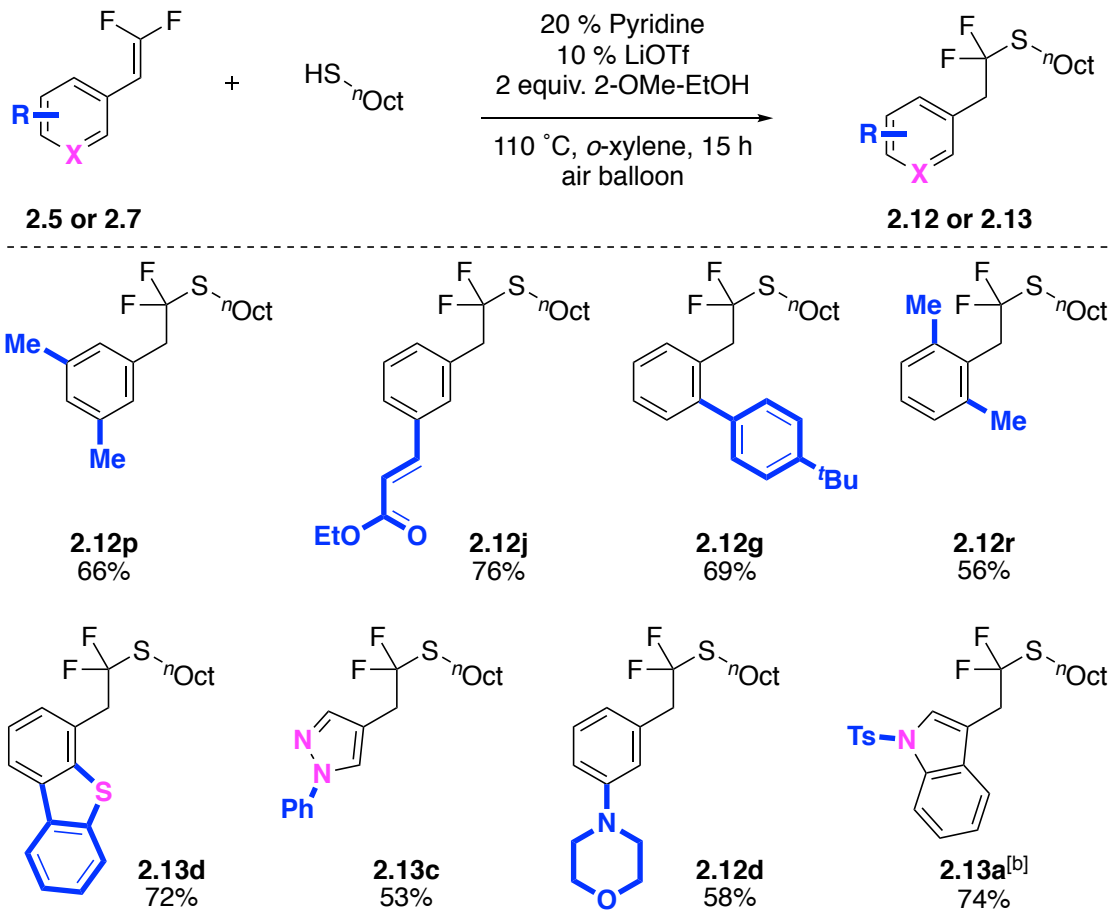
Scheme 2-12: Inorganic Base Catalysis Provides Desired Product



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[a]



[a] Standard conditions: **2.5** or **2.7** (1.0 equiv.), ^{n}OctSH (1.5 equiv.), Pyridine (20.0 mol %), LiOTf (10.0 mol %), 2-OMe-EtOH (2.0 equiv.), *o*-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] ^{n}OctSH (3.0 equiv.).

2.5. Conclusions

In summary, we developed a new organo-catalytic strategy to generate β,β-difluorophenethyl thioethers by directly adding nucleophiles to *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 *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 F^-; however, the mild conditions avoid this undesired unimolecular elimination, contrasting the many reactions of *gem*-difluoroalkenes that selectively generate monofluoroalkene products.[1h]

The organocatalytic strategy enabled two reactions to access to a variety of functionalized β,β-difluorophenethyl thioethers in high yield and selectivity versus the α-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 β,β-difluorophenethyl arylthioethers in high yield and generally >25:1 selectivity, although, as with S_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,[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

1. (a) Faqua, S. A.; Duncan, W. G.; Silverstein, R. M., A one-step synthesis of 1,1-difluoroolefins from aldehydes by a modified wittig synthesis. *Tetrahedron Lett.* **1964,** *5* (23), 1461-1463; (b) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M., A One-Step Synthesis of 1,1-Difluoro Olefins from Aldehydes. *J. Org. Chem.* **1965,** *30* (4), 1027-1029; (c) Li, Q.; Lin, J. H.; Deng, Z. Y.; Zheng, J.; Cai, J.; Xiao, J. C., Wittig *gem*-difluoroolefination of aldehydes with difluoromethyltriphenylphosphonium bromide. *J. Fluorine Chem.* **2014,** *163*, 38-41; (d) Zheng, J.; Cai, J.; Lin, J. H.; Guo, Y.; Xiao, J. C., Synthesis and decarboxylative Wittig reaction of difluoromethylene phosphobetaine. *Chem. Commun.* **2013,** *49* (68), 7513-5; (e) Naae, D. G.; Burton, D. J., Stable Difluoromethylene Olefination Solutions. *Synth. Commun.* **1973,** *3* (3), 197-200; (f) Bhadury, P. S.; Palit, M.; Sharma, M.; Raza, S. K.; Jaiswal, D. K., Fluorinated phosphonium ylides: versatile in situ Wittig intermediates in the synthesis of hydrofluorocarbons. *J. Fluorine Chem.* **2002,** *116* (1), 75-80; (g) Ichitsuka, T.; Takanohashi, T.; Fujita, T.; Ichikawa, J., A versatile difluorovinylation method: Cross-coupling reactions of the 2,2-difluorovinylzinc-TMEDA complex with alkenyl, alkynyl, allyl, and benzyl halides. *J. Fluorine Chem.* **2015,** *170*, 29-37; (h) Zhang, X.; Cao, S., Recent advances in the synthesis and CF functionalization of gem-difluoroalkenes. *Tetrahedron Lett.* **2017,** *58* (5), 375-392; (i) Zheng, J.; Lin, J. H.; Cai, J.; Xiao, J. C., Conversion between difluorocarbene and difluoromethylene ylide. *Chemistry* **2013,** *19* (45), 15261-6; (j) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J., gem-Difluoroolefination of diaryl ketones and enolizable aldehydes with difluoromethyl 2-pyridyl sulfone: new insights into the Julia-Kocienski reaction. *Chemistry* **2014,** *20* (25), 7803-10; (k) Krishnamoorthy, S.;

Kothandaraman, J.; Saldana, J.; Prakash, G. K. S., Direct Difluoromethylenation of Carbonyl Compounds by Using TMSCF3: The Right Conditions. *Eur. J. Org. Chem.* **2016,** *2016* (29), 4965-4969; (l) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J., gem-Difluoroolefination of Diazo Compounds with TMSCF3 or TMSCF2Br: Transition-Metal-Free Cross-Coupling of Two Carbene Precursors. *J. Am. Chem. Soc.* **2015,** *137* (45), 14496-501; (m) Gogsis, T. M.; Sobjerg, L. S.; Lindhardt, A. T.; Jensen, K. L.; Skrydstrup, T., Direct Vinylation and Difluorovinylation of Arylboronic Acids Using Vinyl- and 2,2-Difluorovinyl Tosylates via the Suzuki-Miyaura Cross Coupling. *J. Org. Chem.* **2008,** *73*, 3404–10; (n) Thomoson, C. S.; Martinez, H.; Dolbier, W. R., The use of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate as the difluorocarbene source to generate an in situ source of difluoromethylene triphenylphosphonium ylide. *J. Fluorine Chem.* **2013,** *150*, 53-59; (o) Wang, F.; Li, L.; Ni, C.; Hu, J., Deoxygenative gem-difluoroolefination of carbonyl compounds with (chlorodifluoromethyl)trimethylsilane and triphenylphosphine. *Beilstein J Org Chem* **2014,** *10*, 344-51; (p) Aikawa, K.; Toya, W.; Nakamura, Y.; Mikami, K., Development of (Trifluoromethyl)zinc Reagent as Trifluoromethyl Anion and Difluorocarbene Sources. *Org. Lett.* **2015,** *17* (20), 4996-9; (q) Prakash, G. K. S.; Wang, Y.; Hu, J. B.; Olah, G. A., Nucleophilic difluoromethylation and difluoromethylenation using bromodifluoromethyl phenyl sulfone. *J. Fluorine Chem.* **2005,** *126* (9-10), 1361-1367; (r) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J., Difluoromethyl 2-pyridyl sulfone: a new gem-difluoroolefination reagent for aldehydes and ketones. *Org. Lett.* **2010,** *12* (7), 1444-7; (s) Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M., Difluorophenylsulfanylmethyl radical and difluoromethylene diradical synthons: gem-difluoromethylene building block. *J. Org. Chem.* **2004,** *69* (20), 6913-5; (t) Zhu, L. G.; Li,

Y.; Zhao, Y. C.; Hu, J. B., Nucleophilic (phenylsulfonyl)difluoromethylation of alkyl halides using PhSO2CF2SiMe3: preparation of gem-difluoroalkenes and trifluoromethyl compounds. *Tetrahedron Lett.* **2010,** *51* (47), 6150-6152; (u) Prakash, G. K.; Hu, J.; Wang, Y.; Olah, G. A., Difluoromethyl phenyl sulfone, a difluoromethylidene equivalent: use in the synthesis of 1,1-difluoro-1-alkenes. *Angew. Chem. Int. Ed. Engl.* **2004,** *43* (39), 5203-6; (v) Zhang, L.; Li, Y.; Hu, J., Preparation of 1-aryl-2,2-difluoro enol esters via dehydrosulfonylation of α-(phenylsulfonyl)difluoromethylated benzoates. *J. Fluorine Chem.* **2007,** *128* (7), 755-761; (w) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H., A concise synthesis of functionalised gem-difluoroalkenes, via the addition of organolithium reagents to α-trifluoromethylstyrene. *Tetrahedron Lett.* **1995,** *36* (28), 5003-5006; (x) Amii, H.; Uneyama, K., C-F bond activation in organic synthesis. *Chem. Rev.* **2009,** *109* (5), 2119-83; (y) Ichikawa, J., Synthetic Methods for Heterocycles and Carbocycles Bearing Fluorinated One-Carbon Units (=CF2, CHF2, or CF3): Intramolecular Reaction of 2-Trifluoromethyl-1-alkenes. *J. Synth. Org. Chem Jpn.* **2010,** *68* (11), 1175-1184; (z) Fuchibe, K.; Takahashi, M.; Ichikawa, J., Substitution of two fluorine atoms in a trifluoromethyl group: regioselective synthesis of 3-fluoropyrazoles. *Angew. Chem. Int. Ed. Engl.* **2012,** *51* (48), 12059-62; (aa) Ichikawa, J.; Mori, T.; Iwai, Y., A New Class of Substrates for the Nucleophilic 5-endo-trigCyclization, 1-Trifluoromethylvinyl Compounds: Syntheses of Indoline and Pyrrolidine Derivatives. *Chem. Lett.* **2004,** *33* (10), 1354-1355; (ab) Ichikawa, J.; Ishibashi, Y.; Fukui, H., A novel synthesis of functionalized 1,1-difluoro-1-alkenes via isolable 2,2-difluorovinylsilanes. *Tetrahedron Lett.* **2003,** *44* (4), 707-710; (ac) Ichikawa, J.; Fukui, H.; Ishibashi, Y., 1-trifluoromethylvinylsilane as a CF2=C(-)-CH2+ synthon: synthesis of functionalized 1,1-

difluoro-1-alkenes via isolable 2,2-difluorovinylsilanes. *J. Org. Chem.* **2003,** *68* (20), 7800-5; (ad) Jeon, J. H.; Kim, J. H.; Jeong, Y. J.; Jeong, I. H., Preparation of 2,2-difluoro-1-trialkylsilylethenylstannanes and their cross-coupling reactions. *Tetrahedron Lett.* **2014,** *55* (7), 1292-1295; (ae) Gogsig, T. M.; Sobjerg, L. S.; Lindhardt, A. T.; Jensen, K. L.; Skrydstrup, T., Direct vinylation and difluorovinylation of arylboronic acids using vinyl- and 2,2-difluorovinyl tosylates via the Suzuki-Miyaura cross coupling. *J. Org. Chem.* **2008,** *73* (9), 3404-10; (af) Morken, P. A.; Burton, D. J., Preparation of Beta, Beta-Difluoro-Alpha-(Trifluoromethyl)Styrenes by Palladium-Catalyzed Coupling of Aryl Iodides with Pentafluoropropen-2-Ylzinc Reagent. *J. Org. Chem.* **1993,** *58* (5), 1167-1172.

2. Orsi, D. L.; Altman, R. A., Exploiting the unusual effects of fluorine in methodology. *Chem. Commun.* **2017,** *53* (53), 7168-7181.

3. (a) Rogawski, M. A., Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res* **2006,** *69* (3), 273-94; (b) Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; Mccarthy, J. R., Terminal Difluoro Olefin Analogs of Squalene Are Time-Dependent Inhibitors of Squalene Epoxidase. *J. Am. Chem. Soc.* **1992,** *114* (1), 360-361; (c) Pan, Y.; Qiu, J.; Silverman, R. B., Design, Synthesis, and Biological Activity of a Difluoro-Substituted, Conformationally Rigid Vigabatrin Analogue as a Potent g-Aminobutyric Acid Aminotransferase Inhibitor. *J. Med. Chem.* **2003,** *46*, 5292–3; (d) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*. Imperial College Press: London, 2012; (e) *Fluorine in Medicinal Chemistry and Chemical Biology*. Wiley-Blackwell: West Sussex, UK, 2009; (f) Bobek,

M.; Kavai, I.; De Clercq, E., Synthesis and biological activity of 5-(2,2-difluorovinyl)-2'-deoxyuridine. *J. Med. Chem.* **1987,** *30* (8), 1494-7.

4. (a) Juncosa, J. I.; Takaya, K.; Le, H. V.; Moschitto, M. J.; Weerawarna, P. M.; Mascarenhas, R.; Liu, D.; Dewey, S. L.; Silverman, R. B., Design and Mechanism of (S)-3-Amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic Acid, a Highly Potent gamma-Aminobutyric Acid Aminotransferase Inactivator for the Treatment of Addiction. *J. Am. Chem. Soc.* **2018,** *140* (6), 2151-2164; (b) Wang, Y.; Serradell, N.; Bolos, J., Seletracetam. Antiepileptic drug. *Drugs of the Future* **2006,** *31* (12), 1048-1052.

5. Suda, M., Reactions of 1,1-Difluoro-1-Olefins with Electrophilic Reagents. *Tetrahedron Lett.* **1980,** *21* (26), 2555-2556.

6. (a) Yokota, M.; Fujita, D.; Ichikawa, J., Activation of 1,1-difluoro-1-alkenes with a transition-metal complex: palladium(II)-catalyzed Friedel-Crafts-type cyclization of 4,4-(difluorohomoallyl)arenes. *Org. Lett.* **2007,** *9* (22), 4639-42; (b) Yu, L.; Tang, M. L.; Si, C. M.; Meng, Z.; Liang, Y.; Han, J.; Sun, X., Zinc-Mediated Decarboxylative Alkylation of Gem-difluoroalkenes. *Org. Lett.* **2018,** *20* (15), 4579-4583; (c) Yang, L.; Ji, W. W.; Lin, E.; Li, J. L.; Fan, W. X.; Li, Q.; Wang, H., Synthesis of Alkylated Monofluoroalkenes via Fe-Catalyzed Defluorinative Cross-Coupling of Donor Alkenes with gem-Difluoroalkenes. *Org. Lett.* **2018,** *20* (7), 1924-1927; (d) Tan, D. H.; Lin, E.; Ji, W. W.; Zeng, Y. F.; Fan, W. X.; Li, Q. J.; Gao, H.; Wang, H. G., Copper-Catalyzed Stereoselective Defluorinative Borylation and Silylation of gem-Difluoroalkenes. *Adv. Synth. Catal.* **2018,** *360* (5), 1032-1037; (e) Zhang, J.; Dai, W.; Liu, Q.; Cao, S., Cu-Catalyzed Stereoselective Borylation of gem-Difluoroalkenes with B2pin2. *Org. Lett.* **2017,** *19* (12), 3283-3286; (f) Zell, D.; Dhawa,

U.; Muller, V.; Bursch, M.; Grimme, S.; Ackermann, L., C-F/C-H Functionalization by Manganese(I) Catalysis: Expedient (Per)Fluoro-Allylations and Alkenylations. *Acs Catal* **2017,** *7* (6), 4209-4213; (g) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T., Copper-Catalyzed Regioselective Monodefluoroborylation of Polyfluoroalkenes en Route to Diverse Fluoroalkenes. *J. Am. Chem. Soc.* **2017,** *139* (36), 12855-12862; (h) Lu, X.; Wang, Y.; Zhang, B.; Pi, J. J.; Wang, X. X.; Gong, T. J.; Xiao, B.; Fu, Y., Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of gem-Difluoroalkenes with Unactivated Secondary and Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2017,** *139* (36), 12632-12637; (i) Li, J.; Lefebvre, Q.; Yang, H.; Zhao, Y.; Fu, H., Visible light photocatalytic decarboxylative monofluoroalkenylation of alpha-amino acids with gem-difluoroalkenes. *Chem. Commun.* **2017,** *53* (74), 10299-10302; (j) Kong, L.; Liu, B.; Zhou, X.; Wang, F.; Li, X., Rhodium(iii)-catalyzed regio- and stereoselective benzylic alpha-fluoroalkenylation with gem-difluorostyrenes. *Chem. Commun.* **2017,** *53* (74), 10326-10329; (k) Watabe, Y.; Kanazawa, K.; Fujita, T.; Ichikawa, J., Nickel-Catalyzed Hydroalkenylation of Alkynes through C-F Bond Activation: Synthesis of 2-Fluoro-1,3-dienes. *Synthesis-Stuttgart* **2017,** *49* (16), 3569-3575; (l) Cai, S. H.; Ye, L.; Wang, D. X.; Wang, Y. Q.; Lai, L. J.; Zhu, C.; Feng, C.; Loh, T. P., Manganese-catalyzed synthesis of monofluoroalkenes via C-H activation and C-F cleavage. *Chem. Commun.* **2017,** *53* (62), 8731-8734; (m) Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S., Monofluoroalkenylation of Dimethylamino Compounds through Radical-Radical Cross-Coupling. *Angew. Chem. Int. Ed. Engl.* **2016,** *55* (32), 9416-21; (n) Thornbury, R. T.; Toste, F. D., Palladium-Catalyzed Defluorinative Coupling of 1-Aryl-2,2-Difluoroalkenes and Boronic Acids: Stereoselective Synthesis of Monofluorostilbenes. *Angew. Chem. Int.*

Ed. Engl. **2016,** *55* (38), 11629-32; (o) Kong, L.; Zhou, X.; Li, X., Cobalt(III)-Catalyzed Regio- and Stereoselective alpha-Fluoroalkenylation of Arenes with gem-Difluorostyrenes. *Org. Lett.* **2016,** *18* (24), 6320-6323; (p) Dai, W.; Shi, H.; Zhao, X.; Cao, S., Sterically Controlled Cu-Catalyzed or Transition-Metal-Free Cross-Coupling of gem-Difluoroalkenes with Tertiary, Secondary, and Primary Alkyl Grignard Reagents. *Org. Lett.* **2016,** *18* (17), 4284-7; (q) Xiong, Y.; Huang, T.; Ji, X.; Wu, J.; Cao, S., Nickel-catalyzed Suzuki-Miyaura type cross-coupling reactions of (2,2-difluorovinyl)benzene derivatives with arylboronic acids. *Org Biomol Chem* **2015,** *13* (27), 7389-92; (r) Tian, P.; Feng, C.; Loh, T. P., Rhodium-catalysed C(sp(2))-C(sp(2)) bond formation via C-H/C-F activation. *Nat Commun* **2015,** *6*, 7472.

7. (a) Urban, J. J.; Tillman, B. G.; Cronin, W. A., Fluoroolefins as peptide mimetics: a computational study of structure, charge distribution, hydration, and hydrogen bonding. *J. Phys. Chem. A* **2006,** *110* (38), 11120-9; (b) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A., A theoretical and crystallographic study of the geometries and conformations of fluoro-olefins as peptide analogues. *Tetrahedron* **1986,** *42* (7), 2101-2110; (c) Wipf, P.; Henninger, T. C.; Geib, S. J., Methyl- and (Trifluoromethyl)alkene Peptide Isosteres: Synthesis and Evaluation of Their Potential as β-Turn Promoters and Peptide Mimetics. *J. Org. Chem.* **1998,** *63* (18), 6088-6089; (d) Bégué, J.-P.; Bonnet-Delpon, D., *Bioorganic and Medicinal Chemistry of Fluorine*. Wiley-VCH:Weinheim: 2008; (e) Gante, J., Peptidomimetics - Tailored Enzyme-Inhibitors. *Angew. Chem. Int. Ed.* **1994,** *33* (17), 1699-1720.

8. Yang, M. H.; Matikonda, S. S.; Altman, R. A., Preparation of fluoroalkenes via the Shapiro reaction: direct access to fluorinated peptidomimetics. *Org. Lett.* **2013,** *15* (15), 3894-7.

9. (a) Cox, D. G.; Gurusamy, N.; Burton, D. J., Surprising Stereochemical Control of Wittig Olefination Involving Reaction of Fluorine-Containing Phosphoranium Salt and Aldehydes. *J. Am. Chem. Soc.* **1985,** *107* (9), 2811-2812; (b) Tsai, H. J., Synthesis of phenyl substituted fluoro-olefins. *Tetrahedron Lett.* **1996,** *37* (5), 629-632; (c) van Steenis, Jan H.; van der Gen, A., Synthesis and Horner−Wittig Chemistry of (Fluoromethyl)diphenylphosphane Oxide. *Eur. J. Org. Chem.* **2001,** *2001* (5), 897-910; (d) Lin, J.; Welch, J. T., The stereoselective construction of fluoroalkenoates via the Peterson olefination reaction using tert-butyl α-fluoro-α-(trialkylsilyl)acetates. *Tetrahedron Lett.* **1998,** *39* (52), 9613-9616; (e) Asakura, N.; Usuki, Y.; Iio, H., A new synthesis of α-fluorovinylsulfones utilizing the Peterson olefination methodology. *J. Fluorine Chem.* **2003,** *124* (1), 81-88; (f) Zajc, B.; Kake, S., Exceptionally mild, high-yield synthesis of alpha-fluoro acrylates. *Org. Lett.* **2006,** *8* (20), 4457-60; (g) Pfund, E.; Lebargy, C.; Rouden, J.; Lequeux, T., Modified Julia fluoroolefination: selective preparation of fluoroalkenoates. *J. Org. Chem.* **2007,** *72* (21), 7871-7; (h) Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B., Alpha-fluorovinyl Weinreb amides and alpha-fluoroenones from a common fluorinated building block. *J. Org. Chem.* **2009,** *74* (10), 3689-97.

10. (a) Tius, M. A.; Kawakami, J. K., Vinyl Fluorides from Vinyl Stannanes. *Synth. Commun.* **2006,** *22* (10), 1461-1471; (b) Tius, M. A.; Kawakami, J. K., The Reaction of

Xef2 with Trialkylvinylstannanes - Scope and Some Mechanistic Observations. *Tetrahedron* **1995,** *51* (14), 3997-4010; (c) Greedy, B.; Gouverneur, V., Fluorodesilylation of alkenyltrimethylsilanes: a new route to fluoroalkenes and difluoromethyl-substituted amides, alcohols or ethers. *Chem. Commun.* **2001,** (03), 233-234; (d) Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A., Facile preparation of fluorine-containing alkenes, amides and alcohols via the electrophilic fluorination of alkenyl boronic acids and trifluoroborates. *Synlett* **1997,** *1997* (5), 606-&; (e) Furuya, T.; Ritter, T., Fluorination of boronic acids mediated by silver(I) triflate. *Org. Lett.* **2009,** *11* (13), 2860-3.

11. (a) Sasson, R.; Rozen, S., Bromofluorination of olefins using BrF3; an efficient route for fluoroalkenes and fluoroamines. *J. Fluorine Chem.* **2006,** *127* (7), 962-965; (b) Sano, K.; Fukuhara, T.; Hara, S., Regioselective synthesis of β-fluoro-α,β-unsaturated ketones by the reaction of β-diketones with DFMBA. *J. Fluorine Chem.* **2009,** *130* (8), 708-713; (c) Prakash, G. K.; Chacko, S.; Vaghoo, H.; Shao, N.; Gurung, L.; Mathew, T.; Olah, G. A., Efficient nucleophilic fluoromethylation and subsequent transformation of alkyl and benzyl halides using fluorobis(phenylsulfonyl)methane. *Org. Lett.* **2009,** *11* (5), 1127-30.

12. (a) Bergmann, F.; Kalmus, A.; Breuer, E., β-Fluorostyrene. *J. Am. Chem. Soc.* **1958,** *80* (17), 4540-4543; (b) Ocampo, R.; Dolbier, W. R.; Zuluaga, F., Synthesis of α-Fluoro-β-lactones and Their Thermal Conversion to 1-Fluoroalkenes. *Collect. Czech. Chem. Commun.* **2002,** *67* (9), 1325-1334; (c) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N., Facile synthesis of fluoroalkenes by

palladium-catalyzed reductive defluorination of allylic gem-difluorides. *Org. Lett.* **2007,** *9* (17), 3465-8.

13. (a) Zhang, H.; Zhou, C. B.; Chen, Q. Y.; Xiao, J. C.; Hong, R., Monofluorovinyl tosylate: a useful building block for the synthesis of terminal vinyl monofluorides via Suzuki-Miyaura coupling. *Org. Lett.* **2011,** *13* (4), 560-3; (b) Han, S. Y.; Jeong, I. H., Efficient synthesis of 2,2-diaryl-1,1-difluoroethenes via consecutive cross-coupling reactions of 2,2-difluoro-1-tributylstannylethenyl p-toluenesulfonate. *Org. Lett.* **2010,** *12* (23), 5518-21; (c) Qiu, J.; Gyorokos, A.; Tarasow, T. M.; Guiles, J., Grignard cross-coupling amenable to large scale production of alpha-fluorostyryl and alpha-fluorovinylthiophenes. *J. Org. Chem.* **2008,** *73* (24), 9775-7.

14. (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T., 5-endo-trigonal cyclization of o-substituted gem-difluorostyrenes: Syntheses of 2-fluorinated indoles, benzo[b]furans and benzo[b]thiophenes. *Chem. Commun.* **1997,** (16), 1537-1538; (b) Zhang, B.; Zhang, X.; Hao, J.; Yang, C., Direct Approach to N-Substituted-2-Fluoroindoles by Sequential Construction of C-N Bonds from gem-Difluorostyrenes. *Org. Lett.* **2017,** *19* (7), 1780-1783.

15. (a) Wada, Y.; Ichikawa, J.; Katsume, T.; Nohiro, T.; Okauchi, T.; Minami, T., Intramolecular Cyclizations ofo-Substitutedβ,β-Difluorostyrenes: Synthesis of 3-Fluorinated Isochromenes and Isothiochromenes. *Bull. Chem. Soc. Jpn.* **2001,** *74* (5), 971-977; (b) Ichikawa, J.; Sakoda, K.; Moriyama, H.; Wada, Y., Syntheses of ring-fluorinated isoquinolines and quinolines via intramolecular substitution: Cyclization of 1,1-difluoro-1-alkenes bearing a sulfonamide moiety. *Synthesis-Stuttgart* **2006,** *2006* (10),

1590-1598; (c) Ichikawa, J.; Mori, T.; Miyazaki, H.; Wada, Y., C-C Bond Formation between Isocyanide and β,β-Difluoroalkene Moieties via Electron Transfer: Fluorinated Quinoline and Biquinoline Syntheses. *Synlett* **2004,** (7), 1219-1222; (d) Wada, Y.; Mori, T.; Ichikawa, J., A Facile Synthesis of 2,4-Disubstituted 3-Fluoroquinolines via Intramolecular Cyclization ofo-Cyanomethylamino-β,β-difluorostyrenes. *Chem. Lett.* **2003,** *32* (11), 1000-1001; (e) Mori, T.; Ichikawa, J., KCN-Catalyzed C–C Bond Formation between Imine andgem-Difluoroalkene Moieties: A Facile Synthesis of 2,4-Disubstituted 3-Fluoroquinolines. *Chem. Lett.* **2004,** *33* (5), 590-591; (f) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H., Ring-fluorinated isoquinoline and quinoline synthesis: intramolecular cyclization of o-cyano- and o-isocyano-beta,beta-difluorostyrenes. *Org. Lett.* **2003,** *5* (9), 1455-8; (g) Saito, A.; Okada, M.; Nakamura, Y.; Kitagawa, O.; Horikawa, H.; Taguchi, T., Carbocyclization reactions of terminally difluorinated alkenyl active methine compounds mediated by SnCl4 and amine. *J. Fluorine Chem.* **2003,** *123* (1), 75-80; (h) Ichikawa, J.; Nadano, R.; Mori, T.; Wada, Y., 5-*endo-trig*Cyclization of 1,1-Difluoro-1-alkenes: Synthesis of 3-Butyl-2-fluoro-1-tosylindole. *Organic Syntheses* **2006**; (i) Coe, P. L.; Burdon, J.; Haslock, I. B., A simple stereoselective synthesis of biologically important 2-halo-2,3-dideoxy-arabinose derivatives from 1,1,1,2-tetrafluoroethane (134a) and 1-chloro-2,2,2-trifluoroethane (133a). *J. Fluorine Chem.* **2000,** *102* (1-2), 43-50.

16. Landelle, G.; Champagne, P. A.; Barbeau, X.; Paquin, J. F., Stereocontrolled approach to bromofluoroalkenes and their use for the synthesis of tri- and tetrasubstituted fluoroalkenes. *Org. Lett.* **2009,** *11* (3), 681-4.

17. (a) Jin, G.; Zhang, J.; Wu, W.; Cao, S., Stereoselective synthesis of β-fluoroenyne by the reaction of gem -difluoroalkenes with terminal alkynes. *J. Fluorine Chem.* **2014,** *168*, 240-246; (b) Bardin, V. V.; Adonin, N. Y.; Frohn, H. J., (Fluoroorgano)fluoroboranes and -borates. 14. Preparation of potassium ((perfluoroorgano)ethynyl)trifluoroborates K[RFC=CBF3]. *Organometallics* **2005,** *24* (22), 5311-5317.

18. Zhang, X. X.; Lin, Y. Y.; Zhang, J.; Cao, S., Base-mediated direct fluoroalkenylation of 2-phenyl-1,3,4-oxadiazole, benzothiazole and benzoxazole with *gem*-difluoroalkenes. *Rsc Adv* **2015,** *5* (11), 7905-7908.

19. Huang, X. H.; He, P. Y.; Shi, G. Q., Highly stereoselective addition-elimination reaction of nucleophiles with ethyl 3,3-difluoro-2-[(trimethylsilyl)methyl]propenoate. *J. Org. Chem.* **2000,** *65* (2), 627-629.

20. Zhang, J.; Xu, C.; Wu, W.; Cao, S., Mild and Copper-Free Stereoselective Cyanation of gem-Difluoroalkenes by Using Benzyl Nitrile as a Cyanating Reagent. *Chemistry* **2016,** *22* (29), 9902-8.

21. Ichikawa, J.; Yokota, N.; Kobayashi, M.; Minami, T., The Reaction of Fluorovinyl Ketones with Carbon Nucleophiles: A New General Route to α,β-Unsaturated Ketones. *Synlett* **1993,** *1993* (03), 186-188.

22. Wang, M.; Liang, F.; Xiong, Y.; Cao, S., Synthesis of fluorovinyl aryl ethers by a three-component reaction of gem-difluoroalkenes with arylboronic acids and oxygen. *Rsc Adv* **2015,** *5* (16), 11996-11999.

23. (a) Xiong, Y.; Zhang, X.; Huang, T.; Cao, S., Synthesis of N-(alpha-fluorovinyl)azoles by the reaction of difluoroalkenes with azoles. *J. Org. Chem.* **2014,** *79* (14), 6395-402; (b) Timperley, C. M.; Waters, M. J.; Greenall, J. A., Fluoroalkene chemistry Part 3. Reactions of arylthiols with perfluoroisobutene, perfluoropropene and chlorotrifluoroethene. *J. Fluorine Chem.* **2006,** *127* (2), 249-256; (c) Timperley, C. M., Fluoroalkene chemistry. *J. Fluorine Chem.* **2004,** *125* (5), 685-693; (d) Tae Kim, B.; Ki Min, Y.; Kyun Park, N.; Yun Cho, K.; Howa Jeong, I., Exocyclization of Novel b,b-Difluoro-a-phenylvinyl Sulfide with Bidendate Heteroatom(N,O,S) Nucleophiles. *Heterocycles* **1995,** *41* (4); (e) Ichikawa, J.; Kobayashi, M.; Yokota, N.; Noda, Y.; Minami, T., Reaction of 2,2-difluorovinyl ketones with heteroatom nucleophiles: A general one-pot synthesis of α-oxoketene acetals. *Tetrahedron* **1994,** *50* (40), 11637-11646.

24. (a) Kim, M. S.; Jeong, I. H., A highly stereoselective preparation of CF3-substituted 1-aryl-1,2-diphenylethenes: application to the synthesis of panomifene. *Tetrahedron Lett.* **2005,** *46* (20), 3545-3548; (b) Cong, Z. S.; Li, Y. G.; Chen, L.; Xing, F.; Du, G. F.; Gu, C. Z.; He, L., N-Heterocyclic carbene-catalyzed stereoselective construction of olefinic carbon-sulfur bonds via cross-coupling reaction of gem-difluoroalkenes and thiols. *Org Biomol Chem* **2017,** *15* (18), 3863-3868.

25. (a) Strobach, D. R., Ynamines from 1,1-difluoro-2-aryl and 2-alkylethylenes. *J. Org. Chem.* **1971,** *36* (10), 1438-1440; (b) 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; (c) Gao, F. T.; Fang, Z.; Su, R. R.; Rui, P. X.; Hu, X. G., Hydroximoyl fluorides as the precursors of nitrile oxides: synthesis, stability and [3 + 2]-cycloaddition with alkynes. *Org Biomol Chem* **2018,** *16* (47), 9211-9217.

26. Qiao, Y.; Si, T.; Yang, M. H.; Altman, R. A., Metal-free trifluoromethylation of aromatic and heteroaromatic aldehydes and ketones. *J. Org. Chem.* **2014,** *79* (15), 7122-31.

27. (a) Gao, B.; Zhao, Y.; Hu, J., AgF-mediated fluorinative cross-coupling of two olefins: facile access to alpha-CF3 alkenes and beta-CF3 ketones. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (2), 638-42; (b) Gao, B.; Zhao, Y.; Ni, C.; Hu, J., AgF-mediated fluorinative homocoupling of gem-difluoroalkenes. *Org. Lett.* **2014,** *16* (1), 102-5; (c) Zhang, B.; Zhang, X.; Hao, J.; Yang, C., Palladium-Catalyzed Direct Approach to α-Trifluoromethyl Alcohols by Selective Hydroxylfluorination of gem-Difluoroalkenes. *Eur. J. Org. Chem.* **2018,** *2018* (36), 5007-5015; (d) Tang, H. J.; Lin, L. Z.; Feng, C.; Loh, T. P., Palladium-Catalyzed Fluoroarylation of gem-Difluoroalkenes. *Angew. Chem. Int. Ed. Engl.* **2017,** *56* (33), 9872-9876; (e) Tian, P.; Wang, C. Q.; Cai, S. H.; Song, S.; Ye, L.; Feng, C.; Loh, T. P., F(-) Nucleophilic-Addition-Induced Allylic Alkylation. *J. Am. Chem. Soc.* **2016,** *138* (49), 15869-15872.

28. Dixon, D. D.; Grina, J.; Josey, J. A.; Rizzi, J. P.; Schlachter, S. T.; Wallace, E. M.; Wang, B.; Wehn, P.; Xu, R.; Yang, H. Preparation of cyclic sulfone and sulfoximine analogs as HIF-2α inhibitors. WO 2015095048, 2015.

29. Chen, W.; Igboko, E. F.; Lin, X.; Lu, H.; Ren, F.; Wren, P. B.; Xu, Z.; Yang, T.; Zhu, L. Preparation of 1-(cyclopent-2-en-1-yl)-3-(2-hydroxy-3-(arylsulfonyl)phenyl)urea derivatives as CXCR2 inhibitors. WO 2015181186, 2015.

30. (a) Kumamoto, K.; Miyazaki, H. Preparation of sulfanylmethylpyrazole derivatives and analogs as pesticides. WO 2009028727, 2009; (b) Dallimore, J. W. P.; El Qacemi, M.; Kozakiewicz, A. M.; Longstaff, A.; Mclachlan, M. M. W.; Peace, J. E. Preparation of herbicidal isoxazoline derivatives. WO 2011033251, 2011.

31. (a) Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V., α,α-Difluoro-α-phenylsulfanylmethyl carbanion equivalent: a novel gem-difluoromethylenation of carbonyl compounds. *Tetrahedron* **2006,** *62* (25), 5973-5985; (b) Li, Y.; Hu, J., Fluoride ion-mediated nucleophilic fluoroalkylation of alkyl halides with Me3SiCF2SPh: Synthesis of PhSCF2- and CF2H-containing compounds. *J. Fluorine Chem.* **2008,** *129* (5), 382-385; (c) Kosobokov, M. D.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Hu, J., Reactions of sulfur- and phosphorus-substituted fluoroalkylating silicon reagents with imines and enamines under acidic conditions. *J. Org. Chem.* **2012,** *77* (4), 2080-6; (d) Li, Y.; Hu, J., Stereoselective difluoromethylenation using Me3SiCF2SPh: synthesis of chiral 2,4-disubstituted 3,3-difluoropyrrolidines. *Angew. Chem. Int. Ed. Engl.* **2007,** *46* (14), 2489-92.

32. (a) Betterley, N. M.; Surawatanawong, P.; Prabpai, S.; Kongsaeree, P.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V., Electrophilic difluoro(phenylthio)methylation: generation, stability, and reactivity of alpha-fluorocarbocations. *Org. Lett.* **2013,** *15* (22),

5666-9; (b) Yang, X. Y.; Fang, X.; Yang, X. J.; Zhao, M.; Han, Y. Z.; Shen, Y. J.; Wu, F. H., New preparation of difluoroiodomethylsulfanylbenzenes and their radical addition to unsaturated compounds initiated by sodium dithionite. *Tetrahedron* **2008,** *64* (9), 2259-2269; (c) Choi, Y.; Yu, C.; Kim, J. S.; Cho, E. J., Visible-Light-Induced Arylthiofluoroalkylations of Unactivated Heteroaromatics and Alkenes. *Org. Lett.* **2016,** *18* (13), 3246-9.

33. Suda, M., Radical-Addition Reactions on 1,1-Difluoro-1-Olefins. *Tetrahedron Lett.* **1981,** *22* (25), 2395-2396.

34. Zhang, Z.; Tang, X.; Dolbier, W. R., Jr., Photoredox-Catalyzed Tandem Insertion/Cyclization Reactions of Difluoromethyl and 1,1-Difluoroalkyl Radicals with Biphenyl Isocyanides. *Org. Lett.* **2015,** *17* (18), 4401-3.

35. (a) Brigaud, T.; Laurent, E., Oxidative Fluorination of Sulfides in Presence of Et3n.3hf. *Tetrahedron Lett.* **1990,** *31* (16), 2287-2290; (b) Furuta, S.; Kuroboshi, M.; Hiyama, T., Fluoro-Pummerer Rearrangement under Oxidative Desulfurization-Fluorination Conditions - Facile Synthesis of Oligofluoroalkyl Sulfides. *Tetrahedron Lett.* **1995,** *36* (45), 8243-8246; (c) Gouault, S.; Guérin, C.; Lemoucheux, L.; Lequeux, T.; Pommelet, J.-C., Fluorination of α,α-dichlorosulfides: access to gem-difluorothioethers as useful building blocks. *Tetrahedron Lett.* **2003,** *44* (27), 5061-5064.

36. Pearson, R. G.; Sobel, H.; Songstad, J., Nucleophilic Reactivity Constants toward Methyl Iodide and Trans-[Pt(Py)2cl2]. *J. Am. Chem. Soc.* **1968,** *90* (2), 319-&.

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

38. Bohm, A.; Bach, T., Radical Reactions Induced by Visible Light in Dichloromethane Solutions of Hunig's Base: Synthetic Applications and Mechanistic Observations. *Chemistry* **2016,** *22* (44), 15921-15928.

39. Bunting, J. W.; Mason, J. M.; Heo, C. K. M., Nucleophilicity Towards a Saturated Carbon-Atom - Rate Constants for the Aminolysis of Methyl 4-Nitrobenzenesulfonate in Aqueous-Solution - a Comparison of the N and N-+ Parameters for Amine Nucleophilicity. *J Chem Soc Perk T 2* **1994,** (11), 2291-2300.

40. Ugur, I.; Marion, A.; Parant, S.; Jensen, J. H.; Monard, G., Rationalization of the pKa values of alcohols and thiols using atomic charge descriptors and its application to the prediction of amino acid pKa's. *J Chem Inf Model* **2014,** *54* (8), 2200-13.

41. (a) Jelier, B. J.; Howell, J. L.; Montgomery, C. D.; Leznoff, D. B.; Friesen, C. M., A convenient route to tetraalkylammonium perfluoroalkoxides from hydrofluoroethers. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (10), 2945-9; (b) Lepri, S.; Buonerba, F.; Maccaroni, P.; Goracci, L.; Ruzziconi, R., Are carboxylic esters really refractory to DAST? On the fluorination of α-hydroxyesters with DAST. *J. Fluorine Chem.* **2015,** *171*, 82-91.

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}F NMR with an internal standard of α,α,α–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.

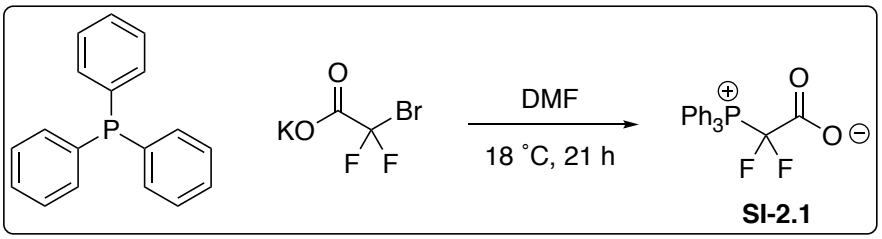
Unless otherwise noted, reagents were purchased from commercial sources and used as received. 1,2 Dichloroethane (DCE, reagent grade, 99+%) and tetramethylguanidine (TMG) were purchased from Alfa Aesar. *N*-methylpyrrolidine (NMP, anhydrous) was purchased from Sigma Aldrich. Solvents, including dimethylformamide (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 (H_2O_2) was purchased from Fisher Scientific. Other

chemical abbreviations utilized in this document include: α,α,α-Trifluorotoluene (TFT), sodium sulfate (Na_2SO_4), magnesium sulfate ($MgSO_4$), ethyl acetate (EtOAc), diethyl ether (Et_2O), ammonium chloride (NH_4Cl), *n*-butyl lithium (^nBuLi), sodium hydroxide (NaOH), sodium metabisulfite ($Na_2S_2O_5$), Room Temperature (R.T.), ^{t}butyl carbonate anhydride (Boc_2O), potassium carbonate (K_2CO_3), 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 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 $CHCl_3$ in the NMR solvent ($CHCl_3$: 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 ($CDCl_3$: 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:



SI-2.1

2,2-difluoro-2-(triphenylphosphonio)acetate (SI-2.1):[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 H_2O, and 3X with 30 mL of Et_2O. 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, ^{1}H NMR in MeOD was used to assess the purity of the material. If impurities are present, the material was washed a second time. The ^{1}H 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 degredation 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.

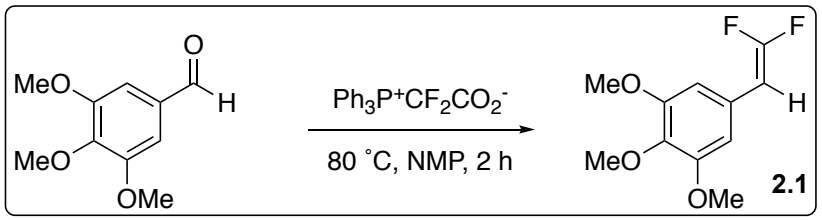
Note 4: If the potassium bromodifluoroacetate is not a powder, presumably due to water, the yield will drop by ~10–15%.

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 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_4Cl. 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 H_2O, and 1X with a saturated brine solution. The

organic layers were dried over Na_2SO_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_4Cl. 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_2O, 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_2O_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_2SO_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.

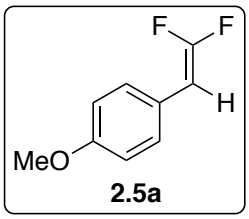
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (s, 2 H), 5.21 (dd, *J* = 25.8, 3.9 Hz, 1 H), 3.86–3.85 (m, 9 H);

^{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 $C_{11}H_{12}F_2O_3$ (M+) 230.0755, found 230.0749, 2.6 ppm.



2.5a

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.

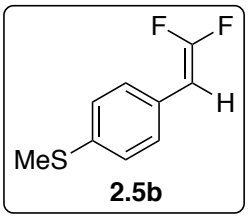
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.23 (dd, *J* = 26.4, 3.8 Hz, 1 H), 3.82 (s, 3 H);

^{13}C NMR (126 MHz, $CDCl_3$): 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;

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_9H_8F_2O$ (M+) 170.0543, found 170.0538, 2.9 ppm.



2.5b

(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, $CDCl_3$): δ 7.26–7.21 (m, 4 H), 5.23 (dd, *J* = 26.3, 3.7 Hz, 1 H), 2.48 (s, 3 H)

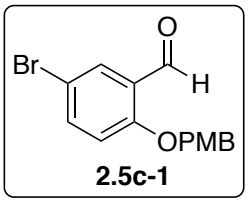
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.2 (dd, *J* = 298.0, 288.1 Hz), 137.3 (t, *J* = 2.3 Hz), 128.0 (dd, *J* = 6.4, 3.5 Hz), 127.1 (t, *J* = 6.4 Hz), 126.7, 81.8 (dd, *J* = 29.4, 13.7 Hz), 15.8

^{19}F NMR (376 MHz, $CDCl_3$): δ –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}

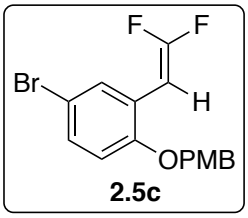
HRMS (HAPCI+): calc. for $C_9H_8F_2S$ (M+) 186.0315, found 186.0302, 1.3 mmu.

Preparation of Compound 2.5c:



2.5c-1

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



2.5c

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, $CDCl_3$): δ 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)

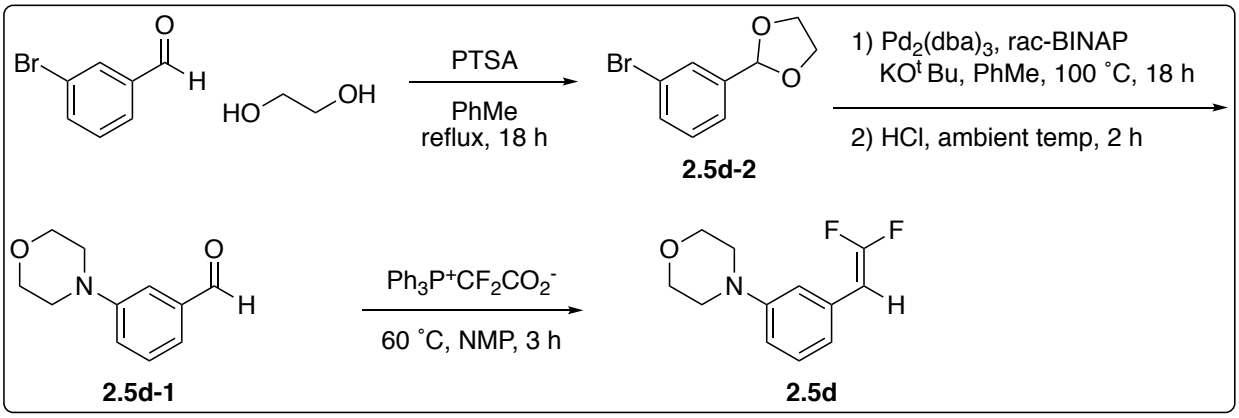
^{13}C NMR (126 MHz, $CDCl_3$): δ 159.7, 156.6 (dd, *J* = 298.2, 288.6 Hz), 155.0 (dd, *J* = 4.7, 1.6 Hz), 131.0 (dd, *J* = 10.7, 2.0 Hz), 130.8, 129.3, 128.4, 121.9 (t, *J* = 6.4 Hz), 114.2, 113.9, 113.4, 75.9 (dd, *J* = 31.9, 12.5 Hz), 70.6, 55.5

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{16}H_{12}BrF_2O_2$ (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 $NaHCO_3$, dried with $MgSO_4$, and concentrated. The product was used as is. The ^{1}H NMR spectrum matched previous reports.[3]

3-morpholinobenzaldehyde (2.5d-1):[3] Compound **2.5d-1** was prepared according to a previous report. The ^{1}H 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.

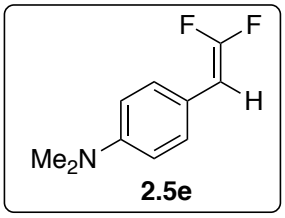
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (t, *J* = 8.2 Hz, 1 H), 6.88–6.86 (m, 2 H), 6.81 (ddd, *J* = 8.3, 2.5, 1.0 Hz, 1 H), 5.24 (dd, *J* = 26.2, 4.0 Hz, 1 H), 3.88–3.85 (m, 4 H), 3.17–3.15 (m, 4 H)

^{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 $C_{12}H_{14}F_2NO$ (M+H) 226.1043, found 226.1062, 1.9 mmu.



2.5e

4-(2,2-difluorovinyl)-*N*,*N*-dimethylaniline (2.5e): Following General Procedure A2, 1.49 g (10.0 mmol) of 4-dimethylaminobenzaldehyde 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)

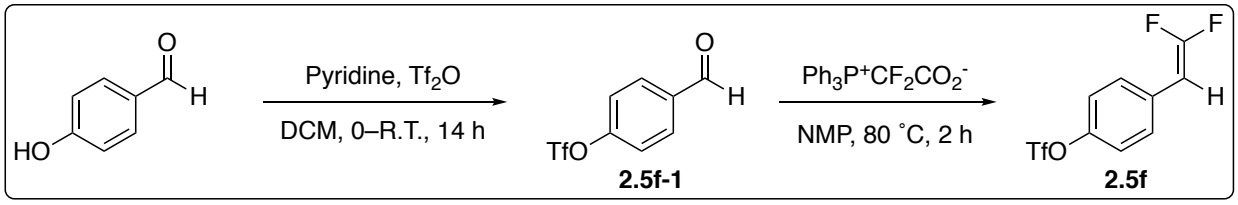
^{13}C NMR (126 MHz, $CDCl_3$): δ 155.7 (dd, *J* = 295.7, 285.3 Hz), 149.5 (t, *J* = 1.8 Hz), 128.6 (dd, *J* = 6.1, 3.5 Hz), 118.3 (t, *J* = 5.9 Hz), 112.7, 81.8 (dd, *J* = 28.7, 14.3 Hz), 40.6

^{19}F NMR (376 MHz, $CDCl_3$): δ –85.89 (dd, *J* = 40.5, 26.8 Hz, 1 F), –88.03 (dd, *J* = 40.5, 4.0 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 $C_{10}H_{12}F_2N$ (M+H) 184.0938, found 184.0930, 0.8 mmu.

Preparation of Compound 2.5f



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

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.

^{1}H NMR (400 MHz, $CDCl_3$): 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)

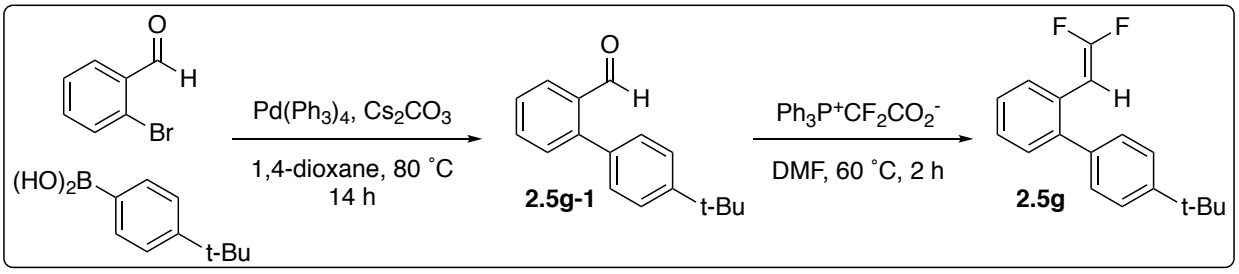
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.7 (dd, *J* = 299.2, 290.2 Hz), 148.2 (t, *J* = 2.7 Hz), 131.1 (dd, *J* = 7.3, 6.1 Hz), 129.4 (dd, *J* = 6.8, 3.6 Hz), 121.8, 118.9 (q, *J* = 320.9 Hz), 81.3 (dd, *J* = 30.4, 13.5 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_9H_5F_5O_3S$ (M+) 287.9880, found 287.9872, 2.8 ppm.

Preparation of Compound 2.5g



4'-(*tert*-butyl)-[1,1'-biphenyl]-2-carbaldehyde (2.5g-1):[5] 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 Cs_2CO_3, 0.29 g (0.25 mmol) of $Pd(PPh_3)_4$ 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 $MgSO_4$ 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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.

^{1}H NMR (500 MHz, $CDCl_3$): 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),

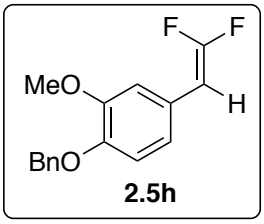
7.26 (d, *J* = 2.0 Hz, 1 H), 7.24 (d, *J* = 1.3 Hz, 1 H), 5.27 (dd, *J* = 26.2, 4.3 Hz, 1 H), 1.37 (s, 9 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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.



2.5h

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}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.6 Hz, 2 H), 7.39–7.35 Hz (m, 2 H), 7.32–7.28 (m, 1 H), 6.90 (d, *J* = 1.9 Hz, 1 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 6.80 (dd, *J* = 8.4, 2.0 Hz, 1 H), 5.21 (dd, *J* = 26.2, 3.9 Hz, 1 H), 5.17 (s, 2 H), 3.89 (s, 3 H)

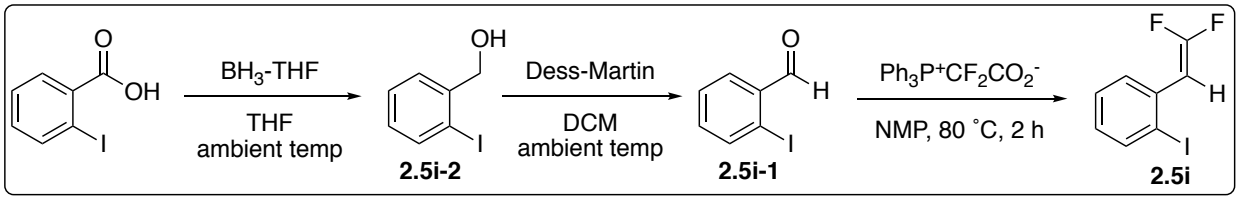
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.0 (dd, *J* = 296.8, 286.9 Hz), 149.8, 147.4 (t, *J* = 2.2 Hz), 137.1, 128.7, 128.0, 127.4, 123.7 (t, *J* = 6.3 Hz), 120.5 (dd, *J* = 6.1, 4.0 Hz), 114.2, 111.2 (dd, *J* = 6.9, 3.1 Hz), 82.0 (dd, *J* = 29.4, 13.7 Hz), 71.1, 56.1

^{19}F NMR (376 MHz, $CDCl_3$): δ –84.07 (dd, *J* = 35.9, 26.2 Hz, 1 F), –85.90 (dd, *J* = 36.0, 3.8 Hz, 1 F)

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 cm^{-1}

HRMS (HAPCI+): calc. for $C_{16}H_{14}F_2O_2$ (M+) 276.0962, found 276.0953, 3.3 ppm.

Preparation of Compound 2.5i



(2-iodophenyl)methanol (2.5i-2):[6] Compound **2.5i-2** was prepared according to a previous report.[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 BH_3•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:H_2O. The THF was removed *in vacuo*, and 50 mL of a saturated aq. solution of K_2CO_3 added. The resulting solution was extracted 3X with 25 mL of Et_2O, and the combined organic layers dried over $MgSO_4$ 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 ^{1}H NMR spectrum matched previous reports.[6]

2-iodobenzaldehyde (2.5i-1):[7] Compound **2.5i-1** was prepared according to a previous report.[7] 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 N_2 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 H_2O. Upon the addition of H_2O, 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 ^{1}H NMR spectrum matched previous reports.[7]

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, $CDCl_3$): δ 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)

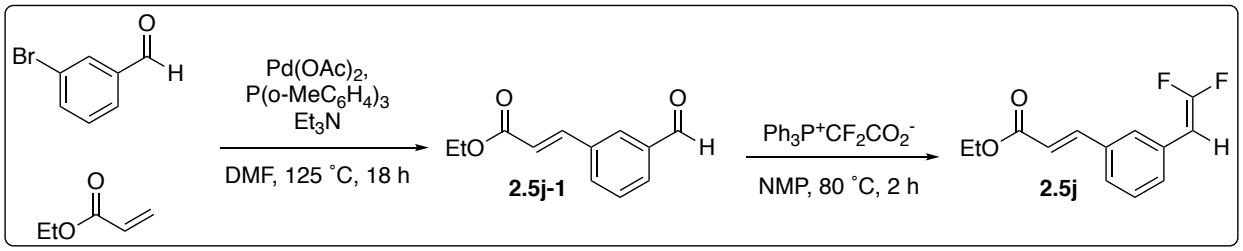
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.7 (dd, *J* = 298.6, 289.0 Hz), 139.6, 134.0 (dd, *J* = 8.0, 5.6 Hz), 128.9 (d, *J* = 1.6 Hz), 128.85 (dd, *J* = 8.7, 1.4 Hz), 128.5, 99.7 (dd, *J* = 5.7, 2.0 Hz), 86.5 (32.1, 12.6 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –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 $C_8H_5F_2I$ (M+) 265.9404, found 265.9400, 1.5 ppm.

Preparation of Compound 2.5j



ethyl (*E*)-3-(3-formylphenyl)acrylate (2.5j-1):[8] Compound **2.5j-1** was prepared according to a previous report.[8] 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*-$MeC_6H_4)_3P$ (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_3N. The system was immediately submerged in a preheated 125 ˚C oil bath and stirred for 18 h. After returning to ambient temperature, the reaction was quenched with H_2O 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 ^1H NMR spectrum matched reference.[8]

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 ˚C 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 ˚C.

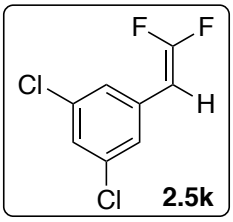
^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 16.0 Hz, 1 H), 7.49 (s, 1 H), 7.43 (td, *J* = 6.2, 3.3 Hz, 1 H), 7.38 (d, *J* = 6.1 Hz, 1 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 5.31 (dd, *J* = 26.0, 3.6 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 1.37 (t, *J* = 7.1 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{13}H_{13}F_2O_2$ (M+H) 239.0884, found 239.0879, 2.1 ppm.



2.5k

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, $CDCl_3$): δ 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)

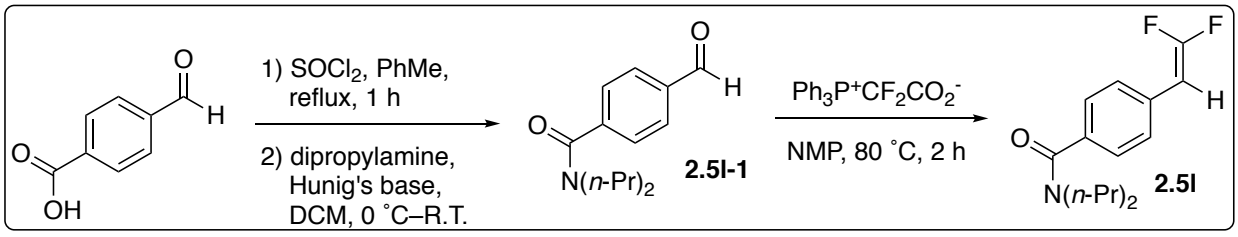
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.9 (dd, *J* = 300.2, 291.1 Hz), 135.4, 133.5 (dd, *J* = 7.7, 6.1 Hz), 127.2 (t, *J* = 2.0 Hz), 126.0 (dd, *J* = 6.9, 3.6 Hz), 81.1 (dd, *J* = 31.0, 13.1 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –78.72 (dd, *J* = 25.2, 23.8 Hz, 1 F), –80.80 (dd, *J* = 23.8, 3.3 Hz, 1 F)

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

HRMS (HAPCI+): calc. for $C_8H_4Cl_2F_2$ (M+) 207.9658, found 207.9648, 4.8 ppm.

Preparation of Compound 2.5l



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

4-(2,2-difluorovinyl)-*N*,*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 ˚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.

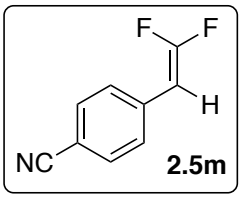
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.31 (m, 4 H), 5.29 (dd, *J* = 26.1, 3.6 Hz, 1 H), 3.45 (bs, 2 H), 3.18 (bs, 2 H), 1.68 (bs, 2 H), 1.53 (bs, 2 H), 0.97 (bs, 3 H), 0.75 (bs, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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^{-1}

HRMS (ESI+): calc. for $C_{15}H_{20}F_2NO$ (M+H) 268.1513, found 268.1517, 0.4 mmu.



2.5m

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.

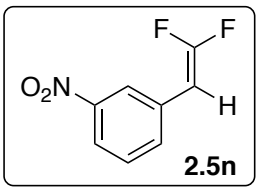
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2 F), 7.36 (d, *J* = 8.4, 2 H), 5.27 (dd, *J* = 25.6, 3.4 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 157.1 (dd, *J* = 301.3, 292.3 Hz), 135.5 (dd, *J* = 7.4, 6.4 Hz), 132.6, 128.2 (dd, *J* = 6.9, 3.6 Hz), 118.8, 110.7 (t, *J* = 2.4 Hz), 82.0 (dd, *J* = 30.5, 12.9 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –77.77 (dd, *J* = 25.5, 20.4 Hz, 1 F), –79.44 (dd, *J* = 20.5, 3.3 Hz, 1 F)

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

HRMS (HAPCI+): calc. for $C_9H_6F_2N$ (M+H) 166.0468, found 166.0462, 3.6 ppm.



2.5n

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 **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.

^{1}H NMR (400 MHz, $CDCl_3$): 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)

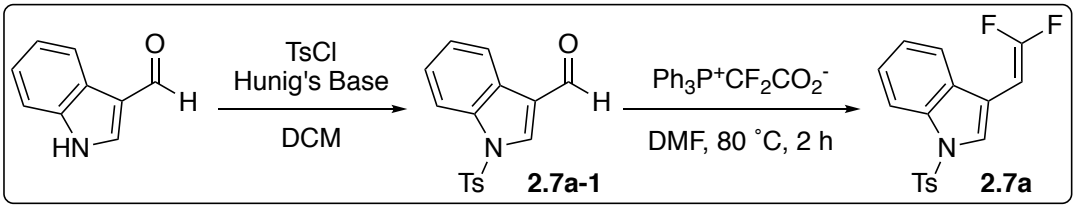
^{13}C NMR (126 MHz, $CDCl_3$): δ 157.1 (dd, *J* = 299.8, 291.5 Hz), 148.7, 133.4 (dd, *J* = 6.7, 3.6 Hz), 132.4 (dd, *J* = 7.8, 6.1 Hz), 129.8, 122.5 (dd, *J* = 6.8, 3.7 Hz), 122.0 (t, *J* = 2.0 Hz), 81.3 (dd, *J* = 30.9, 13.3 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_8H_6F_2NO_2$ (M+H) 186.0367, found 186.0359, 4.3 ppm.

Preparation of Compound 2.7a



1-tosyl-1*H*-indole-3-carbaldehyde (2.7a-1):[10] Compound **2.7a-1** was prepared according to a previous report. The ^{1}H NMR spectrum matched previous reports.[10]

3-(2,2-difluorovinyl)-1-tosyl-1*H*-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.

^{1}H NMR (400 MHz, $CDCl_3$): 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)

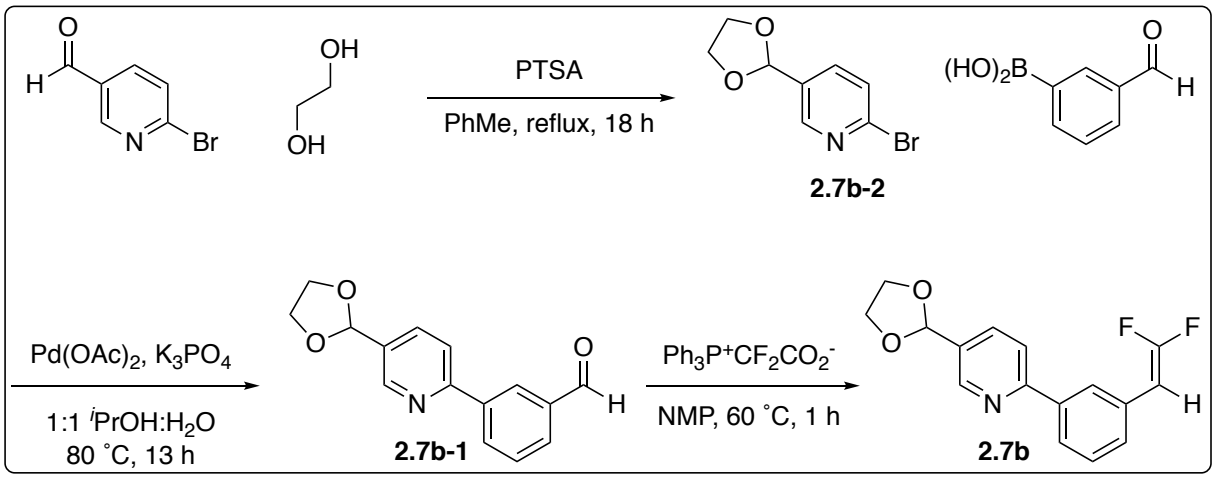
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.8 (dd, *J* = 296.1, 289.9 Hz), 145.2, 135.0, 134.7, 130.0, 129.4 (d, *J* = 3.3 Hz), 126.9, 125.3, 123.5, 123.3 (dd, *J* = 9.8, 3.9 Hz), 119.1 (d, *J* = 1.3 Hz), 113.8, 111.9 (J = 6.6, 5.2 Hz), 72.5 (dd, *J* = 32.1, 18.4 Hz), 21.6

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{14}F_2NO_2S$ (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):[11] Compound 2.**7b-2** was prepared according to a previous report.[11] 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_2O 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_2SO_4 and concentrated under reduced pressure to afford 8.87 g (71% yield) of desired product **2.7b-2** as a clear oil. The ^1H NMR spectrum matched previous reports.[11]

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_3PO_4-$7H_2O$. 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_2O (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_2SO_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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, 1587, 1474, 1356, 1182, 1163, 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.

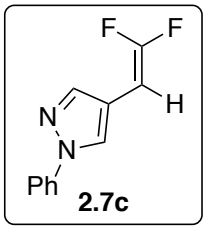
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (dt, *J* = 2.2, 0.7 Hz, 1 H), 7.95 (t, *J* = 1.8 Hz, 1 H), 7.87 (dd, *J* = 8.3, 2.3 Hz, 1 H), 7.84 (dt, *J* = 7.2, 1.7 Hz, 1 H), 7.74 (dd, *J* = 8.2, 0.8 Hz, 1 H), 7.47–7.41 (m, 2 H), 5.91 (s, 1 H), 5.38 (dd, *J* = 26.1, 3.8 Hz, 1 H), 4.18–4.06 (m, 4 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{16}H_{14}F_2NO_2$ (M+H) 290.0993, found 290.0996, 1.0 ppm.



2.7c

4-(2,2-difluorovinyl)-1-phenyl-1*H*-pyrazole (2.7c): Following General Procedure A1, 1.51 g (8.70 mmol) of 1-phenyl-1*H*-pyrazole-4-carbaldehyde was reacted with 5.44 g

(15.0 mmol) of **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 **2.7c** as a colorless solid, m.p. 70–71 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 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)

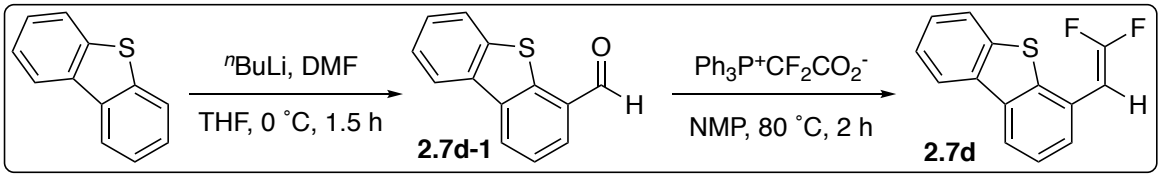
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.3 (dd, *J* = 293.6, 287.3 Hz), 140.0 (dd, *J* = 4.3, 3.0 Hz), 139.9, 129.5, 126.7, 124.5 (t, *J* = 4.9 Hz), 119.1, 113.2 (dd, *J* = 7.2, 4.9 Hz), 72.9 (dd, *J* = 32.0, 18.7 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –82.09 (dd, *J* = 34.7, 27.0 Hz, 1 F), –88.03 (dd, *J* = 34.8, 1.7 Hz, 1 F)

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

HRMS (ESI+): calc. for $C_{11}H_9F_2N_2$ (M+H) 207.0734, found 207.0720, 1.4 mmu.

Preparation of Compound 2.7d



dibenzo[*b*,*d*]thiophene-4-carbaldehyde (2.7d-1):[12] 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_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 *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 $MgSO_4$, 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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[*b*,*d*]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, $CDCl_3$): δ 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)

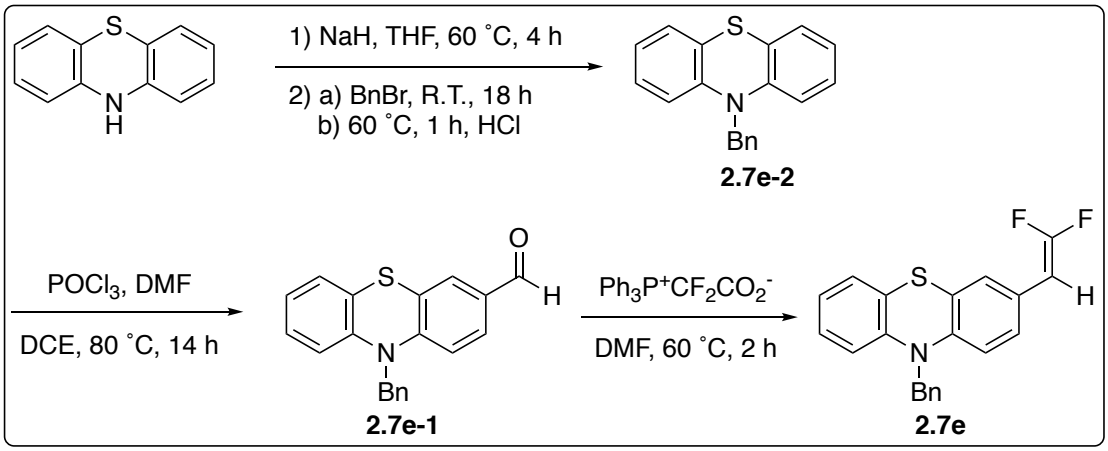
^{13}C NMR (126 MHz, $CDCl_3$): δ 157.1 (dd, *J* = 299.2, 290.2 Hz), 138.8, 136.02, 135.99, 127.1, 125.5 (dd, *J* = 8.9, 1.9 Hz), 125.1, 125.0, 124.8, 123, 122, 120.5 (t, *J* = 1.6 Hz), 80.1 (dd, *J* = 30.4, 14.6 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{14}H_8F_2S$ (M+) 246.0315, found 246.0304, 4.5 ppm.

Preparation of Compound 2.7e



10-benzyl-10*H*-phenothiazine (2.7e-2):[13] Compound **2.7e-2** was prepared according to a previous report.[13] 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 Na_2SO_4 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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-10*H*-phenothiazine-3-carbaldehyde (2.7e-1):[14] Compound **2.7e-1** was prepared according to a previous report.[14] 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 N_2 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_2SO_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)-10*H*-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)

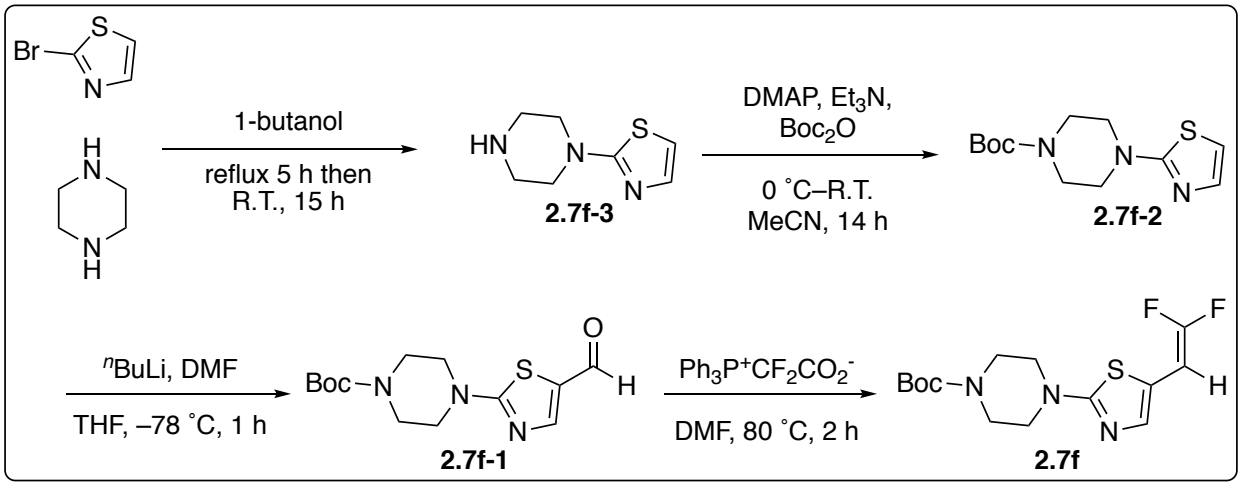
^{13}C NMR (126 MHz, $CDCl_3$): δ 156.0 (dd, *J* = 297.6, 287.7 Hz), 144.2, 143.3 (t, *J* = 2.2 Hz), 136.5, 128.9, 127.5, 127.2, 127.0, 126.6, 125.7 (dd, *J* = 6.6, 3.4 Hz), 124.7 (t, *J* = 6.3 Hz), 123.5, 122.8, 122.6, 115.5, 81.2 (dd, *J* = 29.6, 13.8 Hz), 52.7

^{19}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{21}H_{16}F_2NS$ (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_2CO_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, $CDCl_3$): δ 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_3CN (65 mL) was added *via* cannula transfer followed by the addition of 4.40 mL (31.8 mmol) of Et_3N. The system was cooled to 0 ˚C for the addition of 5.80 mL (25.4 mmol) of Boc_2O 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_2SO_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):**[17] 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 ˚C ice bath for a H_2O 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_2SO_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 ˚C.

^{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 ˚C 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{14}H_{20}F_2N_3O_2S$ (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

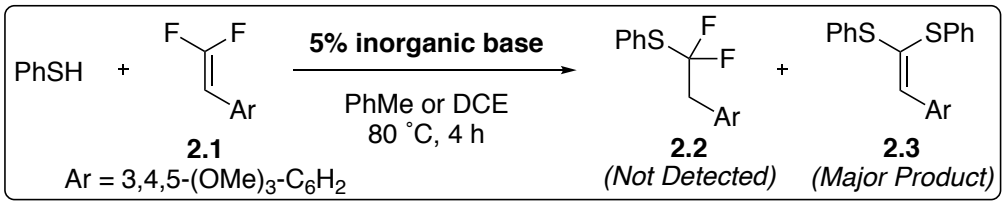
septum and stirred for 3 min at ambient temperature. Subsequently, the vial was placed on a pre-heated reaction block, and stirred at 70–90 ˚C for 0.5–20 h. The vial was cooled to R.T., and 60 µL of α,α,α–trifluorotoluene was added by microsyringe. The solution was stirred at ambient temperature for 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 H_2O. After extraction, the organic layer was dried with $MgSO_4$ or Na_2SO_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 α,α,α–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 H_2O. After extraction, the organic layer was dried with $MgSO_4$ or Na_2SO_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 ^{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 EtOAc and 5 mL saturated $NaHCO_3$ (aq). After extraction, the organic layer was dried with Na_2SO_4 and concentrated, and the crude mixture was purified by flash chromatography.

Preparation and Characterization of Compounds in Scheme 2-6:

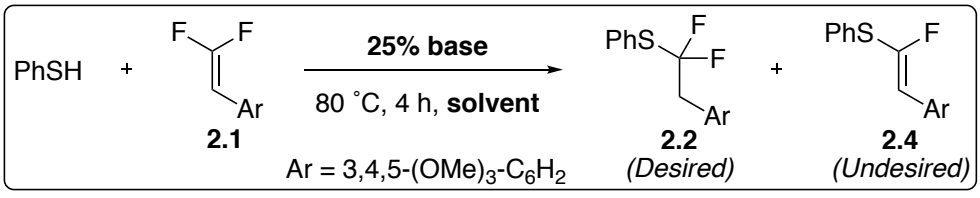
Undesired Reactivity with Inorganic Bases



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_2CO_3, KO-^{t}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.

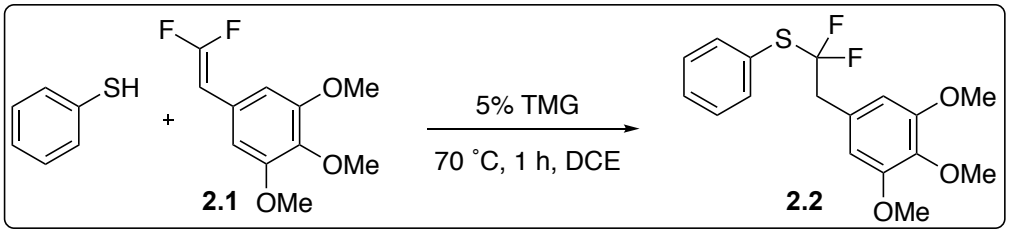
Preparation and Characterization of Compounds Described in Table 2-1



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 (Et_3N, 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 ^{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.

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% Et_2O in PhMe, furnishing 0.14 g (83% yield) of desired product **2.2** as a colorless solid, m.p. 57–58 ˚C.

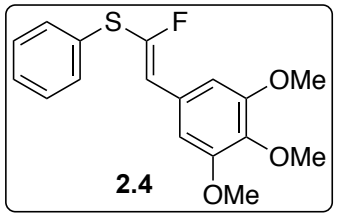
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.4 Hz, 2 H), 7.44–7.35 (m, 3 H), 6.49 (s, 2 H), 3.86 (s, 9 H), 3.37 (t, *J* = 14.7 Hz, 2 H);

^{13}C NMR (126 MHz, $CDCl_3$): 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);

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{19}F_2O_3S$ (M+H) 341.1023, found 341.1007, 4.7 ppm.



2.4

(*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_2O. 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_2O in PhMe to 5% Et_2O 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_2, and subsequently dissolved in anhydrous DCE (0.4 mL, sparged with N_2 for 1 h prior to use). Anhydrous thiophenol (0.030 mL, 0.30 mmol) was added, and then TMG (0.6 µL, 0.005 mmol, sparged with N_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 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: 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_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 µL, 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 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: 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**.

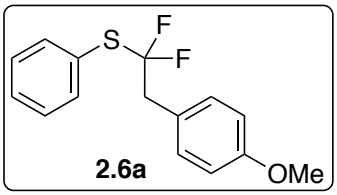
Following a modified General Procedure C, 0.023 g (0.01 mmol) of compound **2.1** and 0.031 g (0.20 mmol) of TEMPO were added to a 1 dram vial. The compound was dissolved in DCE (0.4 mL). The reaction was stirred for 3 min at R.T., and then for 1 h at 70 ˚C. Once returned to R.T., the reaction was standardized 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-D_2: 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-D_2 (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 ^{19}F 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 ^{2}D NMR spectrum. Compound **2.2** yield: 86%, conversion: >99%. No evidence of compound **2.4**. Analysis of the ^{2}D NMR revealed no deuterated resonances (other than DCM-D_2). GC-MS analysis showed no deuterated product. The chromatogram and spectrum were identical to an analogous reaction run in DCM.

Preparation and Characterization of Compounds in Scheme 2-7



2.6a

(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.

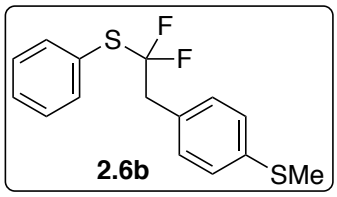
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.3 Hz, 2 H), 7.43–7.34 (m, 3 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 3.81 (s, 3 H), 3.37 (t, *J* = 14.3 Hz, 2 H);

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{15}H_{14}F_2OS$ (M+) 280.0733, found 280.0725, 2.9 ppm.



2.6b

(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 ^{1}H and ^{19}F NMR) as a pale oil.

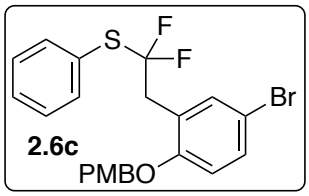
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.6 Hz, 2 H), 7.43–7.34 (m, 3 H), 7.24–7.19 (m, 4 H), 3.38 (t, *J* = 14.7 Hz, 2 H), 2.49 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{15}H_{14}F_2S_2$ (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.

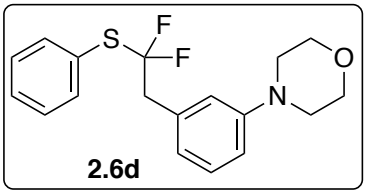
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.5 Hz, 2 H), 7.42–7.32 (m, 7 H), 6.93 (d, *J* = 8.3 Hz, 2 H), 6.83 (d, *J* = 8.7 Hz, 1 H), 5.00 (s, 2 H), 3.83 (s, 3 H), 3.51 (t, *J* = 14.9 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{22}H_{19}BrF_2O_2S$ (M+) 464.03, found 464.0.



2.6d

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.

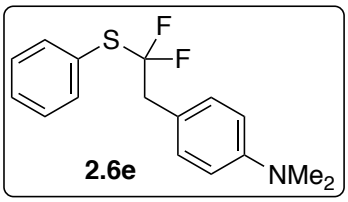
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 6.9 Hz, 2 H), 7.43–7.34 (m, 3 H), 7.25 (t, *J* = 7.7 Hz, 1 H), 6.88 (d, *J* = 8.3 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 2 H), 3.87 (t, *J* = 4.8 Hz, 4 H), 3.39 (t, *J* = 14.8 Hz, 2 H), 3.17 (t, *J* = 4.9 Hz, 4 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{18}H_{20}F_2NOS$ (M+H) 336.1234, found 336.1251, 1.7 mmu.



2.6e

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 ˚C.

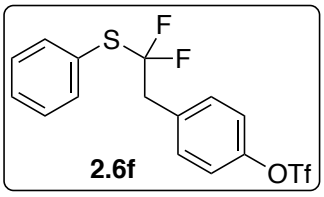
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.57 (m, 2 H), 7.42–7.33 (m, 3 H), 7.16 (d, *J* = 8.2 Hz, 2 H), 6.70 (d, *J* = 8.1 Hz, 2 H), 3.33 (t, *J* = 14.7 Hz, 2 H), 2.96 (s, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 136.2, 131.3, 129.7, 129.4 (t, *J* = 279.9 Hz), 129.1, 127.4 (t, *J* = 2.0 Hz), 119.6, 112.5, 44.4 (t, *J* = 24.2 Hz), 40.7

^{19}F NMR (376 MHz, $CDCl_3$): δ –71.68 (t, *J* = 14.8 Hz, 2 F)

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

HRMS (ESI+): calc. for $C_{16}H_{18}F_2NS$ (M+H) 294.1128, found 294.1123, 1.7 ppm.



2.6f

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).

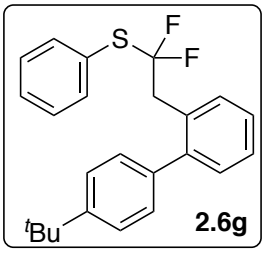
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.56 (m, 2 H), 7.45–7.35 (m, 5 H), 7.27–7.23 (m, 2H), 3.45 (t, *J* = 14.6 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{15}H_{11}F_5O_3S_2$ (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.

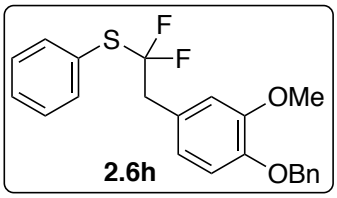
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.8 Hz, 2 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 7.4 Hz, 1 H), 7.36–7.33 (m, 1 H), 7.32 (d, *J* = 8.3 Hz, 2 H), 7.29 (d, *J* = 13.3 Hz, 1 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 3.51 (t, *J* = 15.4 Hz, 2 H), 1.38 (d, *J* = 0.7 Hz, 9 H)

^{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 $C_{24}H_{24}F_2S$ (M+) 382.1567, found 382.1563, 1.0 ppm.



2.6h

(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.

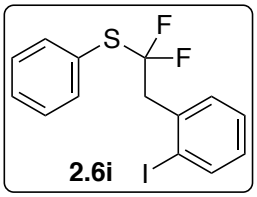
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.57 (m, 2 H), 7.45–7.44 (m, 2 H), 7.42–7.40 (m, 1 H), 7.39–7.35 (m, 4 H), 7.32–7.29 (m, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.83 (d, *J* = 2.0 Hz, 1 H), 6.77 (dd, *J* = 8.3, 2.0 Hz, 1 H), 5.16 (s, 2 H), 3.89 (s, 3 H), 3.36 (t, *J* = 14.6 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 (HAPCI+): calc. for $C_{22}H_{20}F_2O_2S$ (M+) 386.1152, found 386.1153, 0.3 ppm.



2.6i

(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.

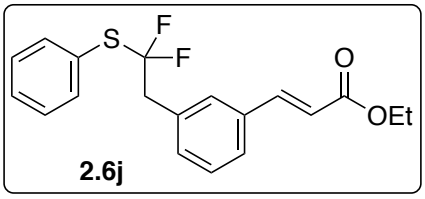
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.63–7.61 (m, 2 H), 7.45–7.35 (m, 4 H), 7.33 (td, *J* = 7.5, 1.3 Hz, 1 H), 6.99 (td, *J* = 7.7, 1.8 Hz, 1 H), 3.69 (t, *J* = 15.0 Hz, 2 H)

^{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 $C_{14}H_{11}F_2S$ (M–I) 249.0550, found 249.0547, 1.2 ppm.



2.6j

ethyl (*E*)-3-(3-(2,2-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.

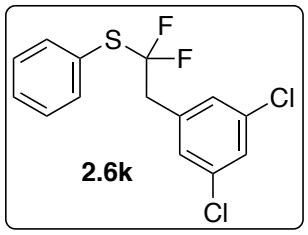
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 16.0 Hz, 1 H), 7.60–7.55 (m, 2 H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.46–7.39 (m, 2 H), 7.40–7.35 (m, 3 H), 7.33–7.29 (m, 1 H), 6.45 (d, *J* = 16.0 Hz, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 3.44 (t, *J* = 14.7 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{19}H_{19}F_2O_2S$ (M+H) 349.1074, found 349.1064, 2.9 ppm.



2.6k

(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. $Na_2S_2O_5$ (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.

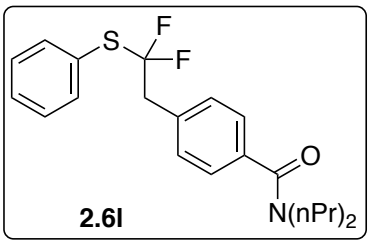
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.57 (m, 2 H), 7.46–7.37 (m, 3 H), 7.33 (t, *J* = 1.9 Hz, 1 H), 7.18 (d, *J* = 1.9 Hz, 2 H), 3.36 (t, *J* = 14.5 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{14}H_{10}Cl_2F_2S$ (M+) 317.9848, found 317.9841, 2.2 ppm.



2.6l

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.

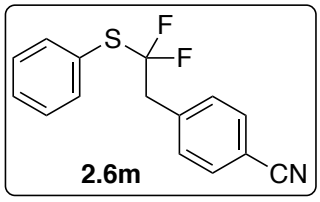
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.7 Hz, 2 H), 7.42–7.29 (m, 7 H), 3.44 (bs, 2 H), 3.43 (t, *J* = 14.8 Hz, 2 H), 3.16 (bs, 2 H), 1.68 (bs, 2 H), 1.53 (bs, 2 H), 0.97 (bs, 3 H), 0.75 (bs, 3 H)

^{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 $C_{21}H_{25}F_2NOSNa$ (M+Na) 400.1523, found 400.1519, 1.0 ppm.



2.6m

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.

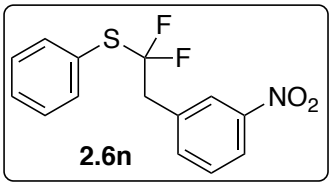
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2 H), 7.56 (d, *J* = 7.5 Hz, 2 H), 7.46–7.36 (m, 5 H), 3.47 (t, *J* = 14.5 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 137.5 (t, *J* = 3.1 Hz), 136.3, 132.3, 131.5, 130.2, 129.3, 128.1 (t, *J* = 280.2 Hz), 126.4 (t, *J* = 2.2 Hz), 118.7, 112.0, 45.2 (t, *J* = 24.8 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –71.85 (t, *J* = 14.5 Hz, 2 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 $C_{15}H_{12}F_2NS$ (M+H) 276.0659, found 276.0654, 1.8 ppm.



2.6n

(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, $CDCl_3$): δ 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)

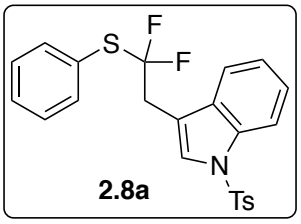
^{13}C NMR (126 MHz, $CDCl_3$): δ 148.4, 136.8, 136.3, 134.1 (t, *J* = 3.1 Hz), 130.2, 129.6, 129.4, 128.1 (t, *J* = 280.0 Hz), 126.4 (t, *J* = 2.3 Hz), 125.6, 123.1, 44.7 (t, *J* = 25.1 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{14}H_{11}F_2NO_2S$ (M+) 295.0479, found 295.0473, 2.0 ppm.

Experimental Procedures and Characterization of Compounds in Scheme 2-9



2.8a

3-(2,2-difluoro-2-(phenylthio)ethyl)-1-tosyl-1*H*-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.

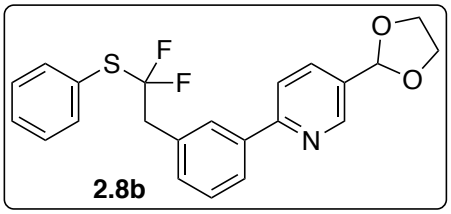
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.3 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.58 (s, 1 H), 7.54 (d, *J* = 7.5 Hz, 2 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.41 (q, *J* = 7.1 Hz, 1 H), 7.34 (dt, *J* = 14.7, 7.6 Hz, 3 H), 7.25 (s, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 3.50 (t, *J* = 14.3 Hz, 2 H), 2.32 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{23}H_{20}F_2NO_2S_2Na$ (M+Na) 466.0723, found 466.0722, 0.6 ppm.



2.8b

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 ^{19}F NMR) as a pale solid, m.p. 77–80 ˚C.

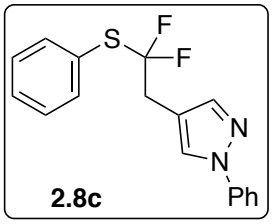
^1H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, *J* = 1.7 Hz, 1 H), 7.95–7.93 (m, 2 H), 7.86 (dd, *J* = 8.2, 2.2 Hz, 1 H), 7.75 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.60–7.58 (m, 2 H), 7.46 (dd, *J* = 8.4, 7.6 Hz, 1 H), 7.43–7.34 (4 H), 5.91 (s, 1 H), 4.18–4.06 (m, 4 H), 3.52 (t, *J* = 14.8 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{22}H_{20}F_2NO_2S$ (M+H) 400.1183, found 400.1175, 2.0 ppm.



2.8c

4-(2,2-difluoro-2-(phenylthio)ethyl)-1-phenyl-1*H*-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 ^{19}F NMR) as a colorless solid, m.p. 65 ˚C.

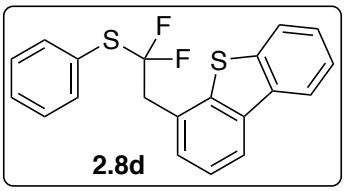
^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.65 (s, 1 H), 7.60 (d, *J* = 7.4 Hz, 2 H), 7.45 (dd, *J* = 8.3, 7.8 Hz, 3 H), 7.39 (dd, *J* = 7.2, 6.7 Hz, 2 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 3.38 (t, *J* = 14.5 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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, $CDCl_3$): δ –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 $C_{17}H_{15}F_2N_2S$ (M+H) 317.0924, found 317.0911, 4.1 ppm.



2.8d

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.

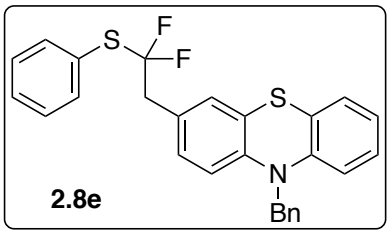
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (ddd, *J* = 8.6, 6.5, 2.8 Hz, 2 H), 7.88–7.86 (m, 1 H), 7.60 (d, *J* = 7.0 Hz, 2 H), 7.49–7.46 (m, 4 H), 7.39 (ddd, *J* = 14.7, 8.2, 6.7 Hz, 3 H), 3.74 (t, *J* = 14.7 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 (HAPCI+): calc. for $C_{20}H_{14}F_2S_2$ (M+) 356.0505, found 356.0516, 3.1 ppm.



2.8e

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.

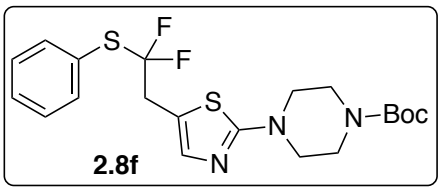
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.55 (m, 2 H), 7.34 (dtd, *J* = 24.1, 12.3, 11.9, 6.0 Hz, 9 H), 7.08 (dd, *J* = 7.6, 1.5 Hz, 1 H), 7.01–6.93 (m, 2 H), 6.89–6.83 (m, 2 H), 6.60 (dd, *J* = 17.9, 8.2 Hz, 2 H), 5.08 (s, 2 H), 3.26 (t, *J* = 14.7 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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}F NMR (376 MHz, $CDCl_3$): δ –71.72 (t, *J* = 14.7 Hz, 2 F)

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

HRMS (ESI+): calc. for $C_{27}H_{22}F_2NS_2$ (M+H) 462.1162, found 462.1182, 2.0 mmu.



2.8f

***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}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.58 (m, 2 H), 7.45–7.35 (m, 3 H), 7.00 (d, *J* = 1.0 Hz, 1 H), 3.55 (dd, *J* = 6.7, 3.8 Hz, 4 H), 3.48–3.41 (m, 6 H), 1.48 (s, 9 H)

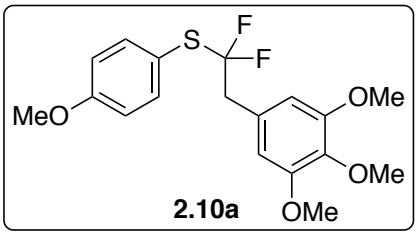
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 154.7, 140.3, 136.4, 130.1, 129.3, 128.3 (t, *J* = 280.0 Hz), 126.7, 116.1 (t, *J* = 3.5 Hz), 80.5, 48.2, 43.0 (bs), 37.3 (t, *J* = 27.1 Hz), 28.5

^{19}F NMR (376 MHz, $CDCl_3$): δ –72.51 (t, *J* = 13.7 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 $C_{20}H_{25}F_2N_3O_2S_2Na$ (M+Na) 464.1254, found 464.1263, 1.9 ppm.

Experimental Procedures and Characterization of Compounds in Scheme 2-10



2.10a

(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_2O 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, $CDCl_3$): δ 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)

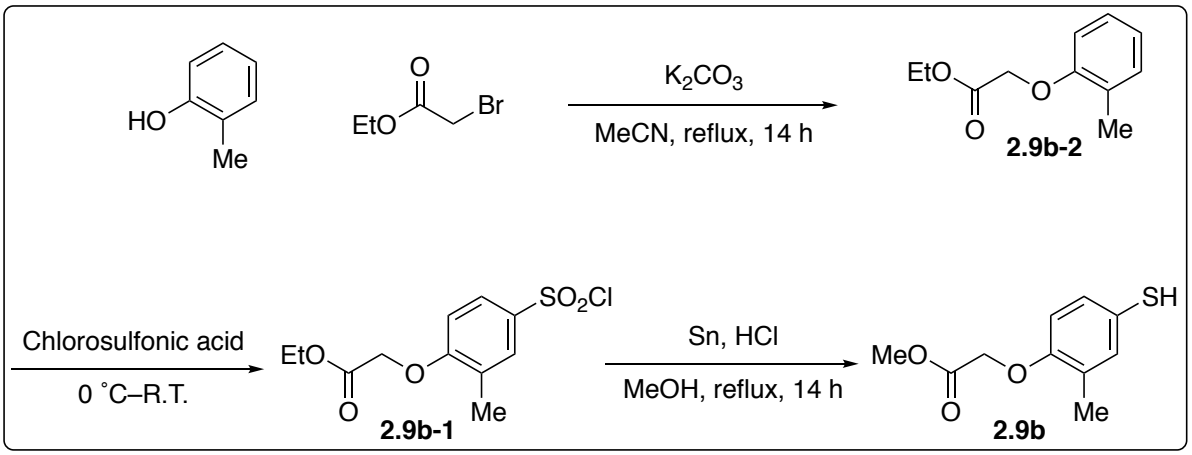
^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2, 153.2, 138.2, 137.6, 128.6 (t, *J* = 279.4 Hz), 127.7 (t, *J* = 3.2 Hz), 117.4 (t, *J* = 2.3 Hz), 114.7, 107.7, 61.0, 56.3, 55.5, 45.4 (t, 24.4 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{18}H_{21}F_2O_4S$ (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 K_2CO_3, and evacuated and backfilled with N_2 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

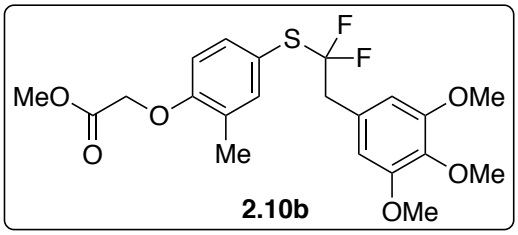
give 10.6 g (97%) of desired product **2.9b-2** as a yellow oil. **2.9b-2** was of sufficient purity to use in the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ 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 K_2CO_3. For full conversion, we recommend anhydrous grade K_2CO_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):[18] Compound **2.9b** was prepared according to a previous report.[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_2O. The organic layer was dried with Na_2SO_4, and concentrated *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 ^1H NMR spectrum matches previous reports.[18]



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 ^{1}H and ^{19}F NMR) as an off-white solid, m.p. 60–63 ˚C.

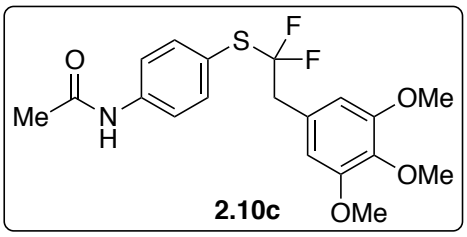
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.35 (m, 2 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 6.49 (s, 2 H), 4.67 (s, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.34 (t, *J* = 14.7 Hz, 2 H), 2.28 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{21}H_{24}F_2O_6SNa$ (M+Na) 465.1159, found 465.1141, 3.9 ppm.



2.10c

***N*-(4-((1,1-difluoro-2-(3,4,5-trimethoxyphenyl)ethyl)thio)phenyl)acetamide (2.10c):** Folllowing 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% Et_3N, to furnish 0.18 g (88% yield) of desired product **2.10c** in 98% purity (as determined by ^1H and ^{19}F NMR) as a colorless solid, m.p. 120–121 ˚C.

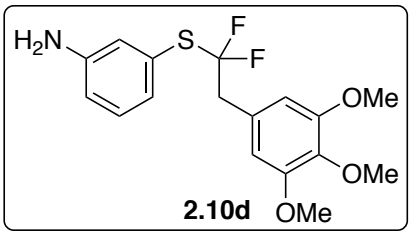
^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (s, 4 H), 7.22 (bs, 1 H), 6.49 (s, 2 H), 3.86 (s, 6H), 3.85 (s, 3 H), 3.34 (t, *J* = 14.7 Hz, 2 H), 2.19 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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, $CDCl_3$): 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 $C_{19}H_{21}F_2NO_4SK$ (M+K) 436.0796, found 436.0792, 0.9 ppm.



2.10d

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 ^{1}H and ^{19}F NMR) as an orange/pink solid, m.p. 87–90 ˚C.

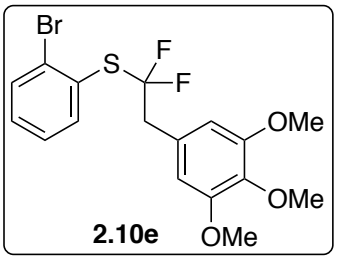
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (t, *J* = 7.8 Hz, 1 H), 6.96 (dt, *J* = 7.7, 1.2 Hz, 1 H), 6.91 (t, *J* = 2.0 Hz, 1 H), 6.71 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1 H), 6.49 (s, 2 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.72 (bs, 2 H), 3.35 (t, *J* = 14.8 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{19}F_2NO_3SNa$ (M+Na) 378.0951, found 378.0958, 1.9 ppm.



2.10e

(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% Et_2O in PhMe, to furnish 0.18 g (84% yield) of desired product **2.10e** as a colorless solid, m.p. 57–58 ˚C.

^{1}H NMR (400 MHz, $CDCl_3$): 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)

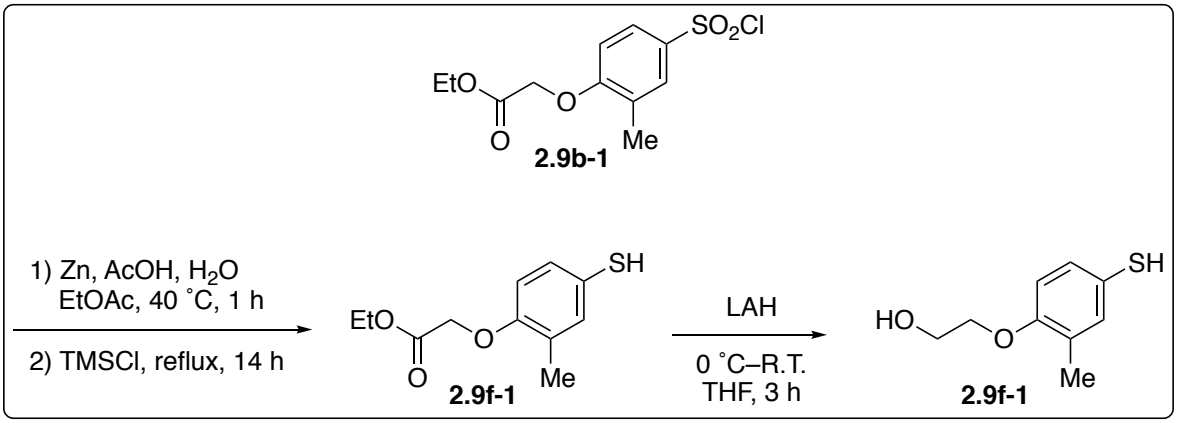
^{13}C NMR (126 MHz, $CDCl_3$): δ 153.2, 137.84, 137.76, 133.7, 131.1, 130.3, 129.0, 128.9 (t, *J* = 281.5 Hz), 128.0, 127.3 (t, *J* = 3.1 Hz), 107.7, 61.0, 56.3, 45.7 (t, *J* = 23.9 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{17}BrF_2O_3S$ (M+) 418.0050, found 418.0050, 0.0 ppm.

Preparation of Compound 2.9f



ethyl 2-(4-mercapto-2-methylphenoxy)acetate (2.9f-1):[19] 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 H_2O 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. NH_4Cl and extracted with EtOAc (3X 50 mL). The organic layer was dried with Na_2SO_4 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

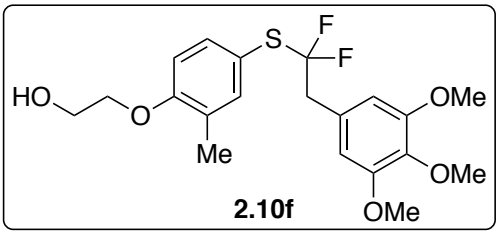
2-(4-mercapto-2-methylphenoxy)ethan-1-ol (2.9f): An oven-dried 100 mL round bottom flask, equipped with a magnetic stirbar, was charged with 0.29 g (7.5 mmol) of lithium aluminum hydride in the glovebox and sealed with a rubber septum. The reaction vessel was removed from the glovebox and submerged in 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_2SO_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.

^{1}H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): δ 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 $C_9H_{11}O_2S$ (M-H) 183.0480, found 183.0443, 3.7 mmu.



2.10f

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.

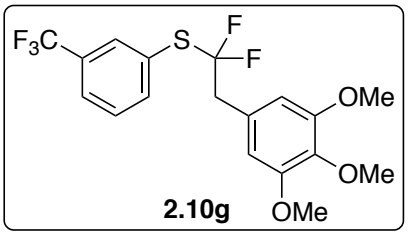
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.35 (m, 2 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 6.50 (s, 2 H), 4.11 (dd, *J* = 5.2, 3.8 Hz, 2 H), 4.02–3.98 (m, 2 H), 3,86 (s, 6 H), 3.85 (s, 3 H), 3.34 (t, *J* = 14.7 Hz, 2 H), 2.23 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{20}H_{24}F_2O_5SNa$ (M+Na) 437.1210, found 437.1221, 2.5 ppm.



2.10g

(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_2O in PhMe, to furnish 0.16 g (78% yield) of desired product **2.10g** as a colorless solid, m.p. 59–60 ˚C.

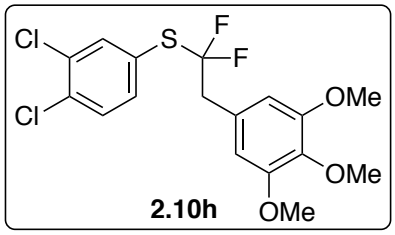
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (s, 1 H), 7.77 (d, *J* = 7.8 Hz, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.50 (t, *J* = 7.8 Hz, 1 H), 6.50 (s, 2 H), 3.87–3.86 (m, 9 H), 3.40 (t, *J* = 14.6 Hz)

^{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 (HAPCI+): calc. for $C_{18}H_{17}F_5O_3S$ (M+) 408.0819, found 408.0812, 1.7 ppm.



2.10h

(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_2O 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)

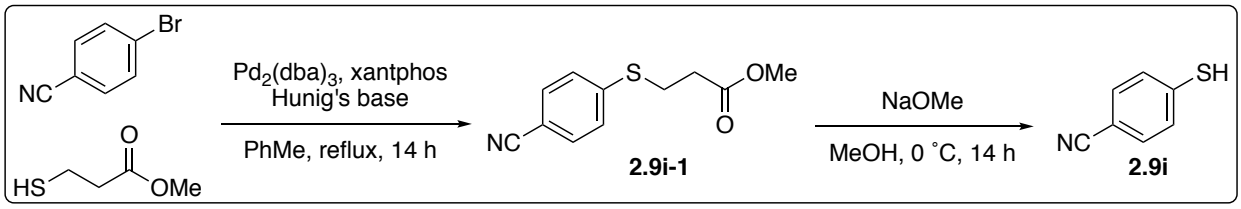
^{13}C NMR (126 MHz, $CDCl_3$): δ 153.3, 137.9, 137.5, 135.2, 134.8, 133.1, 130.9, 128.6 (t, *J* = 281.3 Hz), 127.1 (t, *J* = 3.5 Hz), 126.8 (d, *J* = 2.2 Hz), 107.6, 61.1, 56.3, 45.6 (t, *J* = 23.9 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –78.78 (t, *J* = 14.5 Hz, 2 F)

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 cm^{-1}

HRMS (HAPCI+): calc. for $C_{17}H_{17}Cl_2F_2O_3S$ (M+H) 409.0244, found 409.0241, 0.7 ppm.

Preparation of Compound 9i



4-mercaptobenzonitrile (2.9i):[20] Compound **2.9i** was prepared according to a previous report, with modifications to the first step.[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 *p*-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.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.5 Hz, 2 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 3.71 (s, 3 H), 3.25 (t, *J* = 7.4 Hz, 2 H), 2.69 (t, *J* = 7.4 Hz, 2 H)

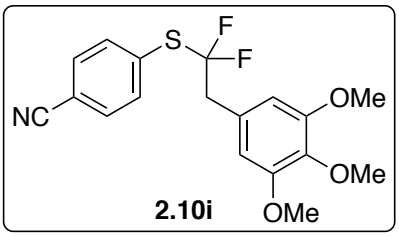
^{13}C NMR (126 MHz, $CDCl_3$): δ 171.8, 143.6, 132.5, 127.4, 118.9, 108.9, 52.2, 33.6, 27.2

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 (HAPCI+): calc. for $C_{11}H_{12}NO_2S$ (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, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 3.67 (s, 1 H).



2.10i

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.

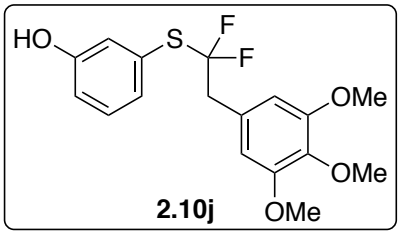
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 6.50 (s, 2 H), 3.41 (t, *J* = 14.5 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{18}H_{18}F_2NO_3S$ (M+H) 366.0975, found 366.0958, 4.6 ppm.



2.10j

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, $CDCl_3$): δ 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)

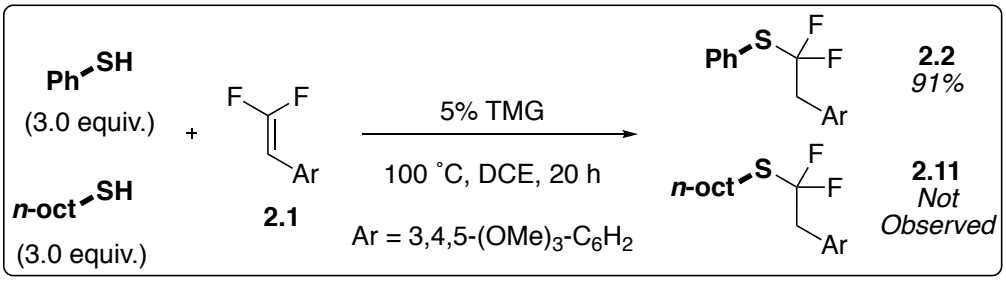
^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 153.2, 137.7, 130.1, 128.8 (t, *J* = 280.1 Hz), 128.4, 128.2 (t, *J* = 2.0 Hz), 127.6 (t, *J* = 3.2 Hz), 122.7, 117.1, 107.7, 61.0, 56.3, 45.5 (t, *J* = 24.4 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –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}

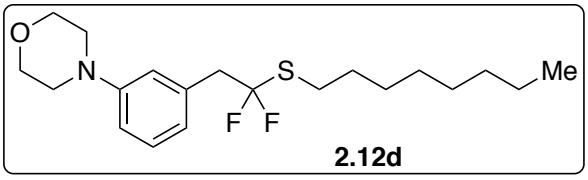
HRMS (ESI+): calc for $C_{17}H_{18}F_2O_4SNa$ (M+Na) 379.0792, found 379.0793, 0.3 ppm.

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



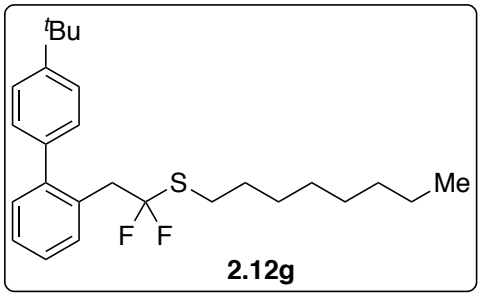
2.12d

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 NMR (500 MHz, $CDCl_3$): δ 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* = 14.50 Hz, 2 H), 3.27–3.25 (m, 4 H), 2.80 (t, *J* = 7.47 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)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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

^{19}F NMR (376 MHz, $CDCl_3$): δ –73.38 (t, *J* = 14.53 Hz, 2 F)



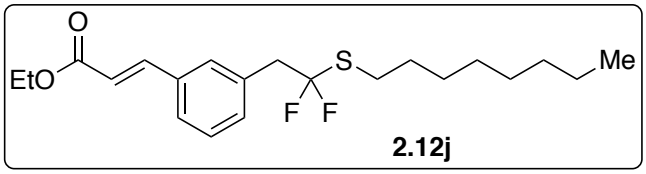
2.12g

(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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ –73.36 (t, *J* = 14.64. Hz, 2 F)



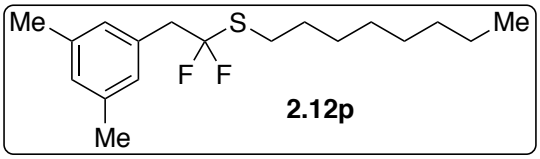
2.12j

ethyl (E)-3-(3-(2,2-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)



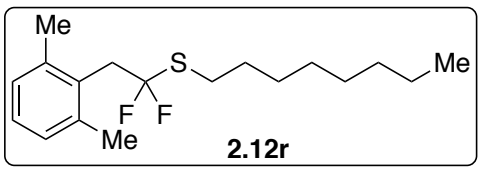
2.12p

(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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ –73.36 (t, *J* = 14.76 Hz, 2 F)



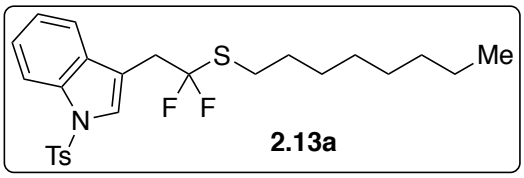
2.12r

(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)



2.13a

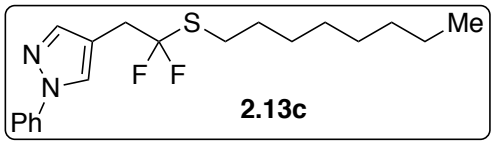
3-(2,2-difluoro-2-(octylthio)ethyl)-1-tosyl-1H-indole (2.13a): Prepared according to General Procedure D, 0.167 g (0.50 mmol) of compound **2.7a** was reacted with 0.26 mL

(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 *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 0.160 g (66 % yield) of desired compound **2.13a** as an orange semisolid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ –72.66 (t, *J* = 14.26 Hz, 2 F)



2.13c

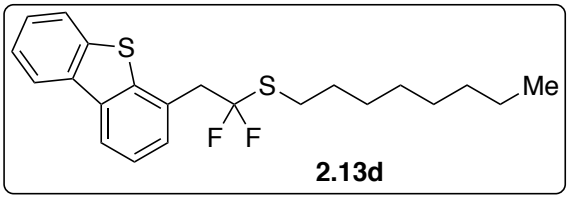
4-(2,2-difluoro-2-(octylthio)ethyl)-1-phenyl-1H-pyrazole (2.13c): Prepared according to General Procedure D, 0.103 g (0.50 mmol) of compound **2.7c** was reacted with 0.13 mL (0.75 mmol) of octanethiol, 0.008 g (0.05 mmol) of lithium triflate, 0.008 mL (0.10

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)



2.13d

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

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).

^{1}H NMR (500 MHz, $CDCl_3$): 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)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): δ –71.76 (t, *J* = 14.41 Hz, 2 F)

References for Chapter 2 Appendix:

1. Zheng, J.; Cai, J.; Lin, J. H.; Guo, Y.; Xiao, J. C., Synthesis and decarboxylative Wittig reaction of difluoromethylene phosphobetaine. *Chem. Commun.* **2013,** *49* (68), 7513-5.

2. Ambler, B. R.; Peddi, S.; Altman, R. A., Ligand-Controlled Regioselective Copper-Catalyzed Trifluoromethylation To Generate (Trifluoromethyl)allenes. *Org. Lett.* **2015,** *17* (10), 2506–9.

3. Nielsen, S. F.; Larsen, M.; Boesen, T.; Schonning, K.; Kromann, H., Cationic Chalcone Antibiotics. Design, Synthesis, and Mechanism of Action. *J. Med. Chem.* **2005,** *48*, 2667–77.

4. Hu, J.; Lu, Y.; Li, Y.; Zhou, J. S., Highly active catalysts of bisphosphine oxides for asymmetric Heck reaction. *Chem. Commun.* **2013,** *49* (82), 9425–7.

5. Ye, F.; Shi, Y.; Zhou, L.; Qing, X.; Zhang, Y.; Wang, J., Expeditious Synthesis of Phenanthrenes via CuBr2-Catalyzed Coupling of Terminal Alkynes and *N*-Tosylhydrazones Derived from *O*-Formyl Biphenyls. *Org. Lett.* **2011,** *13* (19), 5020–3.

6. Chouhan, G.; Alper, H., Synthesis of ring-fused oxazolo- and pyrazoloisoquinolinones by a one-pot Pd-catalyzed carboxamidation and aldol-type condensation cascade process. *J. Org. Chem.* **2009,** *74* (16), 6181–9.

7. Ghosh, D.; Jana, S.; Panja, A.; Anoop, A.; Basak, A., Reactivity of conformationally constrained bispropargyl sulfones: complete preference for 6π-electrocyclization process. *Tetrahedron* **2013,** *69* (41), 8724–30.

8. Biediger, R. J.; Chen, Q.; Decker, E. R.; Holland, G. W.; Kassir, J. M.; Li, W.; Market, R. V.; Scott, I. L.; Wu, C.; Li, J. Preparation of carboxylic acid derivatives that inhibit the binding of integrins to their receptors. US 20040063955, 2004.

9. Qiao, Y.; Si, T.; Yang, M. H.; Altman, R. A., Metal-free trifluoromethylation of aromatic and heteroaromatic aldehydes and ketones. *J. Org. Chem.* **2014,** *79* (15), 7122-31.

10. West, T. H.; Daniels, D. S.; Slawin, A. M.; Smith, A. D., An isothiourea-catalyzed asymmetric [2,3]-rearrangement of allylic ammonium ylides. *J. Am. Chem. Soc.* **2014,** *136* (12), 4476–9.

11. Palani, A.; Xiao, D.; Aslanian, R. G.; Berlin, M. Y.; Rao, A. U.; Chen, X.; Lee, Y. J.; Degrado, S.; Shao, N.; Huang, Y. R.; Liu, Z. Preparation of azine derivatives useful in treatment and prevention of diseases. WO 2010045306, 2010.

12. Tang, L.; Wasserman, E. P.; Neithamer, D. R.; Krystosek, R. D.; Cheng, Y.; Price, P. C.; He, Y.; Emge, T. J., Highly Active Catalysts for the Ring-Opening Polymerization of Ethylene Oxide and Propylene Oxide Based on Products of Alkylaluminum Compounds with Bulky Tetraphenol Ligands. *Macromolecules* **2008,** *41*, 7306–15.

13. Cloeter, M. D.; Kar, K. K.; Matyjaszewski, K.; Mosnacek, J.; Nicolay, R. Synergistic polymerization inhibitor composition and method. 2012.

14. Cao, D.; Peng, J.; Hong, Y.; Fang, X.; Wang, L.; Meier, H., Enhanced Performance of the Dye-Sensitized Solar Cells with Phenothiazine-Based Dyes Containing Double D–A Branches. *Org. Lett.* **2011,** *13* (7), 1610–3.

15. Reich, M.; Schunk, S.; Jostock, R.; Hees, S.; Germann, T.; Engels, M. F.-M. Preparation of disulfonamides as bradykinin receptor modulators. WO 2010051977, 2010.

16. Sun, R.; Cooper, A. B.; Deng, Y.; Wang, T.; Nan, Y.; Zhu, H. Y.; Boga, S. B.; Gao, X.; Kelly, J. M.; Paliwal, S.; Tsui, H.-C.; Doll, R. J.; Shih, N.-Y. Preparation of heterocyclicpyrazoloquinazolinylpyrrolidinylethanone derivatives for use as ERK inhibitors. WO 2008156739, 2008.

17. Anandan, S. K.; Ward, J. S.; Brokx, R. D.; Denny, T.; Bray, M. R.; Patel, D. V.; Xiao, X. Y., Design and synthesis of thiazole-5-hydroxamic acids as novel histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett.* **2007,** *17* (21), 5995–9.

18. (a) Sauerberg, P.; Jeppesen, L.; Polivka, Z.; Sindelar, K. Dicarboxylic Acid Derivatives as PPAR-Agonists. WO 2003DK00895, 2004; (b) Sauerberg, P.; Bury, P. S.; Jeppesen, L.; Mogensen, J. P. Long-chain, unsaturated, aromatic dicarboxylic acid derivatives, their preparation, and therapeutic use for treatment of conditions mediated by peroxisome proliferator-activated receptors (PPAR). WO 2002-DK692, 2003.

19. Conner, S. E.; Mantlo, N. B.; Zhu, G.; Herr, R. J. Preparation of bicyclic derivatives as PPAR modulators. July 21, 2005, 2005.

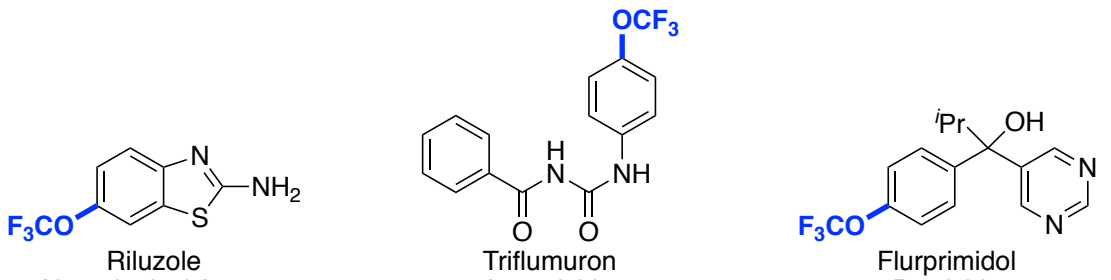
20. Itoh, T.; Mase, T., Practical Thiol Surrogates and Protective Groups for Arylthiols for Suzuki–Miyaura Conditions. *J. Org. Chem.* **2006,** *71*, 2203–6.

Chapter 3 – Organocatalytic Reactions of Alcohols with *gem*-Difluoroalkenes

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 σ-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 α-fluorination of the heteroatom, perturbing normal biological properties. Fluorination α- 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 e^--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]



Riluzole
Neurological Agent
Glutamate Blocker

Triflumuron
Insecticide
Chitin Synthesis Inhibitor

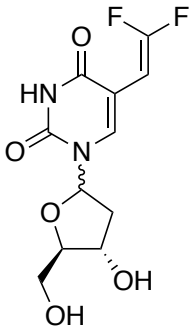
Flurprimidol
Pesticide
Plant Growth Regulator

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**).[3c, 5] However, fluorinated dialkyl ethers are less common, due to the synthetic difficulty in accessing this moiety. *Gem*-difluorinated dialkyl ethers are[6] only synthesized *via* deoxyfluorination[7] or through reactions with gaseous difluoroethylene.[8] The most common method to synthesize *gem*-difluorinated dialkyl ethers involves deoxyfluorination.[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,[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,[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**),[10f, 11] we envisioned that alcohols might react with *gem*-difluoroalkenes to provide the desired *gem*-difluoro dialkyl ethers under mild conditions.

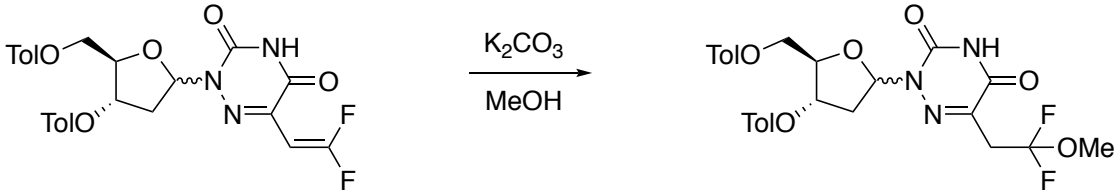
Figure 3-2: *Gem*-Difluoroalkenes in Medicinal Chemistry

a) Gem-*Difluoroalkene-Based Inhibitor of Herpes Simplex Virus Replication*[10f]



Virus	MIC_{50} μg/mL α-anomer	β-anomer
HSV-1 (KOS)	20	0.2
HSV-1 (F)	20	0.3
HSV-1 (McIntyre)	20	0.3
HSV-2 (G)	150	6
HSV-2 (196)	100	10
HSV-2 (Lyons)	70	3

b) Reaction of gem-*Difluoroalkene Containing Aza-Uracil Derivative with Alcohols*[11]

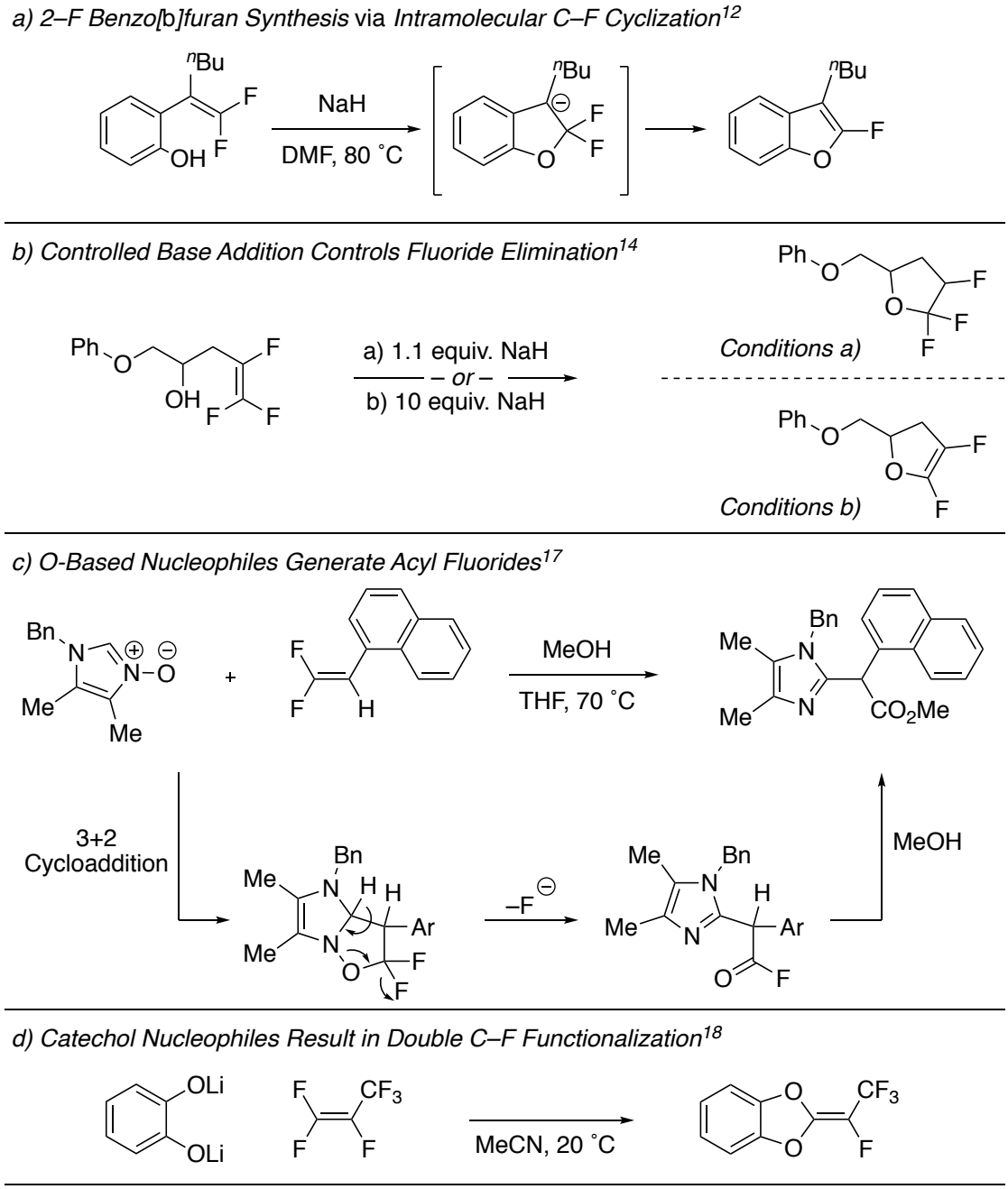


Of the existing reactions of *gem*-difluoroalkenes with alcohols, the vast majority result in a net C–F functionalization reaction to provide mono-fluoroalkenes. For instance, intramolecular nucleophilic cyclizations of *gem*-difluoroalkenes with alcohols generate 2-fluoro benzo[*b*]furans (**Scheme 3-1a**),[12] or other heterocycles, such as furans.[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**).[14] Furthermore, many base-catalyzed intermolecular additions of alcohol nucleophiles to *gem*-difluoroalkenes defluorinated the substrate.[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.[16] This same defluorination occurs when hydroxide is added to *gem*-difluoroalkenes.[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.

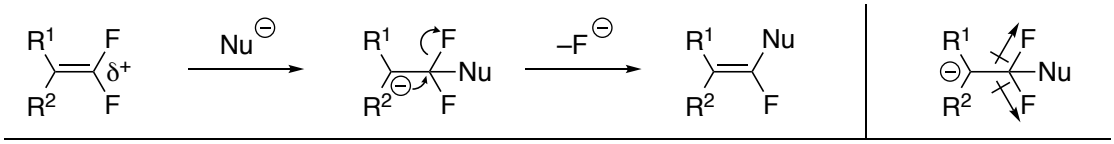
Scheme 3-1: Representative Reactions of *gem*-Difluoroalkenes with O-Based Nucleophiles



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.[1h, 1x] This arises from the unique reactivity of fluorinated alkenes relative to non-fluorinated alkenes. The σ-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 (**Figure 3-3**).[1h, 1x] Unfortunately, the carbanion is less thermodynamically stable than a fluoride anion. Thus, the anionic intermediate undergoes β-fluoride elimination to deliver monofluorinated products (**Figure 3-3**).[1h, 1x, 22]

Figure 3-3: Physicochemistry of *gem*-Difluoroalkenes

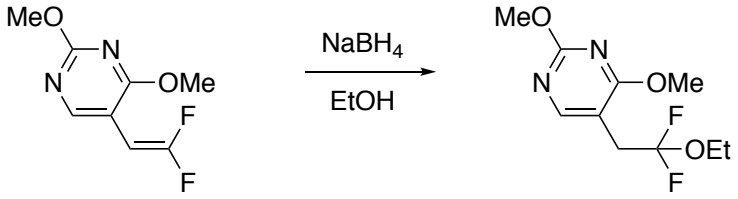


As highlighted by the addition of alcohols to *gem*-difluoroalkene containing uracil derivatives, O-based nucleophiles can react with *gem*-difluoroalkenes without undergoing fluoride elimination, demonstrating the possibility of a general fluorine-retentive hydrofunctionalization reaction of alcohols with *gem*-difluoroalkenes. Under base-catalyzed solvolysis conditions, intermolecular reactions of alcohols with *gem*-difluoroalkenes proceed without β-fluoride elimination (**Scheme 3-2a**).[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.[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-

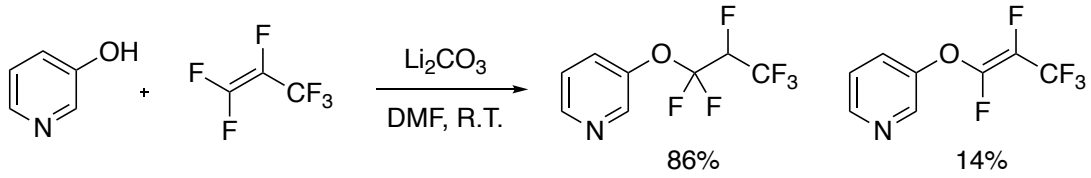
hydroxypyridine nucleophile added into *gem*-difluoroalkenes and selectively retained both fluorine atoms, without using the hydroxypyridine as the solvent (**Scheme 3-2b**).[24]

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

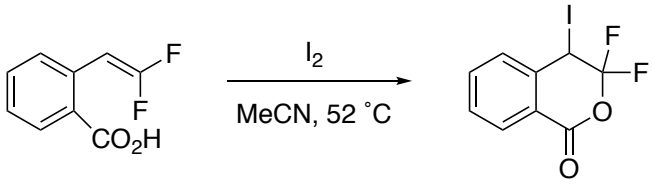
a) Representative Fluorine Retentive Reactions of gem*-Difluoroalkenes with Alcohols*[11]



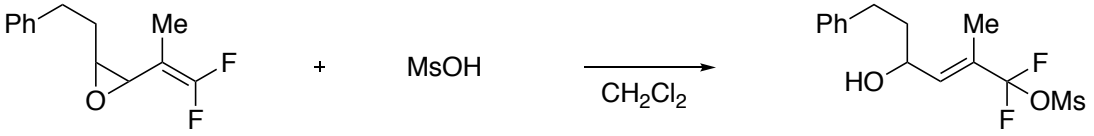
b) Fluorine-Retentive Nucleophilic Addition of 3-Hydroxypyridine to gem*-Difluoroalkenes*[24]



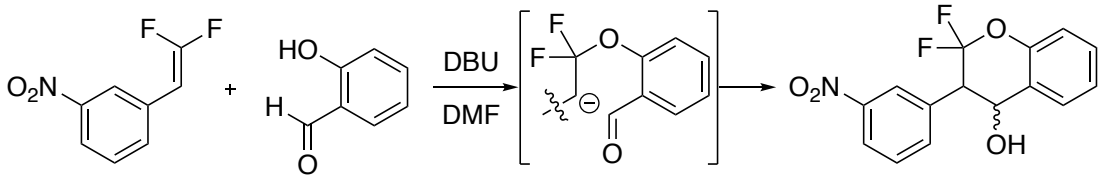
c) Rare Fluorine-Retentive Cyclization Reactions of gem*-Difluoroalkenes*[14]



d) β-Anion Propogation Prevents Fluoride Elimination[26]



e) Intramolecular Trapping of β-Anion with Aldehyde Preventing Fluoride Eliminiation[27]

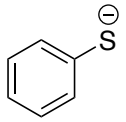
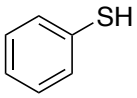
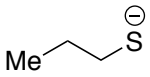
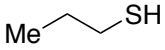
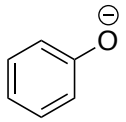
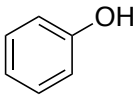


Other rare examples of fluorine-retentive nucleophilic addition of alcohols to difluoroalkenes exploit difunctionalization with strong oxidants or unique reagents. Cyclizations of *gem*-difluoroalkenes with O-based nucleophiles in the presence of either iodine[14, 25] or mercury and a tin-hydride[25b] 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 γ-epoxide. The β-anion preferentially opens the epoxide instead of eliminating fluoride, enabling fluorine retentive nucleophilic addition (**Scheme 3-2d**).[26] In the second example, specially designed nucleophiles position an aldehyde proximal to the β–anion, rapidly trapping the β-anionic intermediate *via* intramolecular cyclization after nucleophilic addition, retaining both fluorine atoms (**Scheme 3-2e**).[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*

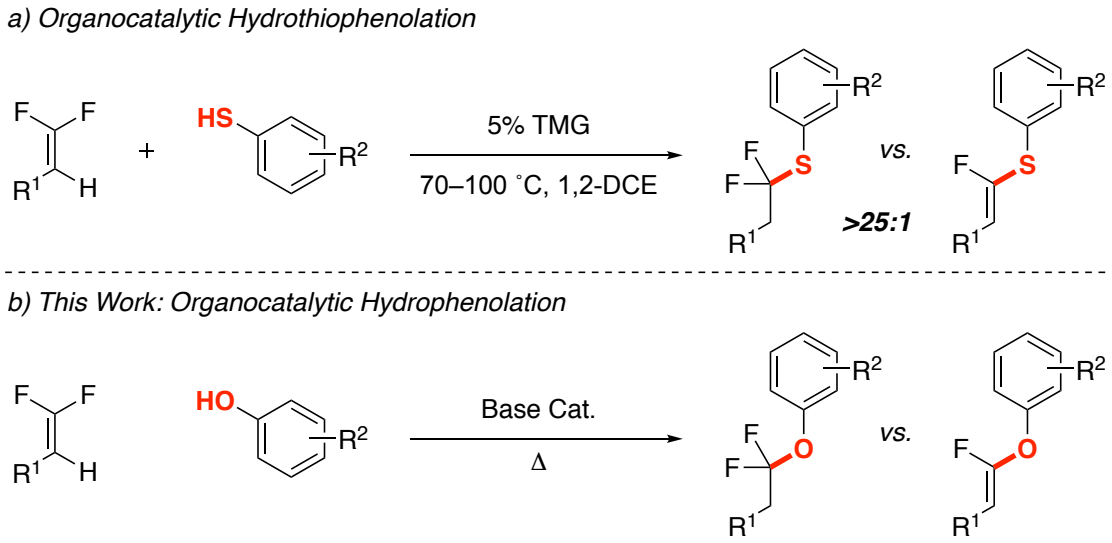
After the successful hydrofunctionalization of *gem*-difluoroalkenes with thiol-based nucleophiles,[28] we envisioned that, due to the similar properties of sulfur and oxygen, *gem*-difluoroalkenes might undergo fluorine-retentive hydrofunctionalization with alcohols under similar conditions. However, alcohol nucleophiles present a greater challenge than thiol nucleophiles, as alcohols possess both lower nucleophilicity[29] and lower acidity[30] than the corresponding thiols (**Figure 3-4**).

Figure 3-4: The Physicochemistry of Alcohols Presents a Greater Challenge than Thiols

Swain-Scott Nucleophilicity (*s*)[29]		Acidity pK_a (H_2O)[30]	
	9.92		6.61
	6.95		10.86
	5.75		9.97

Even with these challenges, we envisioned that employing alcohols in a nucleophilic hydrofunctionalization of *gem*-difluoroalkenes would enable access to an under-represented 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**).

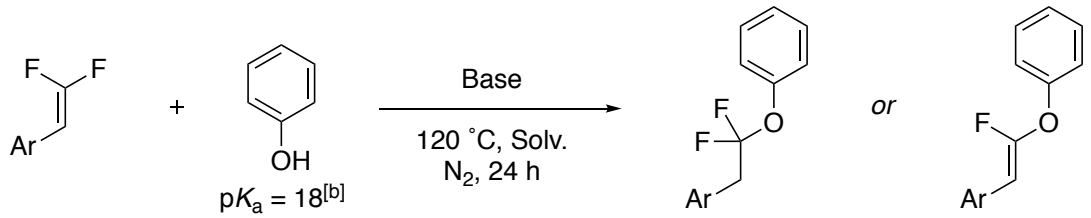
Scheme 3-3: Extension of Hydrofunctionalization Reactions of *gem*-Difluoroalkenes to Phenol Nucleophiles



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 ^{t}BuOK (**entry 3**), 1,8-diazabicylco[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 ^{t}BuOK selectively delivered

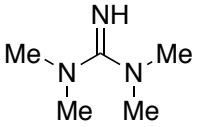
3.4. The use of stronger phosphorazine superbases reduced the selectivity versus α-monofluorovinylether side product **3.4** (**entry 6**), presumably due to deprotonation and β-fluoride elimination of desired product **3.4**. The use of aromatic solvents provided improved selectivity versus other solvents (**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[a]

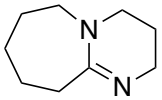


3.1 **3.2** *Ar = 3,4,5-(OMe)$_3$-C$_6$H$_2$* **3.3** **3.4**

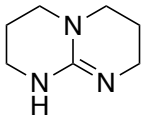
Entry	Base	pK_a[b]	Solv.	Conv.	**3.3**	**3.4**
1[c]	TMG	16	DCE	40	0	0
2	TMG	16	$(NO_2)C_6H_5$	40	22	9
3[d]	^{t}BuOK	N/D	$(NO_2)C_6H_5$	39	7	25
4[d]	DBU	17	$(NO_2)C_6H_5$	30	15	7
5	TBD	21	$(NO_2)C_6H_5$	83	46	14
6	P_2Et	25	$(NO_2)C_6H_5$	72	33	19
7	TMG	16	DMF	84	18	30
8	TMG	16	DMSO	98	6	64
9	TMG	16	Anisole	65	16	3
10	TMG	16	*o*-Xylene	45	17	2
11	TMG	16	Benzonitrile	67	36	18
12	TMG	16	DCB	56	18	3
13	TBD	21	DCB	90	53	10
14[e]	TBD	21	DCB	89	61	11
15[d,e]	TBD	21	DCB	63	31	5
16[e,f]	TBD	21	DCB	>99	70	17
17[g]	TBD	21	DCB	>99	60	17



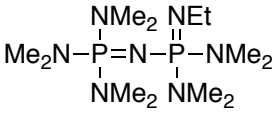
TMG



DBU



TBD



P_2Et

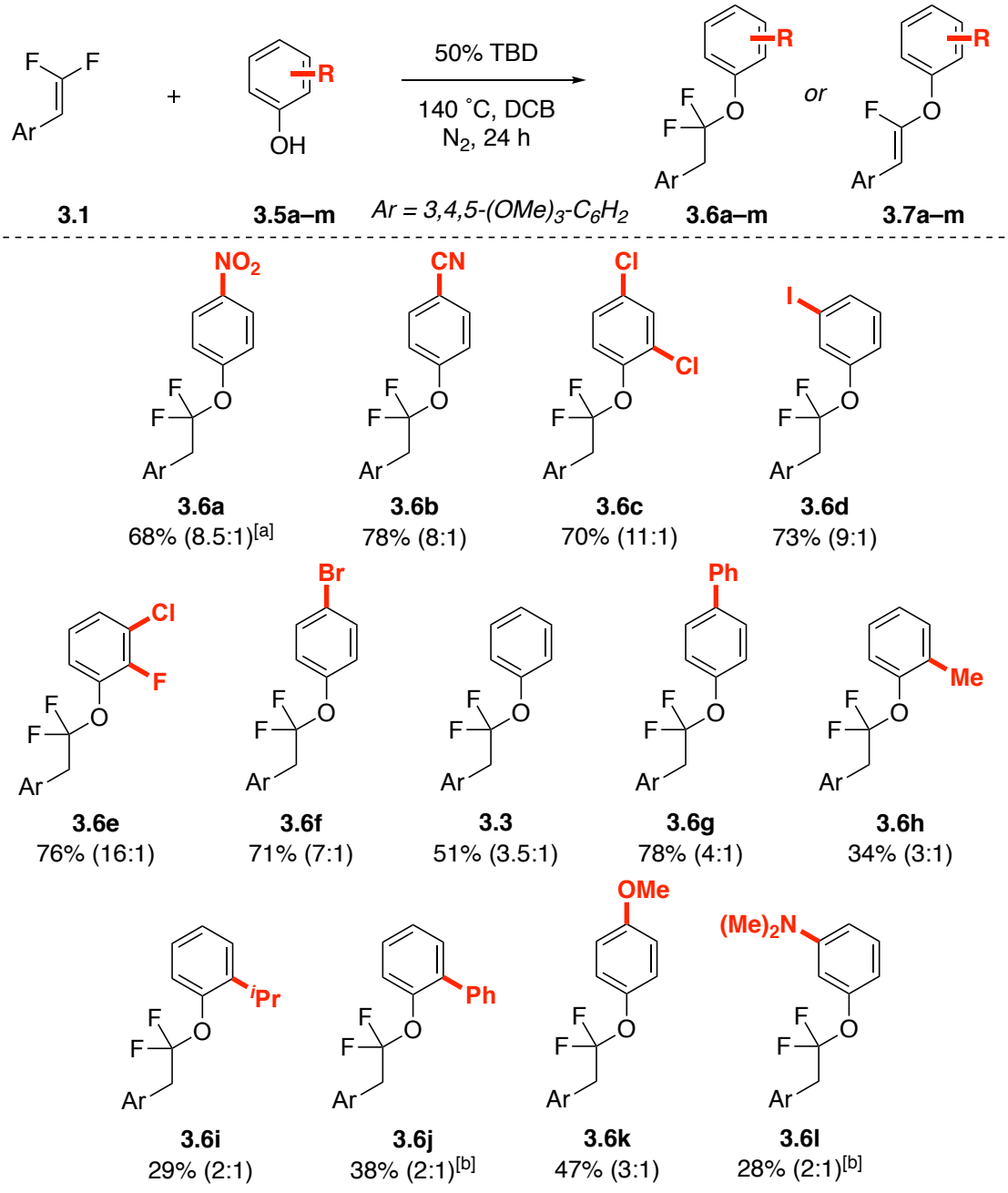
[a] **3.1** (1.0 equiv., 0.10 mmol), **3.2** (5.0 equiv., 0.50 mmol), base (0.25 equiv., 0.025 mmol), solvent (1 M, 0.10 mL), 120 ˚C, for 4 h under an N_2 atmosphere. Conversion of **3.1** and yields of **3.3** and **3.4** were determined by ^{19}F NMR analysis using α,α,α-trifluorotoluene (TFT) as a standard (10 μL, 0.080 mmol). [b] pK_a in THF.[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 N_2 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 phosphorazine 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

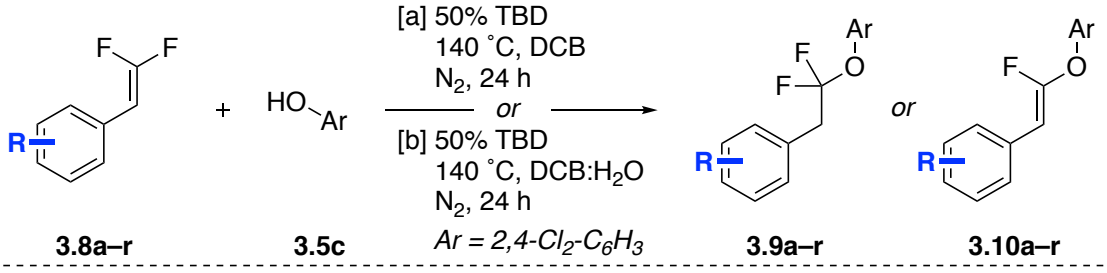


Standard conditions: **3.1** (1.0 equiv., 0.50 mmol), **3.5a–o** (5.0 equiv., 2.5 mmol), TBD (0.50 equiv., 0.25 mmol), DCB (0.5 M, 1.0 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **3.6:3.7** was determined by ^{19}F NMR analysis of the crude reaction mixture using TFT (50 µL, 0.40 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.

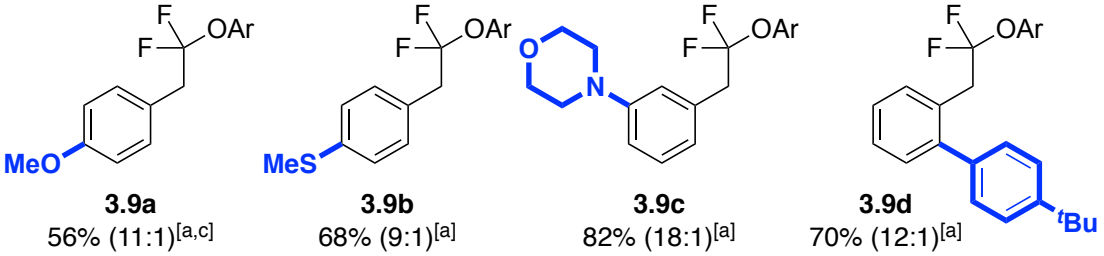
Many synthetically and biomedically useful functional groups were tolerated on the *gem*-difluoroalkene substrate (**Scheme 3-5**). Specifically, the reaction tolerated thioethers and ethers (**3.9a–b**), morpholine (**3.9c**), nitrogen-containing functional groups (**3.9k–l**), halides (**3.9m–p**) 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 ^{t}Bu-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-NO_2 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:H_2O) 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-^{t}Bu)-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–Me_2-substituted substrate not reacting at all (**3.9i**).

Scheme 3-5: Scope of *gem*-Difluoroalkene Electrophiles



3.8a–r **3.5c** **3.9a–r** **3.10a–r**

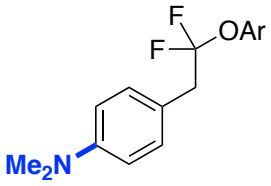


3.9a
56% (11:1)[a,c]

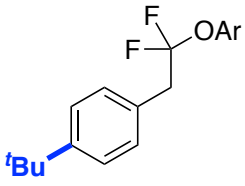
3.9b
68% (9:1)[a]

3.9c
82% (18:1)[a]

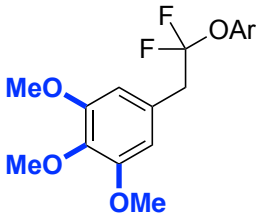
3.9d
70% (12:1)[a]



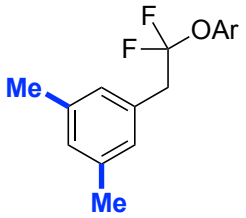
3.9e
<10% (2:3)[a,c,d]



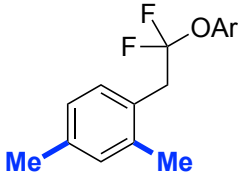
3.9f
40% (22:1)[a]



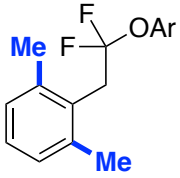
3.3
70% (11:1)[a]



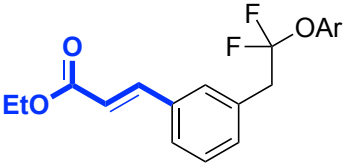
3.9g
56% (20:1)[a]



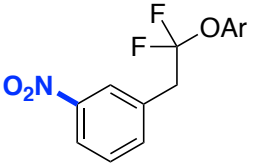
3.9h
24% (14:1)[a]



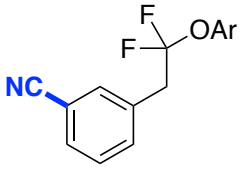
3.9i
0% (N/A)[a]



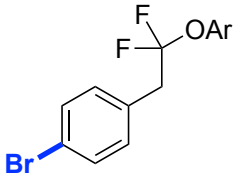
3.9j
62% (8:1)[a]



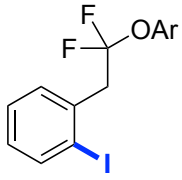
3.9k
48% (5.5:1)[a]



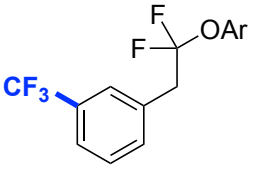
3.9l
50% (4:1)[b]



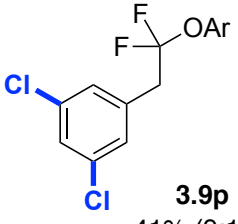
3.9m
59% (5.5:1)[b]



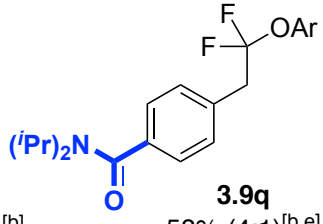
3.9n
46% (6:1)[b]



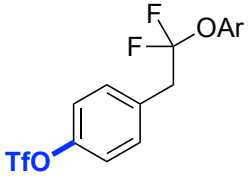
3.9o
49% (4:1)[b]



3.9p
41% (9:1)[b]



3.9q
58% (4:1)[b,e]

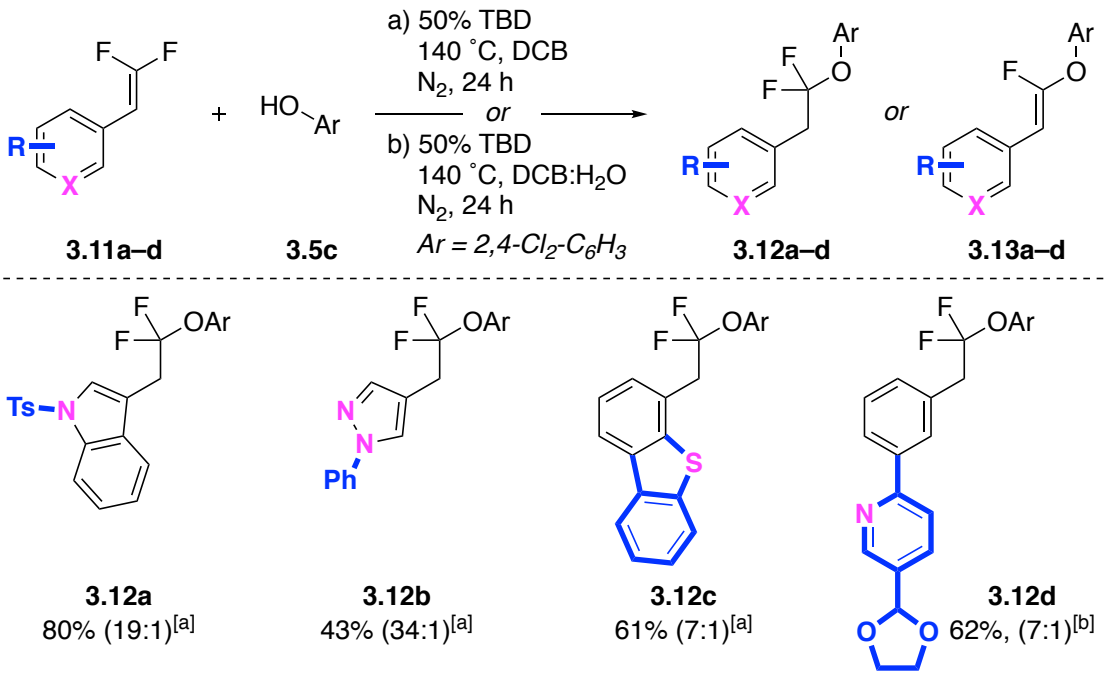


3.9r
52% (5:1)[b,f]

[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 N_2 atmosphere. The selectivity of **3.9:3.10** was determined by ^{19}F 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), H_2O (0.05 M, 0.10 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **3.9:3.10** was determined by ^{19}F 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 ^{19}F 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



[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 N_2 atmosphere. The selectivity of **3.12:3.13** was determined by ^{19}F 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), H_2O (0.05 M, 0.10 mL), 140 ˚C, for 24 h under an N_2 atmosphere. The selectivity of **3.12:3.13** was determined by ^{19}F 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.

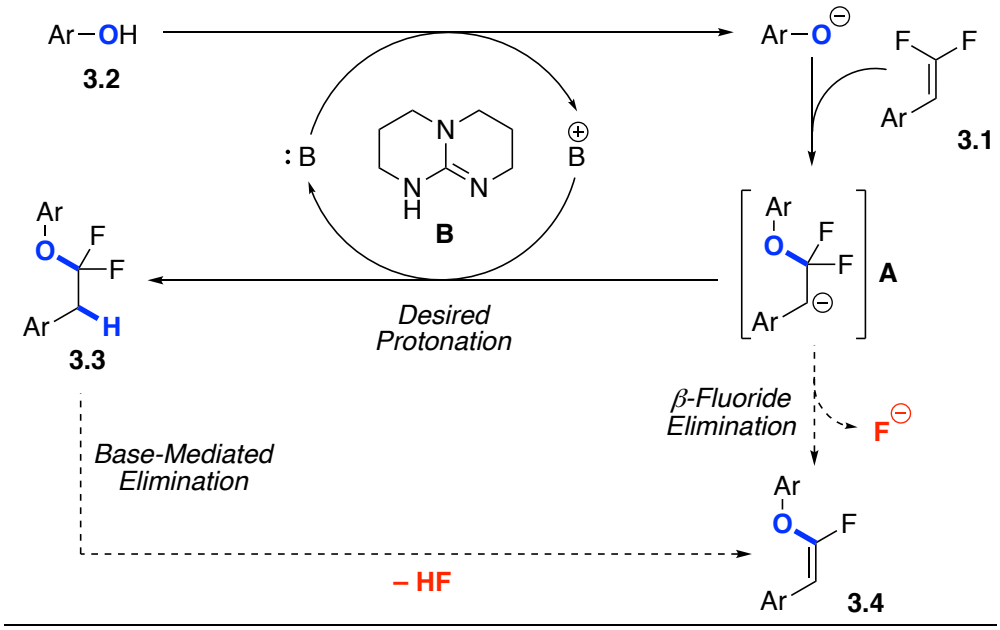
3.3. Mechanistic Considerations

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**. Specfically, 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 pK_as 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[7, 32] to generate the fluorine-based substructure, or require harsh conditions[33] and/or gaseous reagents.[8]

Notably, this method contrasts the many reactions of *gem*-difluoroalkenes that selectively generate monofluoroalkene products.[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

1. (a) Faqua, S. A.; Duncan, W. G.; Silverstein, R. M., A one-step synthesis of 1,1-difluoroolefins from aldehydes by a modified wittig synthesis. *Tetrahedron Lett.* **1964,** *5* (23), 1461-1463; (b) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M., A One-Step Synthesis of 1,1-Difluoro Olefins from Aldehydes. *J. Org. Chem.* **1965,** *30* (4), 1027-1029; (c) Li, Q.; Lin, J. H.; Deng, Z. Y.; Zheng, J.; Cai, J.; Xiao, J. C., Wittig *gem*-difluoroolefination of aldehydes with difluoromethyltriphenylphosphonium bromide. *J. Fluorine Chem.* **2014,** *163*, 38-41; (d) Zheng, J.; Cai, J.; Lin, J. H.; Guo, Y.; Xiao, J. C., Synthesis and decarboxylative Wittig reaction of difluoromethylene phosphobetaine. *Chem. Commun.* **2013,** *49* (68), 7513-5; (e) Naae, D. G.; Burton, D. J., Stable Difluoromethylene Olefination Solutions. *Synth. Commun.* **1973,** *3* (3), 197-200; (f) Bhadury, P. S.; Palit, M.; Sharma, M.; Raza, S. K.; Jaiswal, D. K., Fluorinated phosphonium ylides: versatile in situ Wittig intermediates in the synthesis of hydrofluorocarbons. *J. Fluorine Chem.* **2002,** *116* (1), 75-80; (g) Ichitsuka, T.; Takanohashi, T.; Fujita, T.; Ichikawa, J., A versatile difluorovinylation method: Cross-coupling reactions of the 2,2-difluorovinylzinc-TMEDA complex with alkenyl, alkynyl, allyl, and benzyl halides. *J. Fluorine Chem.* **2015,** *170*, 29-37; (h) Zhang, X.; Cao, S., Recent advances in the synthesis and CF functionalization of gem-difluoroalkenes. *Tetrahedron Lett.* **2017,** *58* (5), 375-392; (i) Zheng, J.; Lin, J. H.; Cai, J.; Xiao, J. C., Conversion between difluorocarbene and difluoromethylene ylide. *Chemistry* **2013,** *19* (45), 15261-6; (j) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J., gem-Difluoroolefination of diaryl ketones and enolizable aldehydes with difluoromethyl 2-pyridyl sulfone: new insights into the Julia-Kocienski reaction. *Chemistry* **2014,** *20* (25), 7803-10; (k) Krishnamoorthy, S.;

Kothandaraman, J.; Saldana, J.; Prakash, G. K. S., Direct Difluoromethylenation of Carbonyl Compounds by Using TMSCF3: The Right Conditions. *Eur. J. Org. Chem.* **2016,** *2016* (29), 4965-4969; (l) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J., gem-Difluoroolefination of Diazo Compounds with TMSCF3 or TMSCF2Br: Transition-Metal-Free Cross-Coupling of Two Carbene Precursors. *J. Am. Chem. Soc.* **2015,** *137* (45), 14496-501; (m) Gogsis, T. M.; Sobjerg, L. S.; Lindhardt, A. T.; Jensen, K. L.; Skrydstrup, T., Direct Vinylation and Difluorovinylation of Arylboronic Acids Using Vinyl- and 2,2-Difluorovinyl Tosylates via the Suzuki-Miyaura Cross Coupling. *J. Org. Chem.* **2008,** *73*, 3404–10; (n) Thomoson, C. S.; Martinez, H.; Dolbier, W. R., The use of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate as the difluorocarbene source to generate an in situ source of difluoromethylene triphenylphosphonium ylide. *J. Fluorine Chem.* **2013,** *150*, 53-59; (o) Wang, F.; Li, L.; Ni, C.; Hu, J., Deoxygenative gem-difluoroolefination of carbonyl compounds with (chlorodifluoromethyl)trimethylsilane and triphenylphosphine. *Beilstein J Org Chem* **2014,** *10*, 344-51; (p) Aikawa, K.; Toya, W.; Nakamura, Y.; Mikami, K., Development of (Trifluoromethyl)zinc Reagent as Trifluoromethyl Anion and Difluorocarbene Sources. *Org. Lett.* **2015,** *17* (20), 4996-9; (q) Prakash, G. K. S.; Wang, Y.; Hu, J. B.; Olah, G. A., Nucleophilic difluoromethylation and difluoromethylenation using bromodifluoromethyl phenyl sulfone. *J. Fluorine Chem.* **2005,** *126* (9-10), 1361-1367; (r) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J., Difluoromethyl 2-pyridyl sulfone: a new gem-difluoroolefination reagent for aldehydes and ketones. *Org. Lett.* **2010,** *12* (7), 1444-7; (s) Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M., Difluorophenylsulfanylmethyl radical and difluoromethylene diradical synthons: gem-difluoromethylene building block. *J. Org. Chem.* **2004,** *69* (20), 6913-5; (t) Zhu, L. G.; Li,

Y.; Zhao, Y. C.; Hu, J. B., Nucleophilic (phenylsulfonyl)difluoromethylation of alkyl halides using PhSO2CF2SiMe3: preparation of gem-difluoroalkenes and trifluoromethyl compounds. *Tetrahedron Lett.* **2010,** *51* (47), 6150-6152; (u) Prakash, G. K.; Hu, J.; Wang, Y.; Olah, G. A., Difluoromethyl phenyl sulfone, a difluoromethylidene equivalent: use in the synthesis of 1,1-difluoro-1-alkenes. *Angew. Chem. Int. Ed. Engl.* **2004,** *43* (39), 5203-6; (v) Zhang, L.; Li, Y.; Hu, J., Preparation of 1-aryl-2,2-difluoro enol esters via dehydrosulfonylation of α-(phenylsulfonyl)difluoromethylated benzoates. *J. Fluorine Chem.* **2007,** *128* (7), 755-761; (w) Bégué, J.-P.; Bonnet-Delpon, D.; Rock, M. H., A concise synthesis of functionalised gem-difluoroalkenes, via the addition of organolithium reagents to α-trifluoromethylstyrene. *Tetrahedron Lett.* **1995,** *36* (28), 5003-5006; (x) Amii, H.; Uneyama, K., C-F bond activation in organic synthesis. *Chem. Rev.* **2009,** *109* (5), 2119-83; (y) Ichikawa, J., Synthetic Methods for Heterocycles and Carbocycles Bearing Fluorinated One-Carbon Units (=CF2, CHF2, or CF3): Intramolecular Reaction of 2-Trifluoromethyl-1-alkenes. *J. Synth. Org. Chem Jpn.* **2010,** *68* (11), 1175-1184; (z) Fuchibe, K.; Takahashi, M.; Ichikawa, J., Substitution of two fluorine atoms in a trifluoromethyl group: regioselective synthesis of 3-fluoropyrazoles. *Angew. Chem. Int. Ed. Engl.* **2012,** *51* (48), 12059-62; (aa) Ichikawa, J.; Mori, T.; Iwai, Y., A New Class of Substrates for the Nucleophilic 5-endo-trigCyclization, 1-Trifluoromethylvinyl Compounds: Syntheses of Indoline and Pyrrolidine Derivatives. *Chem. Lett.* **2004,** *33* (10), 1354-1355; (ab) Ichikawa, J.; Ishibashi, Y.; Fukui, H., A novel synthesis of functionalized 1,1-difluoro-1-alkenes via isolable 2,2-difluorovinylsilanes. *Tetrahedron Lett.* **2003,** *44* (4), 707-710; (ac) Ichikawa, J.; Fukui, H.; Ishibashi, Y., 1-trifluoromethylvinylsilane as a CF2=C(-)-CH2+ synthon: synthesis of functionalized 1,1-

difluoro-1-alkenes via isolable 2,2-difluorovinylsilanes. *J. Org. Chem.* **2003,** *68* (20), 7800-5; (ad) Jeon, J. H.; Kim, J. H.; Jeong, Y. J.; Jeong, I. H., Preparation of 2,2-difluoro-1-trialkylsilylethenylstannanes and their cross-coupling reactions. *Tetrahedron Lett.* **2014,** *55* (7), 1292-1295; (ae) Gogsig, T. M.; Sobjerg, L. S.; Lindhardt, A. T.; Jensen, K. L.; Skrydstrup, T., Direct vinylation and difluorovinylation of arylboronic acids using vinyl- and 2,2-difluorovinyl tosylates via the Suzuki-Miyaura cross coupling. *J. Org. Chem.* **2008,** *73* (9), 3404-10; (af) Morken, P. A.; Burton, D. J., Preparation of Beta, Beta-Difluoro-Alpha-(Trifluoromethyl)Styrenes by Palladium-Catalyzed Coupling of Aryl Iodides with Pentafluoropropen-2-Ylzinc Reagent. *J. Org. Chem.* **1993,** *58* (5), 1167-1172.

2. Orsi, D. L.; Altman, R. A., Exploiting the unusual effects of fluorine in methodology. *Chem. Commun.* **2017,** *53* (53), 7168-7181.

3. (a) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Muller, K., Fluorination Patterning: A Study of Structural Motifs That Impact Physicochemical Properties of Relevance to Drug Discovery. *J. Med. Chem.* **2015,** *58* (22), 9041-60; (b) Leroux, F. R.; Manteau, B.; Vors, J. P.; Pazenok, S., Trifluoromethyl ethers--synthesis and properties of an unusual substituent. *Beilstein J Org Chem* **2008,** *4*, 13; (c) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R., New trends in the chemistry of α-fluorinated ethers, thioethers, amines and phosphines. *J. Fluorine Chem.* **2010,** *131* (2), 140-158.

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,

D. C.; Narayanan, A.; Unwalla, R.; Lovering, F.; Denny, R. A.; Zhou, H.; Bunnage, M. E., Fluorine in drug design: a case study with fluoroanisoles. *ChemMedChem* **2015,** *10* (4), 715-26.

5. Landelle, G.; Panossian, A.; Leroux, F. R., Trifluoromethyl Ethers and -Thioethers as Tools for Medicinal Chemistry and Drug Discovery. *Curr. Top. Med. Chem.* **2014,** *14* (7), 941-951.

6. (a) Dixon, D. D.; Grina, J.; Josey, J. A.; Rizzi, J. P.; Schlachter, S. T.; Wallace, E. M.; Wang, B.; Wehn, P.; Xu, R.; Yang, H. Preparation of cyclic sulfone and sulfoximine analogs as HIF-2α inhibitors. WO 2015095048, 2015; (b) Chen, W.; Igboko, E. F.; Lin, X.; Lu, H.; Ren, F.; Wren, P. B.; Xu, Z.; Yang, T.; Zhu, L. Preparation of 1-(cyclopent-2-en-1-yl)-3-(2-hydroxy-3-(arylsulfonyl)phenyl)urea derivatives as CXCR2 inhibitors. WO 2015181186, 2015; (c) Kumamoto, K.; Miyazaki, H. Preparation of sulfanylmethylpyrazole derivatives and analogs as pesticides. WO 2009028727, 2009; (d) Dallimore, J. W. P.; El Qacemi, M.; Kozakiewicz, A. M.; Longstaff, A.; Mclachlan, M. M. W.; Peace, J. E. Preparation of herbicidal isoxazoline derivatives. WO 2011033251, 2011.

7. (a) Brigaud, T.; Laurent, E., Oxidative Fluorination of Sulfides in Presence of Et3n.3hf. *Tetrahedron Lett.* **1990,** *31* (16), 2287-2290; (b) Furuta, S.; Kuroboshi, M.; Hiyama, T., Fluoro-Pummerer Rearrangement under Oxidative Desulfurization-Fluorination Conditions - Facile Synthesis of Oligofluoroalkyl Sulfides. *Tetrahedron Lett.* **1995,** *36* (45), 8243-8246; (c) Gouault, S.; Guérin, C.; Lemoucheux, L.; Lequeux, T.;

Pommelet, J.-C., Fluorination of α,α-dichlorosulfides: access to gem-difluorothioethers as useful building blocks. *Tetrahedron Lett.* **2003,** *44* (27), 5061-5064.

8. Zhang, Z.; Tang, X.; Dolbier, W. R., Jr., Photoredox-Catalyzed Tandem Insertion/Cyclization Reactions of Difluoromethyl and 1,1-Difluoroalkyl Radicals with Biphenyl Isocyanides. *Org. Lett.* **2015,** *17* (18), 4401-3.

9. Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N., Discovery of 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride as a deoxofluorinating agent with high thermal stability as well as unusual resistance to aqueous hydrolysis, and its diverse fluorination capabilities including deoxofluoro-arylsulfinylation with high stereoselectivity. *J. Am. Chem. Soc.* **2010,** *132* (51), 18199-205.

10. (a) Rogawski, M. A., Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res* **2006,** *69* (3), 273-94; (b) Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; Mccarthy, J. R., Terminal Difluoro Olefin Analogs of Squalene Are Time-Dependent Inhibitors of Squalene Epoxidase. *J. Am. Chem. Soc.* **1992,** *114* (1), 360-361; (c) Pan, Y.; Qiu, J.; Silverman, R. B., Design, Synthesis, and Biological Activity of a Difluoro-Substituted, Conformationally Rigid Vigabatrin Analogue as a Potent g-Aminobutyric Acid Aminotransferase Inhibitor. *J. Med. Chem.* **2003,** *46*, 5292–3; (d) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications*. Imperial College Press: London, 2012; (e) *Fluorine in Medicinal Chemistry and Chemical Biology*. Wiley-Blackwell: West Sussex, UK, 2009; (f) Bobek, M.; Kavai, I.; De Clercq, E., Synthesis and biological activity of 5-(2,2-difluorovinyl)-2'-deoxyuridine. *J. Med. Chem.* **1987,** *30* (8), 1494-7.

11. Mitchell, W. L.; Ravenscroft, P.; Hill, M. L.; Knutsen, L. J.; Judkins, B. D.; Newton, R. F.; Scopes, D. I., Synthesis and antiviral properties of 5-(2-substituted vinyl)-6-aza-2'-deoxyuridines. *J. Med. Chem.* **1986,** *29* (5), 809-16.

12. (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T., 5-endo-trigonal cyclization of o-substituted gem-difluorostyrenes: Syntheses of 2-fluorinated indoles, benzo[b]furans and benzo[b]thiophenes. *Chem. Commun.* **1997,** (16), 1537-1538; (b) Zhang, B.; Zhang, X.; Hao, J.; Yang, C., Direct Approach to N-Substituted-2-Fluoroindoles by Sequential Construction of C-N Bonds from gem-Difluorostyrenes. *Org. Lett.* **2017,** *19* (7), 1780-1783.

13. Wada, Y.; Ichikawa, J.; Katsume, T.; Nohiro, T.; Okauchi, T.; Minami, T., Intramolecular Cyclizations ofo-Substitutedβ,β-Difluorostyrenes: Synthesis of 3-Fluorinated Isochromenes and Isothiochromenes. *Bull. Chem. Soc. Jpn.* **2001,** *74* (5), 971-977.

14. Coe, P. L.; Burdon, J.; Haslock, I. B., A simple stereoselective synthesis of biologically important 2-halo-2,3-dideoxy-arabinose derivatives from 1,1,1,2-tetrafluoroethane (134a) and 1-chloro-2,2,2-trifluoroethane (133a). *J. Fluorine Chem.* **2000,** *102* (1-2), 43-50.

15. (a) Tellier, F.; Audouin, M.; Sauvêtre, R., Synthesis of α-trifluoromethyl unsaturated acids and derivatives. *J. Fluorine Chem.* **2002,** *113* (2), 167-175; (b) Tellier, F.; Audouin, M.; Sauvêtre, R., [3,3]-Sigmatropic rearrangement of allyl (or propargyl) fluorovinyl ethers. Synthesis of α-trifluoromethyl unsaturated acids and derivatives. *Tetrahedron Lett.* **2001,** *42* (14), 2665-2667; (c) Luzina, E. L.; Popov, A. V., Synthesis

and anticancer activity of N-bis(trifluoromethyl)alkyl-N'-thiazolyl and N-bis(trifluoromethyl)alkyl-N'-benzothiazolyl ureas. *Eur. J. Med. Chem.* **2009,** *44* (12), 4944-53; (d) Jeong, I. H.; Park, T. W.; Kim, B. T., Efficient One Step Procedure for the Synthesis of α-Trifluoromethylated Arylacetates. *Synth. Commun.* **1998,** *28* (11), 1981-1987; (e) England, D. C., Fluoroketenes .10. Synthesis and Chemistry of a Perfluoroacylketene and a Related Perfluorovinyl Ketone. *J. Org. Chem.* **1981,** *46* (1), 147-153.

16. (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) Hayashi, S.-i.; Nakai, T.; Ishikawa, N., DEFLUORINATION REACTIONS OFgem-DIFLUORO- AND MONOFLUOROOLEFINS. NOVEL METHODS FOR ONE-CARBON HOMOLOGATIONS OF CARBONYL COMPOUNDS LEADING TO ALDEHYDES, CARBOXYLIC ACIDS, AND ESTERS. *Chem. Lett.* **1980,** *9* (6), 651-654.

17. (a) Loska, R.; Szachowicz, K.; Szydlik, D., Synthesis of alkyl aryl(heteroaryl)acetates from N-oxides, 1,1-difluorostyrenes, and alcohols. *Org. Lett.* **2013,** *15* (22), 5706-9; (b) Szpunar, M.; Loska, R., A General Synthesis of Bis(o-azaheteroaryl)methane Derivatives fromN-Oxides of Azines and Azoles. *Eur. J. Org. Chem.* **2015,** *2015* (10), 2133-2137.

18. Tae Kim, B.; Ki Min, Y.; Kyun Park, N.; Yun Cho, K.; Howa Jeong, I., Exocyclization of Novel b,b-Difluoro-a-phenylvinyl Sulfide with Bidendate Heteroatom(N,O,S) Nucleophiles. *Heterocycles* **1995,** *41* (4).

19. Bayliff, A. E.; Bryce, M. R.; Chambers, R. D., Polyhalogenoheterocyclic compounds. Part 38. Reactions of fluorinated-alkenes and -cycloalkenes with difunctional nucleophiles. *J. Chem. Soc., Perkin Trans. 1* **1987**.

20. Ichikawa, J.; Kobayashi, M.; Yokota, N.; Noda, Y.; Minami, T., Reaction of 2,2-difluorovinyl ketones with heteroatom nucleophiles: A general one-pot synthesis of α-oxoketene acetals. *Tetrahedron* **1994,** *50* (40), 11637-11646.

21. Ausekle, E.; Ehlers, P.; Villinger, A.; Langer, P., One-Pot Synthesis of Dibenzo[b, d]oxepines via Olefinic C-F Bond Functionalization and Intramolecular Pd-Catalyzed C-H Arylation. *J. Org. Chem.* **2018,** *83* (22), 14195-14202.

22. Suda, M., Reactions of 1,1-Difluoro-1-Olefins with Electrophilic Reagents. *Tetrahedron Lett.* **1980,** *21* (26), 2555-2556.

23. (a) Paleta, O.; Svoboda, J.; Dědek, V., Haloacrylic acids XX. Dimerisation of trifluoroacrylates. Kinetically and thermodynamically controlled reactions. *J. Fluorine Chem.* **1983,** *23* (2), 171-191; (b) Matsukawa, Y.; Mizukado, J.; Quan, H. D.; Tamura, M.; Sekiya, A., Palladium(0)-catalyzed hydroalkoxylation of hexafluoropropene: synthesis of hydrofluoroethers under neutral conditions. *Angew. Chem. Int. Ed. Engl.* **2005,** *44* (7), 1128-30; (c) Il'in, A. A.; Bakhmutov, Y. L.; Ivanova, L. M.; Furin, G. G.; Tolstikova, T. G.; Sukhinin, V. S., Synthesis and use of partially fluorinated dialkyl ethers derived from hexafluoropropylene. *Russ. J. Appl. Chem.* **2004,** *77* (1), 98-101; (d) Nguyen, T.; Wakselman, C., Transformation de l'hexafluoropropène en alcool trifluoroallylique, précurseur des α-fluoroacrylates. *J. Fluorine Chem.* **1995,** *74* (2), 273-277; (e) Middleton,

W. J.; Bingham, E. M., The synthesis of antiinflammatory α-(trifluoromethyl) arylacetic acids. *J. Fluorine Chem.* **1983,** *22* (6), 561-574.

24. Fuss, A.; Koch, V., Chemistry of 3-Hydroxypyridine .3. Synthesis of Substituted 3-[Fluoro(Chloro)Alkoxy]Pyridines from Halo-3-Hydroxypyridines or Amino-3-Hydroxypyridines. *Synthesis-Stuttgart* **1990,** *1990* (7), 604-608.

25. (a) Morikawa, T.; Kumadaki, I.; Shiro, M., Electrophilic Cyclization Reaction of Gem-Difluoroolefin Derivatives - Syntheses of 6,6-Difluorotetrahydro-2-Pyrones and 2,2-Difluorotetrahydropyran Via Halogen Induced Cyclization. *Chem. Pharm. Bull.* **1985,** *33* (11), 5144-5146; (b) Kendrick, D. A.; Kolb, M., An improved cyclisation protocol for the synthesis of δ,δ-difluoro-δ-lactones. *J. Fluorine Chem.* **1989,** *45* (2), 273-276.

26. (a) Ueki, H.; Kitazume, T., Regio- and stereoselective reactions of gem-difluorinated vinyloxiranes with heteronucleophiles. *J. Org. Chem.* **2005,** *70* (23), 9354-63; (b) Mae, M.; Amii, H.; Uneyama, K., First synthesis of 3,3-difluoroserine and cysteine derivatives via Mg(0)-promoted selective C-F bond cleavage of trifluoromethylimines. *Tetrahedron Lett.* **2000,** *41* (41), 7893-7896; (c) Ueki, H.; Chiba, T.; Yamazaki, T.; Kitazume, T., Highly regio- and stereocontrolled SN2′ reactions of gem-difluorinated vinyloxiranes with monoalkylcopper reagents. *Tetrahedron* **2005,** *61* (47), 11141-11147.

27. Li, J.; Xu, C.; Wei, N.; Wang, M., Synthesis of 2,2-Difluorinated 4-Isoflavanols/4-Thioisoflavanols via a Base-Catalyzed [4 + 2] Annulation Reaction of gem-Difluoroolefins. *J. Org. Chem.* **2017,** *82* (21), 11348-11357.

28. Orsi, D. L.; Easley, B. J.; Lick, A. M.; Altman, R. A., Base Catalysis Enables Access to alpha,alpha-Difluoroalkylthioethers. *Org. Lett.* **2017,** *19* (7), 1570-1573.

29. Pearson, R. G.; Sobel, H.; Songstad, J., Nucleophilic Reactivity Constants toward Methyl Iodide and Trans-[Pt(Py)2cl2]. *J. Am. Chem. Soc.* **1968,** *90* (2), 319-&.

30. Ugur, I.; Marion, A.; Parant, S.; Jensen, J. H.; Monard, G., Rationalization of the pKa values of alcohols and thiols using atomic charge descriptors and its application to the prediction of amino acid pKa's. *J Chem Inf Model* **2014,** *54* (8), 2200-13.

31. (a) Kolomeitsev, A. A.; Koppel, I. A.; Rodima, T.; Barten, J.; Lork, E.; Roschenthaler, G. V.; Kaljurand, I.; Kutt, A.; Koppel, I.; Maemets, V.; Leito, I., Guanidinophosphazenes: design, synthesis, and basicity in THF and in the gas phase. *J. Am. Chem. Soc.* **2005,** *127* (50), 17656-66; (b) Kaljurand, I.; Rodima, T.; Pihl, A.; Maemets, V.; Leito, I.; Koppel, I. A.; Mishima, M., Acid-base equilibria in nonpolar media. 4. Extension of the self-consistent basicity scale in THF medium. Gas-phase basicities of phosphazenes. *J. Org. Chem.* **2003,** *68* (26), 9988-93.

32. (a) Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V., α,α-Difluoro-α-phenylsulfanylmethyl carbanion equivalent: a novel gem-difluoromethylenation of carbonyl compounds. *Tetrahedron* **2006,** *62* (25), 5973-5985; (b) Li, Y.; Hu, J., Fluoride ion-mediated nucleophilic fluoroalkylation of alkyl halides with Me3SiCF2SPh: Synthesis of PhSCF2- and CF2H-containing compounds. *J. Fluorine Chem.* **2008,** *129* (5), 382-385; (c) Kosobokov, M. D.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Hu, J., Reactions of sulfur- and phosphorus-substituted fluoroalkylating silicon reagents with imines and

enamines under acidic conditions. *J. Org. Chem.* **2012,** *77* (4), 2080-6; (d) Li, Y.; Hu, J., Stereoselective difluoromethylenation using Me3SiCF2SPh: synthesis of chiral 2,4-disubstituted 3,3-difluoropyrrolidines. *Angew. Chem. Int. Ed. Engl.* **2007,** *46* (14), 2489-92; (e) Betterley, N. M.; Surawatanawong, P.; Prabpai, S.; Kongsaeree, P.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V., Electrophilic difluoro(phenylthio)methylation: generation, stability, and reactivity of alpha-fluorocarbocations. *Org. Lett.* **2013,** *15* (22), 5666-9; (f) Yang, X. Y.; Fang, X.; Yang, X. J.; Zhao, M.; Han, Y. Z.; Shen, Y. J.; Wu, F. H., New preparation of difluoroiodomethylsulfanylbenzenes and their radical addition to unsaturated compounds initiated by sodium dithionite. *Tetrahedron* **2008,** *64* (9), 2259-2269; (g) Choi, Y.; Yu, C.; Kim, J. S.; Cho, E. J., Visible-Light-Induced Arylthiofluoroalkylations of Unactivated Heteroaromatics and Alkenes. *Org. Lett.* **2016,** *18* (13), 3246-9.

33. (a) Jelier, B. J.; Howell, J. L.; Montgomery, C. D.; Leznoff, D. B.; Friesen, C. M., A convenient route to tetraalkylammonium perfluoroalkoxides from hydrofluoroethers. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (10), 2945-9; (b) Lepri, S.; Buonerba, F.; Maccaroni, P.; Goracci, L.; Ruzziconi, R., Are carboxylic esters really refractory to DAST? On the fluorination of α-hydroxyesters with DAST. *J. Fluorine Chem.* **2015,** *171*, 82-91.

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 α,α,α–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 form 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-methylpyrrolidine (NMP), α,α,α-trifluorotoluene (TFT), sodium sulfate (Na_2SO_4), magnesium sulfate ($MgSO_4$), ethyl acetate (EtOAc), diethyl ether (Et_2O), ammonium chloride (NH_4Cl), *n*butyl lithium (*n*BuLi), sodium hydroxide (NaOH), room temperature (R.T.), *t*butyl carbonate anhydride (Boc_2O), potassium carbonate (K_2CO_3), and hydrochloric acid (HCl).

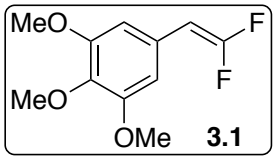
Proton nuclear magnetic resonance (^{1}H NMR) and fluorine nuclear magnetic resonance (^{19}F NMR) were taken on a Bruker DRX 500 spectrometer (500 and 376 MHz respectively). Fluorine nuclear magnetic resonance (^{19}F NMR) was taken on a Bruker AVIII 400 Avance spectrometer (376 MHz). Proton and carbon 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 (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 ($CHCl_3$: 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 ($CDCl_3$: 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 N_2 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 CO_2 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 H_2O. Subsequently, Et_2O was added to the reaction, and the mixture was washed with H_2O (five times), and the aqueous layer was back-extracted with Et_2O (two times). The combined organic layers were dried over Na_2SO_4 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, H_2O_2 (30% in H_2O) was added to the mother

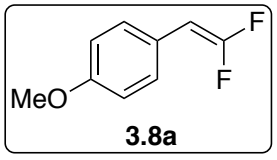
liquor and allowed to react for 30 min to oxidize the residual triphenylphosphine. The organic layer was washed with H_2O (three times), dried over Na_2SO_4, concentrated, and subjected to normal phase flash chromatography using EtOAc and hexanes.

Preparation of *Gem*-Difluoroalkenes:



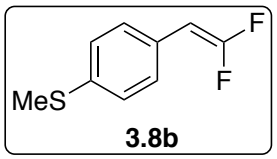
3.1

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.



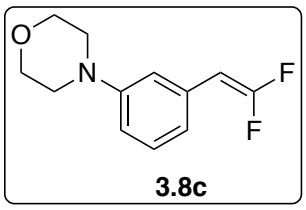
3.8a

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.



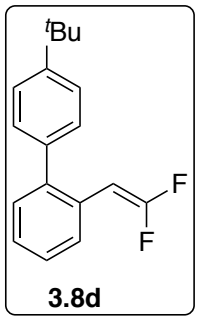
3.8b

(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.



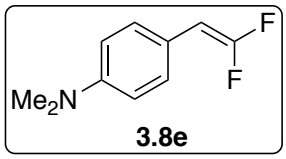
3.8c

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.



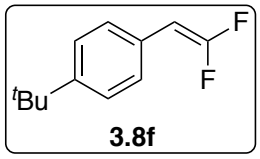
3.8d

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.



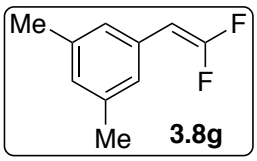
3.8e

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.



3.8f

1-(*tert*-butyl)-4-(2,2-difluorovinyl)benzene (3.8f): Following General Procedure A, 4-tert-butylbenzaldehyde (3.34 mL, 20mmol) was reacted with PPh_3 (6.3 g, 24 mmol) and $BrCF_2CO_2K$ (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% Et_2O 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 PPh_3 (6.23 g, 22.5 mmol) and $BrCF_2CO_2K$ (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

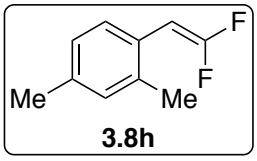
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (bs, 2 H), 6.90 (bs, 1 H), 5.21 (dd, *J* = 26.41, 4.03 Hz, 1H), 2.32 (s, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 (HAPCI+): calc. for $C_{10}H_{10}F_2$ (M+) 168.0751, found 168.0744, 4.2 ppm.



3.8h

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 $BrCF_2CO_2K$ (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

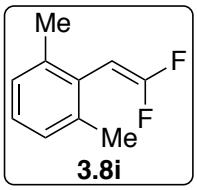
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.44, 2.00 Hz, 1 H), 7.02 (dd, *J* = 4.24, 2.31 Hz, 2 H), 5.34 (dd, *J* = 25.61, 3.94 Hz, 1 H), 2.32 (s, 3 H), 2.27 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –84.76 (dd, *J* = 33.14, 4.06 Hz, 1 F), –85.53 (ddd, *J* = 33.09, 25.53, 1.83 Hz, 1F)

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 (HAPCI+): calc. for $C_{10}H_{10}F_2$ (M+) 168.0751, found 168.0745, 3.6 ppm.



3.8i

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 $BrCF_2CO_2K$ (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.

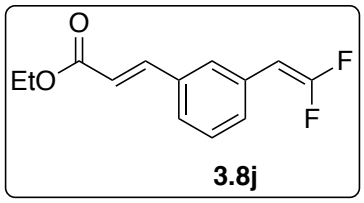
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 8.57, 6.35 Hz, 1 H), 7.07 (d, *J* = 7.53 Hz, 2 H), 5.23 (dd, *J* = 27.50, 2.26 Hz, 1 H), 2.29 (s, 6 H)

^{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, $CDCl_3$): δ –83.38 (dd, *J* = 32.45, 26.96 Hz, 1 F), –87.16 (dd, *J* = 33.11, 2.37 Hz, 1 F)

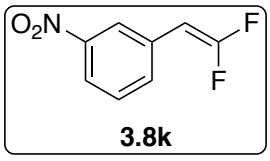
IR (film): 3024, 2956, 2923, 2330, 1736, 1586, 1468, 1445, 1380, 1329, 1276, 1254, 1222, 1166, 1096, 1032, 932, 850, 802, 768, 746, 698, 599, 537 cm^{-1}

HRMS (HAPCI+): calc. for $C_{10}H_{10}F_2$ (M) 168.0751, found 168.0741, 1.0 mmu.



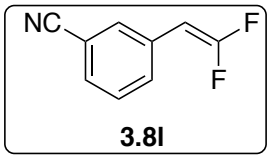
3.8j

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.



3.8k

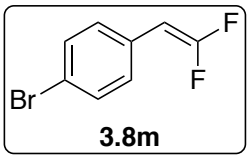
1-(2,2-difluorovinyl)-3-nitrobenzene (3.8k): Compound **3.8k** corresponds to compound **2.5n** in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.



3.8l

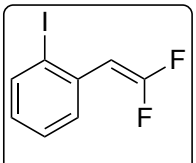
3-(2,2-difluorovinyl)benzonitrile (3.8l): Following General Procedure A, 3-cyanobenzaldehyde (6.55 g, 50mmol) was reacted with PPh_3 (15.75 g, 60 mmol) and $BrCF_2CO_2K$ (15.97 g, 75 mmol) in NMP (25 mL, 2 M). Following workup, the product was

purified by flash chromatography using a gradient of 0–50% Et_2O 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]



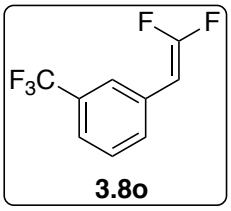
3.8m

1-bromo-4-(2,2-difluorovinyl)benzene (3.8m): Following General Procedure A, 4-bromobenzaldehyde (3.7 g, 20mmol) was reacted with PPh_3 (6.3 g, 24 mmol) and $BrCF_2CO_2K$ (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% Et_2O 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]



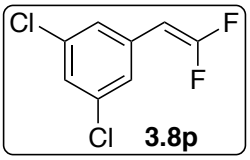
3.8n

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.



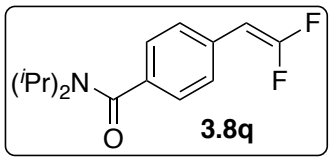
3.8o

1-(2,2-difluorovinyl)-3-(trifluoromethyl)benzene (3.8o): Following General Procedure A, 3-trifluoromethylbenzaldehyde (2.7 mL, 20mmol) was reacted with PPh_3 (6.3 g, 24 mmol) and $BrCF_2CO_2K$ (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% Et_2O 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]



3.8p

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.



3.8q

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 PPh_3 (1.50 g, 5.30 mmol) and $BrCF_2CO_2K$ (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).

^{1}H NMR (500 MHz, DMSO-D$_6$, 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)

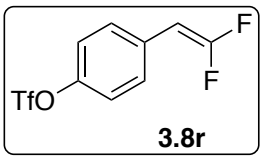
^{1}H NMR (500 MHz, DMSO-D$_6$, 60 °C): δ 7.41 (d, *J* = 7.92 Hz, 2 H), 7.28 (d, *J* = 7.89 Hz, 2 H), 5.79 (dd, *J* = 27.83, 4.01 Hz, 1 H), 3.64 (hept, *J* = 6.41 Hz, 2 H), 1.28 (bs, 12 H)

^{13}C NMR (126 MHz, DMSO-D$_6$, 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

^{19}F NMR (376 MHz, DMSO-D$_6$, 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)

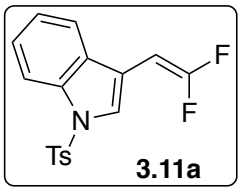
IR (film): 3434, 2252, 2126, 1729, 1660, 1345, 1276, 1052, 1024, 1005, 822, 760, 623 cm^{-1}

HRMS (ESI+): calc. for $C_{15}H_{20}F_2NO$ (M+H) 268.1513, found 268.1500, 1.3 mmu.



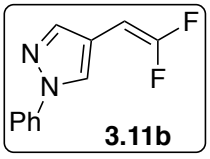
3.8r

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.



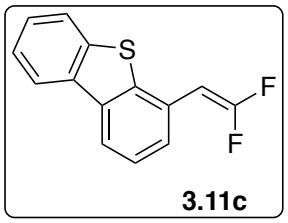
3.11a

3-(2,2-difluorovinyl)-1-tosyl-1*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.



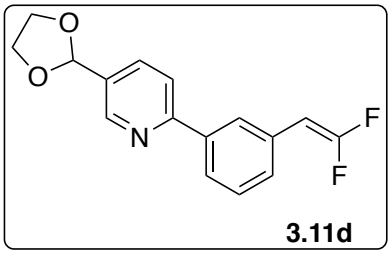
3.11b

4-(2,2-difluorovinyl)-1-phenyl-1*H*-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.



3.11c

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.



3.11d

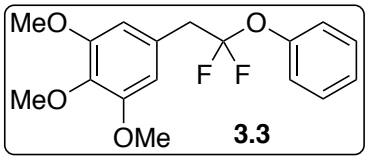
2-(3-(2,2-difluorovinyl)phenyl)-5-(1,3-dioxolan-2-yl)pyridine (3.11d): Compound **3.11d** corresponds to compound **2.8b** in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

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_2SO_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_2O 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 H_2O (0.10 mL, distilled under N_2 to remove dissolved O_2) was added via syringe transfer (PTFE syringe with oven-dried stainless-steel needle) under N_2. 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 ^{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_2SO_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_2O in MeCN to 100% MeCN to provide the desired product in >95% purity.

Compounds in Table 3-1:



3.3

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 H_2O, furnishing 0.080 g (49% yield) of desired product **3.3** as a colorless solid (MP = 65–66 ˚C)

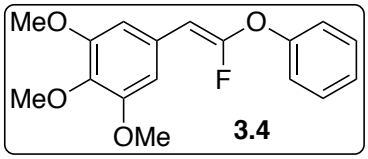
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.93 Hz, 2 H), 7.19 (t, *J* = 7.48 Hz, 1 H), 7.14 (d, *J* = 7.95 Hz, 2 H), 6.60 (s, 2 H), 3.87 (s, 9 H), 3.39 (t, *J* = 11.01 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.2, 150.5, 137.6 (d, *J* = 1.43 Hz), 129.4, 127.7 (t, *J* = 3.29 Hz), 125.6, 123.8, 121.7 (t, *J* = 266.95 Hz), 107.6, 60.9, 56.2, 42.5 (t, *J* = 30.28 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –70.44 (t, *J* = 11.05 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 (HAPCI+): calc. for $C_{17}H_{18}F_2O_4$ (M+) 324.1173, found 324.1171, 0.6 ppm.



3.4

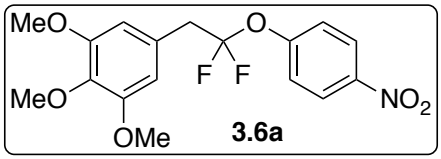
(Z)-5-(2-fluoro-2-phenoxyvinyl)-1,2,3-trimethoxybenzene (3.4): Following General Procedure B-1, 0.115 g (0.50 mmol) of compound **3.1** was reacted with 0.236 g (2.50 mmol) of phenol in the presence of 0.033 g (0.25 mmol) of TBD at 140 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by reverse-phase flash chromatography using a gradient of 2–100% MeCN in H_2O, furnishing desired product 0.024 g (16% yield) **3.4** as an orange oil; Characterization represents major isomer

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 8.66, 7.48 Hz, 2 H), 7.17–7.14 (m, 3 H), 6.66 (s, 2 H), 5.65 (d, *J* = 5.63 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.7, 154.0 (d, *J* = 3.50 Hz), 153.3, 130.1, 127.6 (d, *J* = 8.43 Hz), 124.5, 117.5, 116.3, 105.0 (d, *J* = 4.09 Hz), 92.7 (d, *J* = 38.61 Hz), 61.0, 56.1

^{19}F NMR (376 MHz, $CDCl_3$): δ –83.38 (d, *J* = 5.55 MHz, 1 F).

Compounds in Scheme 3-4:



3.6a

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_2O, furnishing 0.125 g (69% yield, 97% purity) of desired product **3.6a** as a dark yellow solid (MP = 117–120 ˚C)

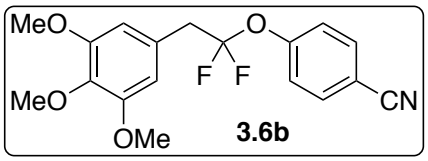
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 9.16 Hz, 2 H), 7.28 (d, *J* = 8.93 Hz, 2 H), 6.57 (s, 2 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 3.42 (t, *J* = 11.37 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{17}H_{18}F_2NO_6$ (M+H) 370.1102, found 370.1099, 0.8 ppm.



3.6b

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_2O, furnishing 0.143 g (82% yield, 94% purity) of desired product **3.6b** as a yellow oil

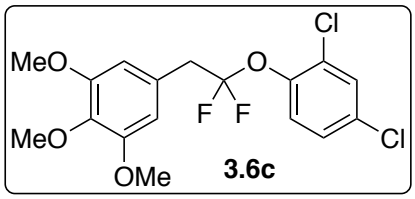
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.81 Hz, 2 H), 7.23 (d, *J* = 8.37 Hz, 2 H), 6.56 (s, 2 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.40 (t, *J* = 11.28 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –71.23 (t, *J* = 11.45 Hz, 2 F)

IR (film): 2940, 2842, 2253, 2231, 1596, 1505, 1464, 1424, 1360, 1325, 1296, 1253, 1241, 1210, 1173, 1156, 1129, 1068, 1004, 908, 841, 802, 732, 649 cm^{-1}

HRMS (ESI+): calc. for $C_{18}H_{17}F_2NO_4Na$ (M+Na): 372.1023, found 372.1026, 0.8 ppm.



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_2O, furnishing 0.145 g (72% yield) of desired product **3.6c** as a clear oil

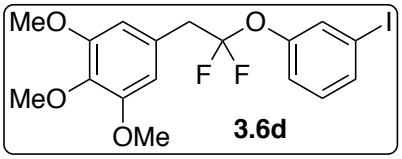
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 2.46 Hz, 1 H), 7.27–7.25 (m, 1 H), 7.19 (dd, *J* = 8.83, 2.46 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.85 (s, 3 H), 3.43 (t, *J* = 11.03 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{17}H_{16}Cl_2F_2O_4$ (M+) 392.0394, found 394.0424, 3.8 ppm.



3.6d

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_2O, furnishing 0.158 g (71% yield, 98% purity) of desired product **3.6d** as a brown oil

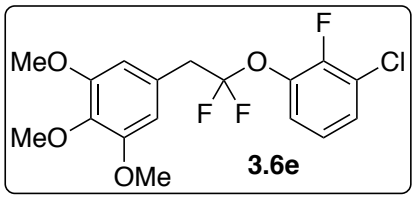
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53–7.50 (m, 2 H), 7.12 (dd, *J* = 8.25, 2.15 Hz, 1 H), 7.03 (t, *J* = 8.01 Hz, 1 H), 6.56 (s, 2 H), 3.86 (s, 9 H), 3.36 (t, *J* = 11.08 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{17}H_{17}F_2IO_4$ (M+) 450.0, found 449.9.



3.6e

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_2O, furnishing 0.139 g (74% yield, 95% purity) of desired product **3.6e** as a clear solid (MP = 50–51 ˚C)

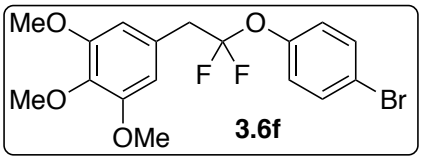
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (ddd, *J* = 8.07, 6.34, 1.56 Hz, 1 H), 7.19 (ddd, *J* = 8.32, 6.81, 1.40 Hz, 1 H), 7.01 (td, *J* = 8.26, 1.86 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.43 (t, *J* = 11.06 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ ;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 NMR (376 MHz, $CDCl_3$): δ –71.19 (td, *J* = 11.30, 5.34 Hz, 2 F), –131.17 (p, *J* = 6.19 Hz, 1 F)

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 cm^{-1}

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



3.6f

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 ˚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_2O, furnishing 0.137 g (68% yield, 97% purity) of desired product **3.6f** (or 2) as a clear oil

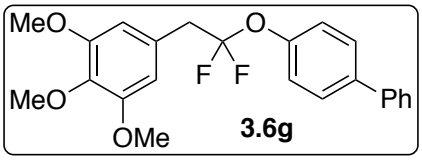
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.83 Hz, 2 H), 7.01 (d, *J* = 8.62 Hz, 2 H), 6.57 (s, 2 H), 3.86 (s, 9 H), 3.37 (t, *J* = 11.08 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 153.2, 149.4, 137.7 (t, *J* = 1.62 Hz), 132.4, 127.4, 123.7 (t, *J* = 267.88 Hz), 123.6, 118.6, 107.6, 60.9, 56.2, 42.4 (t, *J* = 29.85 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –70.87 (t, *J* = 11.24 Hz, 2 F)

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 cm^{-1}

HRMS (HAPCI+): calc. for $C_{17}H_{17}BrF_2O_4$ (M+) 402.0278, found 402.0267, 2.7 ppm.



3.6g

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 ˚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

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**

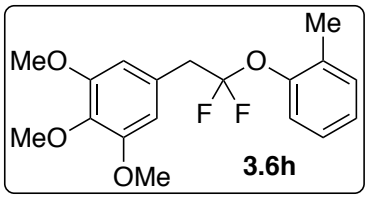
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.54 (m, 4 H), 7.44 (t, *J* = 7.55 Hz, 2 H), 7.35 (t, *J* = 7.37 Hz, 1 H), 7.22 (d, *J* = 8.23 Hz, 2 H), 6.62 (s, 2 H), 3.88 (s, 9 H), 3.42 (t, *J* = 10.95 Hz, 2 H)

^{13}C NMR (126 MHz, CDCl3): δ 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, CDCl3): δ –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 $C_{23}H_{22}F_2O_4$ (M+) 400.1486, found 400.1478, 2.0 ppm.



3.6h

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

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 H_2O, furnishing 0.068 g (40% yield) of desired product **3.6h** as a pale yellow oil

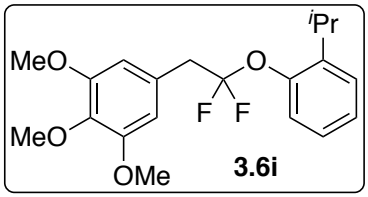
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.37, 1.74 Hz, 1 H), 7.15 (t, *J* = 7.00 Hz, 2 H), 7.08 (dt, *J* = 7.45, 6.99, 1.39 Hz, 1 H), 6.60 (s, 2 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.41 (t, *J* = 10.56 Hz, 2 H), 2.05 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{18}H_{20}F_2O_4$ (M+) 338.1330, found 338.1320, 3.0 ppm.



3.6i

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-isoporpylphenol 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_2O, furnishing 0.061 g (34% yield) of desired product **3.6i** as a clear oil

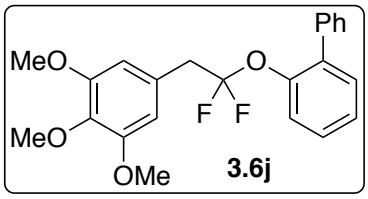
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.26 (m, 2 H), 7.18 (dt, *J* = 6.21, 2.47 Hz, 2 H), 6.64 (s, 2 H), 3.90 (s, 9 H), 3.45 (t, *J* = 10.31 Hz, 2 H), 2.90 (p, *J* = 6.89 Hz, 1 H), 1.08 (d, *J* = 6.92 Hz, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{20}H_{24}F_2O_4$ (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 H_2O, furnishing 0.127 g (40 % yield, 63% purity) of compound **3.6j** as a pale oil

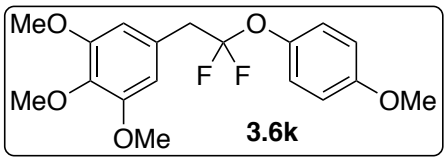
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42–7.38 (m, 1 H), 7.34–7.29 (m, 7 H), 7.25 (td, *J* = 7.44, 1.28 Hz, 1 H), 6.35 (s, 2 H), 3.84 (s, 3 H), 3.75 (s, 6 H), 3.19 (t, *J* = 10.75 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{23}H_{22}F_2O_4$ (M+) 400.1486, found 400.1486, 0.0 ppm.



3.6k

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 H_2O, furnishing 0.089 g (51% yield, 95% purity) of desired product **3.6k** as a colorless solid (MP = 64–66 ˚C)

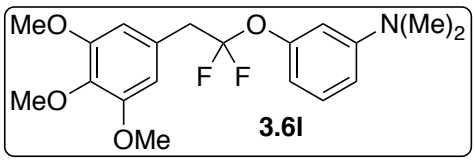
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.58 Hz, 2 H), 6.83 (d, *J* = 8.99 Hz, 2 H), 6.59 (s, 2 H), 3.86 (s, 9 H), 3.77 (s, 3 H), 3.36 (t, *J* = 10.92 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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)

^{19}F NMR (376 MHz, $CDCl_3$): δ –70.65 (t, *J* = 11.00 Hz, 2 F)

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}

HRMS (HAPCI+): calc. for $C_{18}H_{20}F_2O_5$ (M+) 354.1279, found 354.1269, 2.8 ppm.



3.6l

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 H_2O, furnishing 0.051 g (28% yield, 97% purity) of compound **3.6l** as a yellow semisolid

^{1}H NMR (500 MHz, $CDCl_3$): 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)

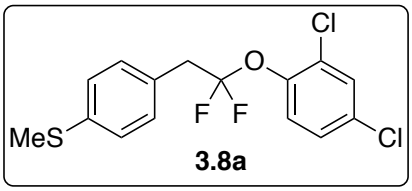
^{13}C NMR (126 MHz, $CDCl_3$): δ 153.1, 151.7, 151.6 (t, *J* = 2.25 Hz), 137.6, 129.6, 127.9 (t, *J* = 3.21 Hz), 123.9 (t, *J* = 266.13 Hz), 109.7, 109.5, 107.6, 105.9, 61.0, 56.2, 42.6 (t, *J* = 30.60 Hz), 40.6

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{19}H_{24}F_2NO_4$ (M+H) 368.1673, found 368.1662, 3.0 ppm.

Compounds in Scheme 3-5:



3.8a

(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_2O, furnishing 0.112 g (68% yield, 98% purity) of desired product **3.9a** as a tan solid (MP = 69–70 ˚C)

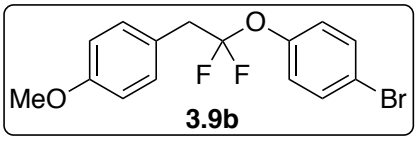
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 2.18 Hz, 1 H), 7.32 (d, *J* = 8.05 Hz, 2 H), 7.25 (d, *J* = 8.37 Hz, 2 H), 7.23 (d, *J* = 8.65 Hz, 1 H), 7.18 (ddd, *J* = 8.78, 2.49, 0.98 Hz, 1 H), 3.45 (t, *J* = 11.11 Hz, 2 H), 2.49 (d, *J* = 1.07 Hz, 3 H)

^{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

^{19}F NMR (376 MHz, $CDCl_3$): δ –71.10 (t, *J* = 11.09 Hz, 2 F)

IR (film): 2924, 1476, 1433, 1408, 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 $C_{15}H_{12}Cl_2F_2OS$ (M+) 347.9954, found 347.9944, 2.9 ppm.



3.9b

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 H_2O, furnishing 0.097 g (56% yield) of desired product **3.9b** as a peach solid (MP = 51–52 ˚C)

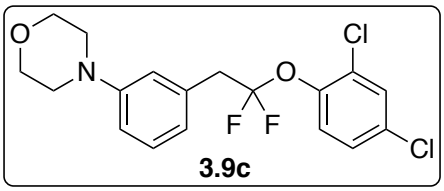
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.87 Hz, 2 H), 7.29 (d, *J* = 8.25 Hz, 2 H), 7.01 (d, *J* = 8.50 Hz, 2 H), 6.91 (d, *J* = 8.80 Hz, 2 H), 3.82 (s, 3 H), 3.39 (t, *J* = 11.12 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): δ –71.48 (t, *J* = 11.20 Hz, 2 F)

IR (film): 3005, 2937, 2838, 1614, 1585, 1515, 1486, 1464, 1442, 1352, 1324, 1303, 1248, 1200, 1179, 1127, 1116, 1087, 1067, 1036, 1013, 908, 847, 821, 796, 785, 764, 736, 697, 677, 650 cm^{-1}

HRMS (HAPCI+): calc. for $C_{15}H_{13}BrF_2O_2$ (M+) 342.0067, found 342.0067, 0.0 ppm.



3.9c

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 H_2O, furnishing 0.148 g (78% yield, 94% purity) of desired product **3.9c** as a yellow solid (MP = 61–64 ˚C)

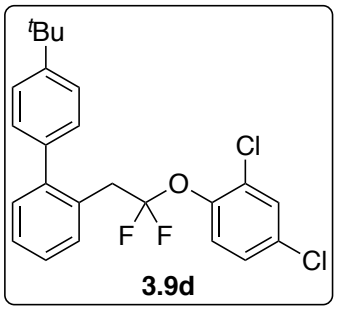
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 2.47 Hz, 1 H), 7.32 (d, *J* = 7.91 Hz, 1 H), 7.30–7.28 (m, 1 H), 7.23 (dd, *J* = 8.82, 2.49 Hz, 1 H), 7.00 (t, *J* = 1.92 Hz, 1 H), 6.97 (d, *J* = 7.50 Hz, 1 H), 6.93 (dd, *J* = 8.25, 2.42 Hz, 1 H), 3.92–3.90 (m, 4 H), 3.51 (t, *J* = 11.24 Hz, 2 H), 3.24–3.22 (m, 4 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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}F NMR (376 MHz, $CDCl_3$): δ –70.77 (t, *J* = 11.30 Hz, 2 F)

IR (film): 2967, 2860, 2250, 1604, 1585, 1495, 1476, 1449, 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}

HRMS (ESI+): calc. for $C_{18}H_{18}Cl_2F_2NO_2$ (M+H) 388.0683, found 388.0669, 3.6 ppm.



3.9d

4'-(tert-butyl)-2-(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_2O, furnishing 0.153 g (70% yield, 97% purity) of desired product **3.9d** as a colorless solid (MP = 76–78 ˚C).

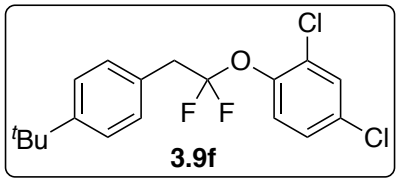
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1 H), 7.64–7.62 (m, 3 H), 7.55 (d, *J* = 7.86 Hz, 2 H), 7.49 (t, *J* = 7.68 Hz, 1 H), 7.46 (d, *J* = 2.10 Hz, 1 H), 7.43 (d, *J* = 7.62 Hz, 1 H), 7.31 (dd, *J* = 8.90, 1.31 Hz, 1 H), 7.24 (dt, *J* = 8.85, 1.77 Hz, 1 H), 3.63 (t, *J* = 11.07 Hz, 2 H), 1.45 (s, 9H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{24}H_{22}Cl_2F_2O$ (M+) 434.1016, found 434.0999, 3.9 ppm.



3.9f

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_2O, furnishing 0.074 g (41% yield) of desired product **3.9f** as a clear oil

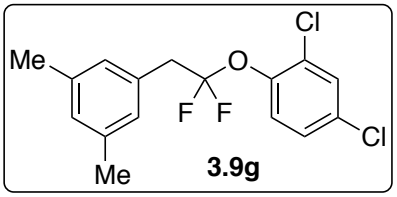
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–7.40 (m, 3 H), 7.35 (d, *J* = 8.11 Hz, 2 H), 7.28–7.26 (m, 1 H), 7.20 (ddd, *J* = 8.83, 2.51, 0.80 Hz, 1 H), 3.50 (t, *J* = 11.31 Hz, 2 H), 1.36 (9 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{18}H_{18}Cl_2F_2O$ (M+) 358.0703, found 358.0701, 0.6 ppm.



3.9g

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 H_2O, furnishing 0.092 g (55% yield) of desired product **3.9g** as a pale-yellow oil

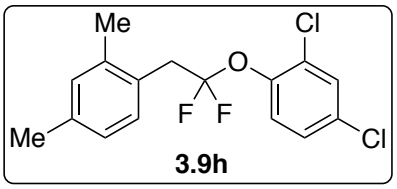
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 2.46 Hz, 1 H), 7.25 (d, *J* = 8.62 Hz, 1 H), 7.18 (dd, *J* = 8.81, 2.49 Hz, 1 H), 7.02 (s, 2 H), 6.97 (s, 1 H), 3.42 (t, *J* = 11.40 Hz, 2 H), 2.33 (s, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{16}H_{14}Cl_2F_2O$ (M+) 330.0390, found 330.0391, 0.3 ppm.



3.9h

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 H_2O, furnishing 0.050 g (27% yield, 92% purity) of compound **3.9h** as a pale-yellow semisolid.

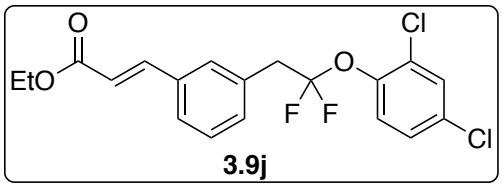
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 2.45 Hz, 1 H), 7.25–7.22 (m, 2 H), 7.17 (dd, *J* = 8.81, 2.42 Hz, 1 H), 7.04 (s, 1 H), 7.01 (d, *J* = 7.91 Hz, 1 H), 3.50 (t, *J* = 11.33 Hz, 2 H), 2.40 (s, 3 H), 2.31 (s, 3 H)

^{13}C (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{16}H_{14}Cl_2F_2O$ (M+) 330.0, found 330.0.



3.9j

ethyl (E)-3-(3-(2-(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_2O, furnishing 0.127 g (64% yield) of desired product **3.9j** as a colorless solid (MP = 70–72 ˚C).

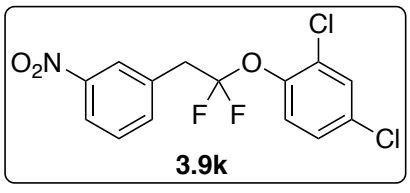
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 16.02 Hz, 1 H), 7.56 (s, 1 H), 7.49 (d, *J* = 7.46 Hz, 1 H), 7.42–7.36 (m, 3 H), 7.23 (d, *J* = 8.78 Hz, 1 H), 7.17 (dd, *J* = 8.83, 2.49 Hz, 1 H), 6.47 (d, *J* = 16.04 Hz, 1 H), 4.27 (q, *J* = 7.12 Hz, 2 H), 3.51 (t, *J* = 10.93 Hz, 2 H), 1.34 (t, *J* = 7.13 Hz, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{19}H_{16}Cl_2F_2O_3$ (M+) 400.0445, found 400.0435, 2.5 ppm.



3.9k

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 H_2O, furnishing 0.083 g (47% yield, 94% purity) of desired product **3.9k** as a clear solid (MP = 96–97 ˚C).

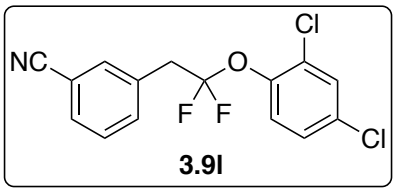
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, *J* = 2.07 Hz, 1 H), 8.22 (dd, *J* = 8.29, 2.46 Hz, 1 H), 7.75 (d, *J* = 7.72 Hz, 1 H), 7.55 (t, *J* = 7.94 Hz, 1 H), 7.39 (d, *J* = 2.45 Hz, 1 H), 7.24 (d, *J* = 9.03 Hz, 1 H), 7.20 (dd, *J* = 8.77, 2.33 Hz, 1 H), 3.61 (t, *J* = 10.49 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{14}H_9Cl_2F_2NO_3$ (M+) 346.9928, found 346.9925, 0.9 ppm.



3.9l

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 H_2O, furnishing 0.080 g (49% yield) of desired compound **3.9l** as a colorless solid (MP = 81–83 ˚C).

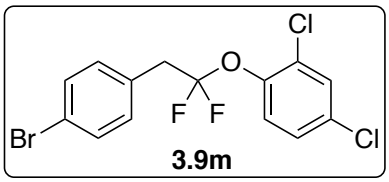
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 2.26 Hz, 1 H), 7.65–7.63 (m, 2 H), 7.48 (dt, *J* = 8.52, 4.29 Hz, 1 H), 7.39 (t, *J* = 2.03 Hz, 1 H), 7.24–7.18 (m, 2 H), 3.53 (t, *J* = 10.57 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{15}H_9Cl_2F_2NO$ (M+) 327.0029, found 327.0031, 0.6 ppm.



3.9m

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 H_2O, furnishing 0.113 g (59% yield) of desired compound **3.9m** as a colorless solid (MP = 52–53 ˚C).

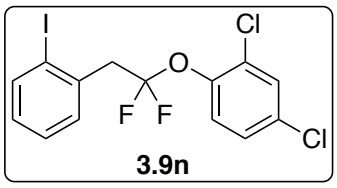
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.28, 1.66 Hz, 2 H), 7.40 (d, *J* = 2.33 Hz, 1 H), 7.28 (d, *J* = 8.66 Hz, 2 H), 7.22 (dd, *J* = 8.82, 1.45 Hz, 1 H), 7.19 (dd, *J* = 8.82, 2.30 Hz, 1 H), 3.45 (t, *J* = 10.89 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 145.2, 132.4, 131.7, 131.5, 130.6 (t, *J* = 3.23 Hz), 130.4, 128.5, 127.8, 124.2, 123.8 (t, *J* = 269.87 Hz), 122.2, 41.7 (t, *J* = 29.56 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –71.02 (t, *J* = 10.82 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 $C_{14}H_9BrCl_2F_2O$ (M+) 379.9182, found 379.9169, 3.4 ppm.



3.9n

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 H_2O, furnishing 0.105 g (49% yield) of desired compound **3.9n** as a colorless solid (MP = 54–55 ˚C).

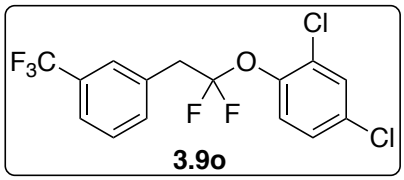
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 7.91, 1.30 Hz, 1 H), 7.52 (dd, *J* = 7.77, 1.56 Hz, 1 H), 7.40 (d, *J* = 2.48 Hz, 1 H), 7.35 (td, *J* = 7.56, 1.30 Hz, 1 H), 7.27–7.25 (m, 1 H), 7.19 (dd, *J* = 8.79, 2.51 Hz, 1 H), 7.01 (td, *J* = 7.66, 1.71 Hz, 1 H), 3.77 (t, *J* = 10.94 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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 NMR (376 MHz, $CDCl_3$): δ –69.75 (t, *J* = 10.84 Hz, 2 F)

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}

HRMS (HAPCI+): calc. for $C_{14}H_9Cl_2F_2IO$ (M+) 427.9043, found 427.9029, 3.3 ppm.



3.9o

2,4-dichloro-1-(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 H_2O, furnishing 0.094 g (51% yield) of desired compound **3.9o** as a clear oil.

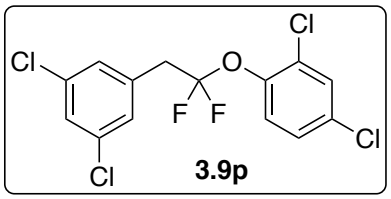
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1 H), 7.60 (t, *J* = 7.69 Hz, 2 H), 7.49 (t, *J* = 7.84 Hz, 1 H), 7.40 (t, *J* = 2.00 Hz, 1 H), 7.24 (dd, *J* = 8.82, 1.38 Hz, 1 H), 7.19 (dd, *J* = 8.83, 2.36 Hz, 1 H), 3.56 (t, *J* = 10.71 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$, 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 $C_{15}H_9Cl_2F_5O$ (M+) 369.9951, found 369.9934, 4.6 ppm.



3.9p

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 H_2O, furnishing 0.078 g (42% yield, 98% purity) of desired compound **3.9p** as a pinkish colorless solid (MP = 46–47 ˚C).

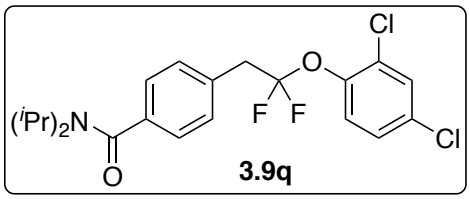
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 2.38 Hz, 1 H), 7.35 (t, *J* = 1.92 Hz, 1 H), 7.31 (d, *J* = 1.95 Hz, 2 H), 7.24 (d, *J* = 8.69 Hz, 1 H), 7.20 (dd, *J* = 8.81, 2.41 Hz, 1 H), 3.45 (t, *J* = 10.60 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 145.1, 135.1, 134.7, 131.7, 130.5, 129.3, 128.5, 128.3, 127.8, 124.1, 123.5 (t, *J* = 269.84 Hz), 41.7 (t, *J* = 30.06 Hz)

^{19}F NMR (376 MHz, $CDCl_3$): δ –70.61 (t, *J* = 10.57 Hz, 2 F)

IR (film): 1592, 1570, 1476, 1436, 1385, 1351, 1258, 1062, 867, 800, 763, 702, 643, 565 cm^{-1}

HRMS (HAPCI+): calc. for $C_{14}H_8Cl_4F_2O$ (M+) 369.9297, found 369.9300, 0.8 ppm.



3.9q

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 H_2O, furnishing 0.126 g (59% yield, 94% purity) of desired compound **3.9q** as an orange solid (MP = 81–83 ˚C).

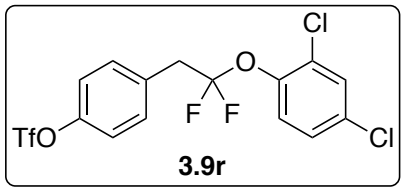
^{1}H NMR (500 MHz, $CDCl_3$, 25 ˚C): δ 7.40 (d, *J* = 7.91 Hz, 2 H), 7.37 (d, *J* = 2.48 Hz, 1 H), 7.29 (d, *J* = 7.88 Hz, 2 H), 7.23 (d, *J* = 8.90 Hz, 1 H), 7.18 (dd, *J* = 8.82, 2.47 Hz, 1 H), 3.74 (bs, 1 H), 3.49 (t, *J* = 10.96 Hz, 2 H), 1.46 (bs, 6 H), 1.21 (bs, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.8, 145.2, 138.6, 132.1 (t, *J* = 3.17 Hz), 131.5, 130.9, 130.3, 128.5, 127.8, 126.2, 125.8, 124.2, 124.0 (t, *J* = 270.95 Hz), 41.99 (t, *J* = 29.30 Hz), 20.9

^{19}F NMR (376 MHz, $CDCl_3$): δ –70.73 (t, *J* = 11.26 Hz, 2 F)

IR (film): 2993, 2969, 2933, 1628, 1474, 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 $C_{21}H_{23}Cl_2F_2NO_2Na$ (M+Na) 452.0972, found 452.0966, 1.3 ppm.



3.9r

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 H_2O, furnishing 0.110 g (49% yield) of desired compound **3.9r** as a light brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): 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)

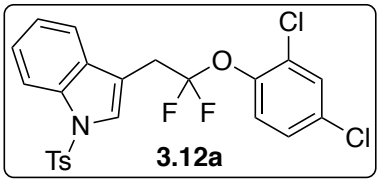
^{13}C NMR (126 MHz, $CDCl_3$): δ 149.4, 145.0 (t, *J* = 1.72 Hz), 132.7, 132.2 (t, *J* = 3.48 Hz), 131.7, 130.4, 129.7, 127.8, 124.2 (t, *J* = 2.10 Hz), 123.6 (t, *J* = 269.31 Hz), 121.5, 118.9 (q, *J* = 320.68 Hz), 41.6 (t, *J* = 29.85 Hz)

^{19}F NMR (376 MHz, $CDCl_3$, delay time = 5 s): δ –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 $C_{15}H_9Cl_2F_5O_4S$ (M+) 449.9519, found 449.9516, 0.7 ppm.

Compounds in Scheme 3-6:



3.12a

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_2O, furnishing 0.209 g (84% yield, 96% purity) of desired product **3.12a** as an orange solid (MP = 90–93 ˚C).

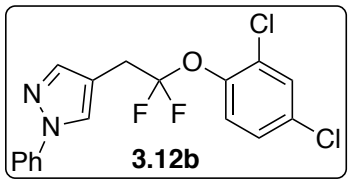
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.28 Hz, 1 H), 7.78 (d, *J* = 8.16 Hz, 2 H), 7.68 (s, 1 H), 7.60 (d, *J* = 7.85 Hz, 1 H), 7.38 (d, *J* = 2.34 Hz, 1 H), 7.35 (t, *J* = 7.75 Hz, 1 H), 7.27 (t, *J* = 7.32 Hz, 1 H), 7.22–7.16 (m, 5 H), 3.61 (t, *J* = 10.78 Hz, 2 H), 2.32 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{23}H_{18}Cl_2F_2NO_3S$ (M+H) 496.0353, found 496.0371, 3.6 ppm.



3.12b

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_2O, furnishing 0.081 g (44% yield) of desired product **3.12b** as a yellow solid (MP = 44–46 ˚C).

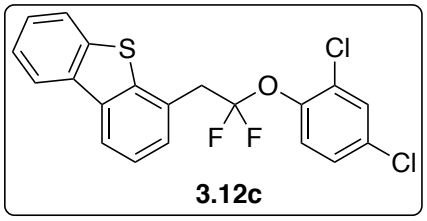
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (s, 1 H), 7.74 (s, 1 H), 7.70–7.68 (m, 2 H), 7.45 (dd, *J* = 8.56, 7.31 Hz, 2 H), 7.42 (d, *J* = 2.45 Hz, 1 H), 7.30–7.26 (m, 2 H), 7.20 (dd, *J* = 8.85, 2.52 Hz, 1 H), 3.47 (t, *J* = 10.99 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{17}H_{13}Cl_2F_2N_2O$ (M+H) 369.0373, found 369.0347, 2.6 mmu.



3.12c

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_2O,

furnishing 0.119 g (58% yield, 93% purity) of desired product **3.12c** as a colorless solid (MP = 119–121 ˚C).

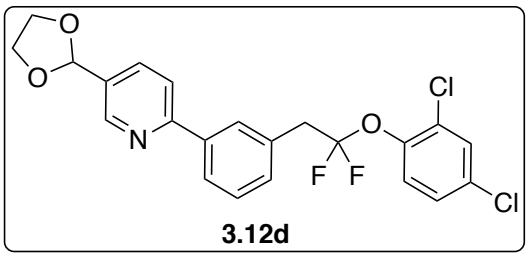
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.98 Hz, 2 H), 7.90–7.88 (m, 1 H), 7.57 (d, *J* = 7.39 Hz, 1 H), 7.52–7.47 (m, 3 H), 7.40 (s, 1), 7.25 (d, *J* = 8.79 Hz, 1 H), 7.18 (d, *J* = 7.87 Hz, 1 H), 3.82 (t, *J* = 10.93 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{20}H_{12}Cl_2F_2OS$ (M+) 407.9954, found 407.9940, 3.4 ppm.



3.12d

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 H_2O, furnishing 0.137 g (61% yield, 95% purity) of desired compound **3.12d** as a yellow solid (MP = 84–86 ˚C).

^{1}H NMR (500 MHz, $CDCl_3$): 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)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{22}H_{18}Cl_2F_2NO_3$ (M+H) 452.063, found 452.0627, 1.1 ppm.

References for Chapter 3 Appendix:

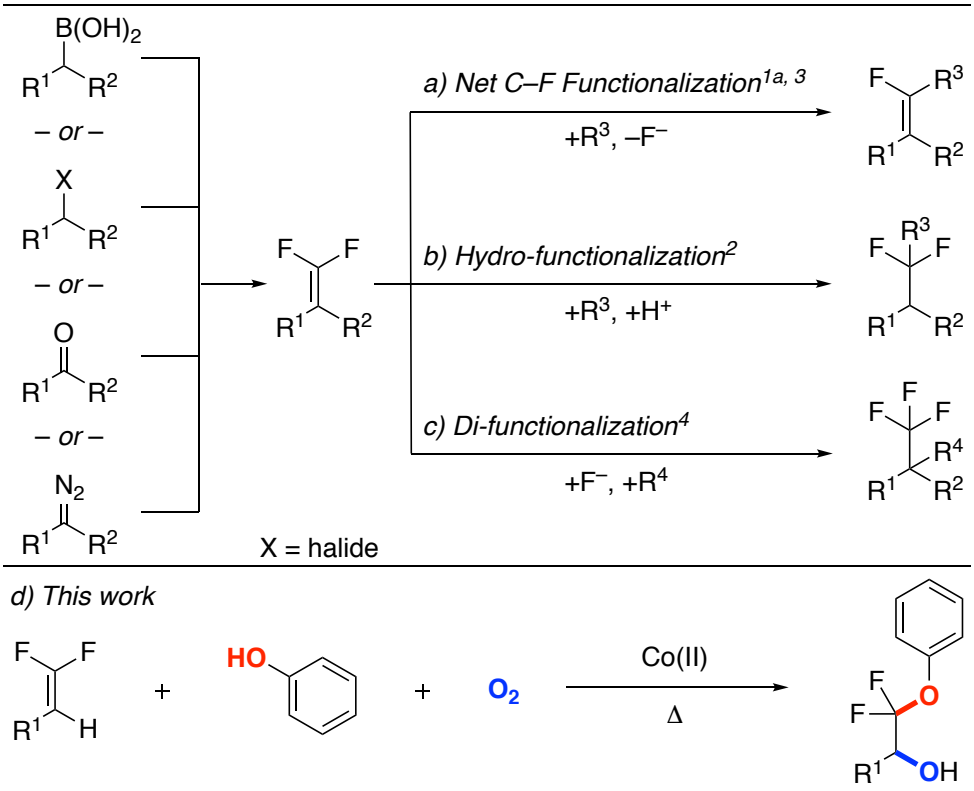
1. Li, Q.; Lin, J.-H.; Deng, Z.-Y.; Zheng, J.; Cai, J.; Xiao, J.-C., Wittig *gem*-difluoroolefination of aldehydes with difluoromethyltriphenylphosphonium bromide. *J. Fluorine Chem.* **2014,** *163*, 38–41.

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 intermediate[2a, 2b] or 2) exploiting a fluorination–metalation sequence (**Figure 4-1b, c**).[4]

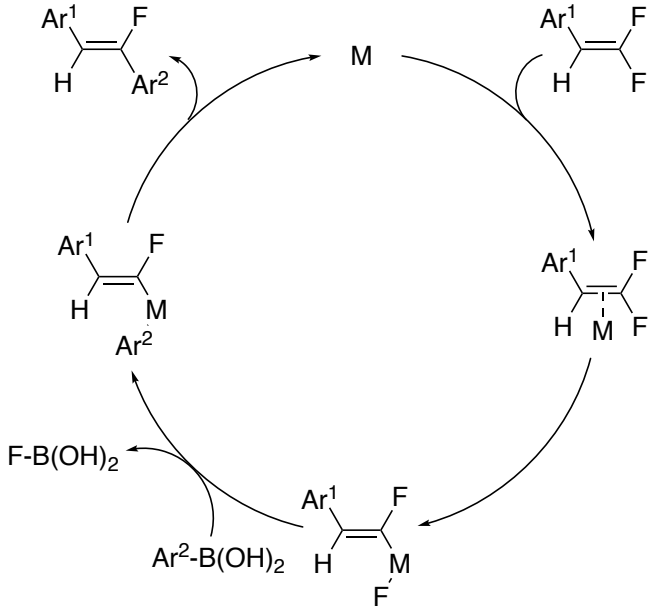
Figure 4-1: Representative Reactions of *gem*-Difluoroalkenes.



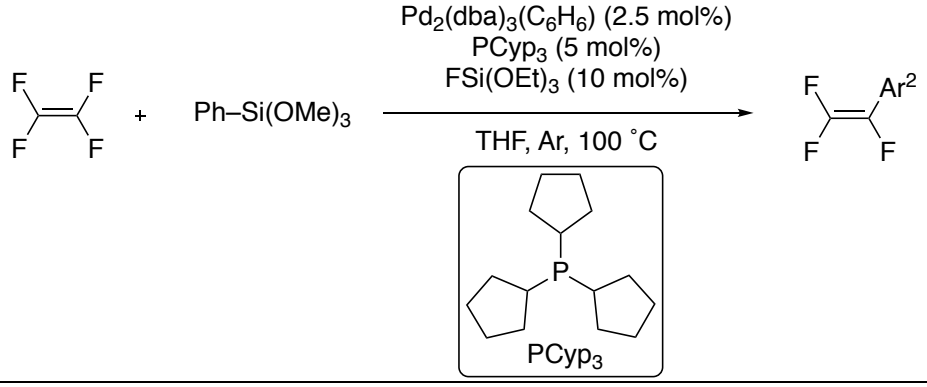
Transition metals catalyze C–F functionalization reactions of *gem*-difluoroalkenes following distinct reactivity patterns relative to functionalization of other C–halogen bonds. Typically, transition metals perform oxidative addition to the C–X bond to begin catalytic reactions. However, the strong 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

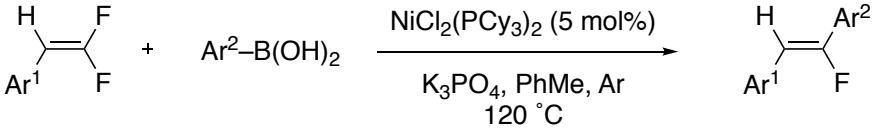
a) Representative Mechanism of C–F Oxidative Addition



b) Oxidative Addition to C–F Bonds Under Pd Catalysis[6a]



c) Oxidative Addition to C–F Bonds Under Ni Catalysis[7b]

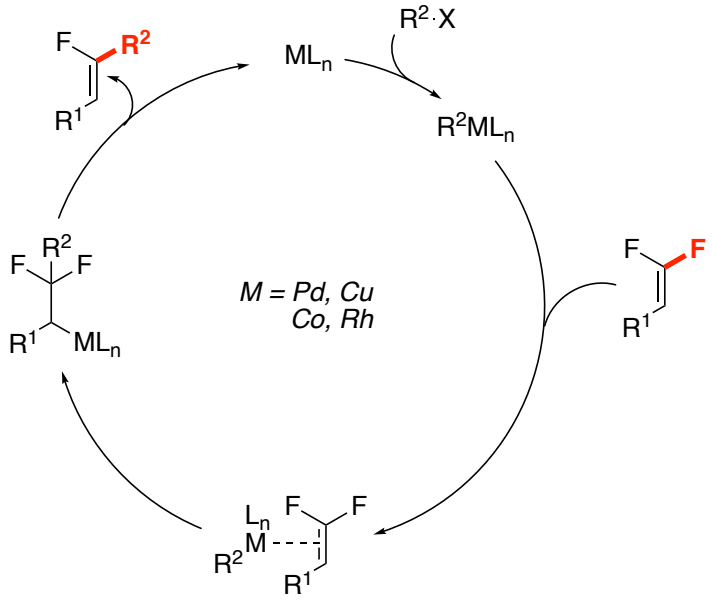


Frequently, the metal-catalyzed reactions of *gem*-difluoroalkenes avoid oxidative addition to the C–F bond. Instead, the reactions initiate through two mechanisms, olefin-

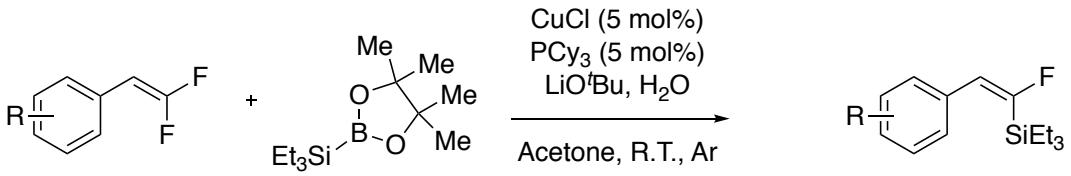
metal coordination[3d, 3p, 9] or C–H oxidative addition (**Scheme 4-2a**).[3n, 3o, 3r, 10] These reaction pathways are accessible by a wide variety of metal catalyst systems, including Cu (**Scheme 4-2b**),[3d, 3e, 3g, 3p, 9e, 9f, 11] Rh (**Scheme 4-2c**),[3j, 3r] Co,[3o] Fe,[3c] Mn,[3f, 3l] Zn,[3b] Ni,[3h, 3k] and Pd[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 β-fluoride elimination from the metallated intermediate to provide a M–F and the mono-fluorinated product (**Scheme 4-2a**).

Scheme 4-2: Transition-Metal Catalyzed Reactions of *gem*-Difluoroalkenes Avoiding C–F Oxidative Addition

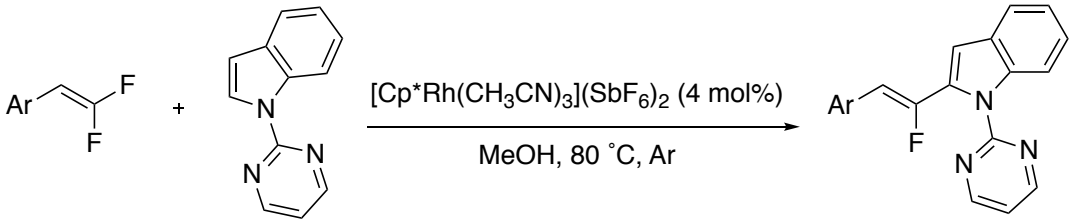
a) Metal Catalyzed Reactions of Difluoroalkene without C–F Oxidative Addition



b) Cu-Catalyzed C–F Functionalization via *Metal-Alkene Coordination*[3e]



c) Rh-Catalyzed C–F Functionalization via *C–H Oxidative Addition*[3j]

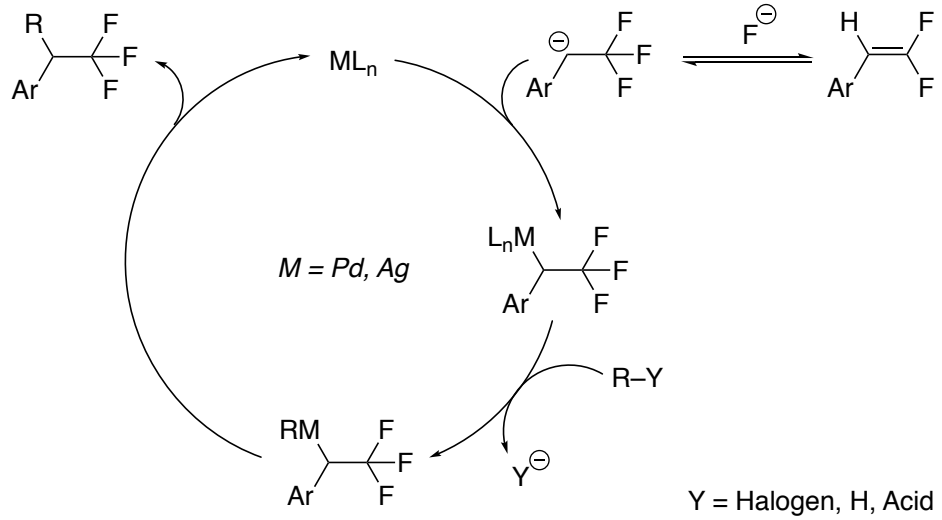


A second mode of reactivity with transition metals involves fluoride addition to *gem*-difluoroalkenes to establish an equilibrium between the unstable anionic intermediate and the starting *gem*-difluoroalkene. Once the equilibrium forms, a transition metal traps the

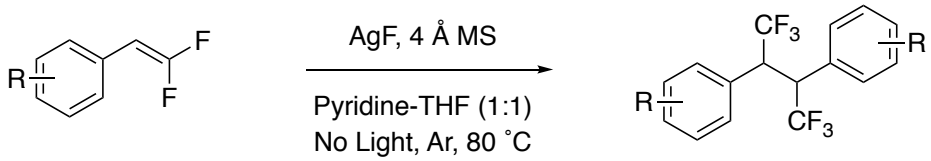
β-anionic intermediate and performs further bond-forming reactions (**Scheme 4-3a**). This strategy enables Ag-catalyzed homo-dimerization of the β-anionic intermediate (**Scheme 4-3b**)[4b] or Ag-catalyzed cross coupling with olefins[4a] after fluorination. More recent examples of this strategy exploit Pd-catalysis[4c-f] or photocatalysis[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**)[4c] or allyl functionalities,[4e, 12] b) enable oxidative cross-coupling with olefins[4a] or arenes (**Scheme 4-3b**),[4d] or c) initiate 3+2 annulations with alkynes.[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.[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

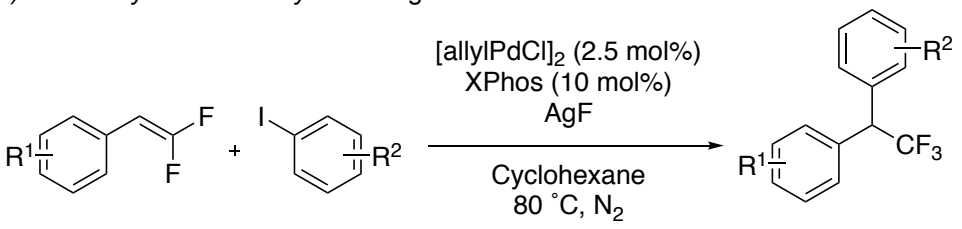
a) Representative Mechanism:
Fluorinative Difunctionalization of gem*-Difluoroalkenes*



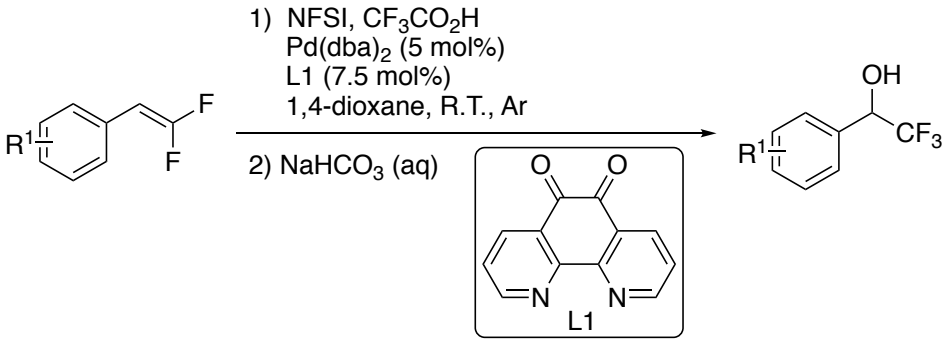
b) Ag-Catalyzed Homodimerization of gem*-Difluoroalkenes*[4b]



c) Pd-Catalyzed Fluoroarylation of gem*-Difluoroalkenes*[4d]



c) Pd-Catalyzed Hydroxylfluorination of gem*-Difluoroalkenes*[4c]



4.2. Dioxygenation Reactions of Alkenes

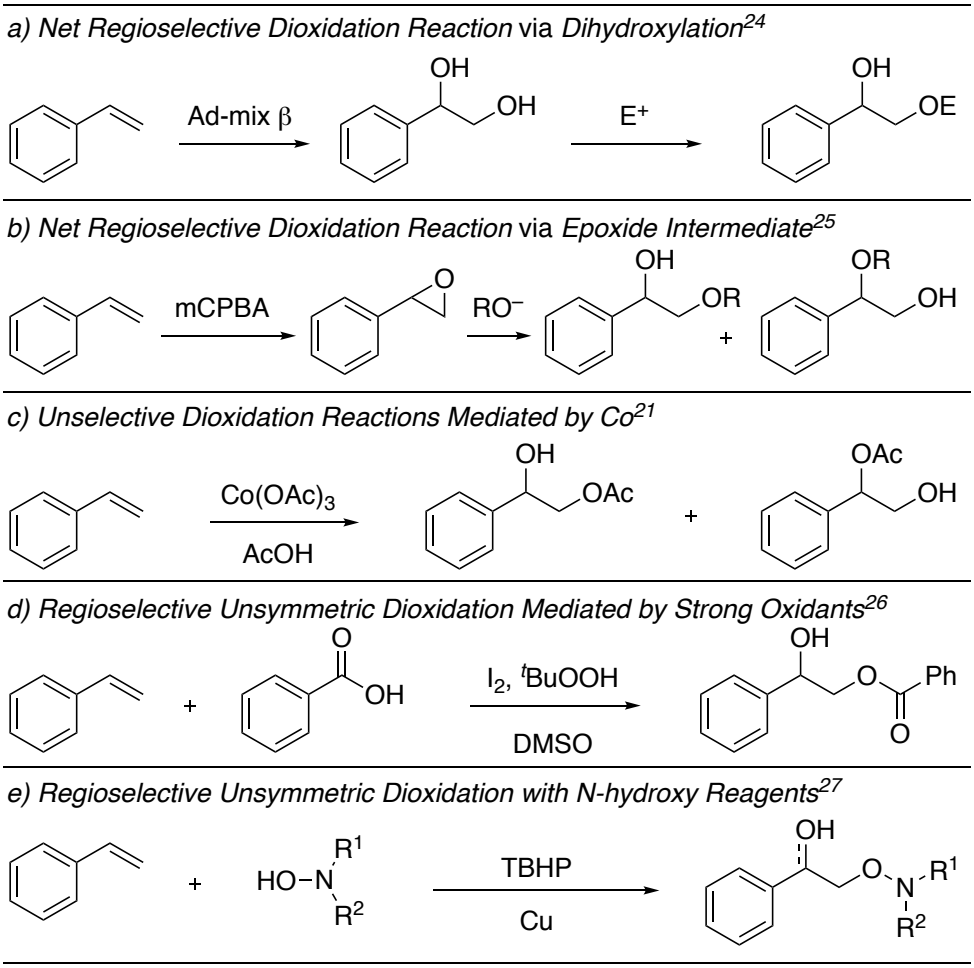
Alkenes undergo C–C or C–heteroatom bond formation *via* both nucleophilic and electrophilic strategies, making them a valuable functional handle in synthetic chemistry. Oxidation reactions of alkenes represent a particularly valuable strategy for rapid, late stage functionalization of simple compounds. 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**),[25] or non-selective oxidation with two different oxygen containing functional groups (**Figure 4-2c**).[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**),[26] or N-hydroxy reagents as coupling partners (**Figure 4-2e**).[27] These latter reactions proceed through a net anti-Markovnikov addition of functionalized oxygen groups to styrenes, an addition only recently achieved with alcohols.[28]

Figure 4-2: Representative Net Regioselective Unsymmetric Dioxidation Reactions of Styrenes.



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.[29]

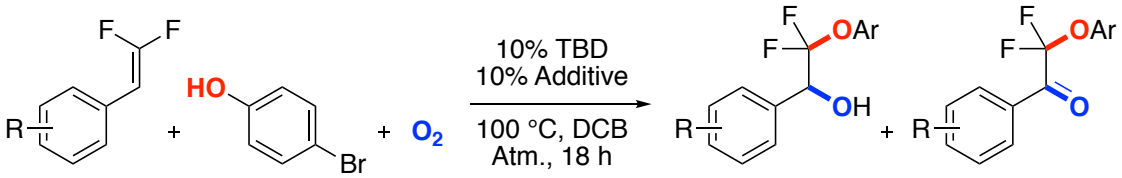
4.3. Co-Catalyzed Selective Unsymmetric Dioxidation of β,β-Difluorostyrenes

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 β-phenoxy-β,β-difluorobenzyl alcohols. This work exploits a regioselective addition of phenols and molecular oxygen to β,β-difluorostyrenes *via* one-electron redox chemistry with Co. The reaction avoids β-fluoride elimination through oxidation of the β-anionic intermediate to provide the stable β-phenoxy-β,β-difluorobenzyl alcohol products. Notably, the products bear fluorine within sufficient vicinity to modulate the acidity and basicity of both O-based functional groups,[30] which influences the solubility,[31] lipophilicity,[30a, 32] molecular conformation,[33] and ligand-protein interactions relative to the non-fluorinated analogs.[34] Further, the positioning of the F-atoms at the metabolic soft spot can block cytochrome P-450 mediated O-dealkylation processes,[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[2a] and phenols,[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 unsymmertic dioxygenation product formed β-phenoxy-

β,β-difluorobenzyl alcohols and ketones with exclusive regioselectivity. In contrast to O_2, external oxidants, including MnO_2, $K_2S_2O_8$, 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, O_2, and 90–140 ˚C proved most effective (**Table 4-1, entry 17**).

Table 4-1: Optimization of Selective Dioxygenation of Difluoroalkenes[a]



4.1 **4.2** *R = 3,4,5-(OMe)$_3$* **4.3** **4.4**

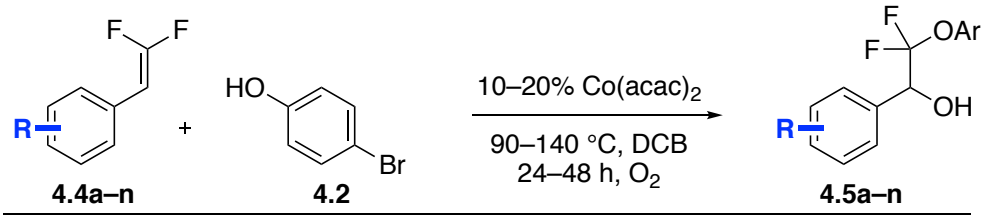
Entry	Additive	Atmosphere	Conv.[b]	4.3[b]	4.4[b]
1	–	O_2	92	41	31
2	MnO_2	Air	100	0	0
3	$K_2S_2O_8$	Air	79	8	0
4	NMO	Air	33	0	0
5	Oxone	Air	63	0	0
6	$Pd(OAc)_2$	O_2	95	38	26
7	$FeCl_3$	O_2	96	38	23
8	CuCl	O_2	96	24	23
9	$AgNO_3$	O_2	95	32	27
10	$[Ir(cod)Cl]_2$	O_2	74	30	22
11	$RhCl_3$–H_2O	O_2	94	46	29
12	$Co(acac)_2$	O_2	94	74	13
13[c]	$Co_2(CO)_8$	O_2	96	8	13
14[c]	$Co(PPh_3)_3Cl$	O_2	93	39	28
15[c]	$Co(acac)_3$	O_2	95	65	6
16[c]	CoS_2	O_2	87	5	8
17[c,d]	$Co(acac)_2$	O_2	100	71[e]	3

[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-Triazabicylco[4.4.0]dec-5-ene (TBD, 10%, 0.010 mmol), 100 ˚C, 18 h. [b] As determined by ^{19}F 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.

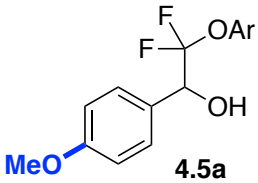
Under these conditions, a broad range of *gem*-difluoroalkenes were competent in the reaction, with most substrates providing >10:1 selectivity for the alcohol product over the

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 ^{19}F 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**).

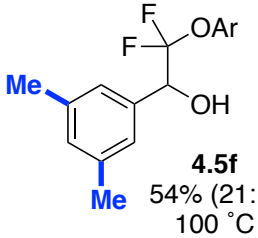
Scheme 4-4: Scope of β,β-Difluorostyrenes[a]



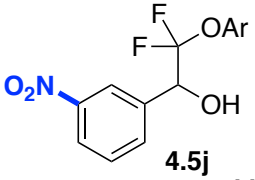
4.4a–n **4.2** **4.5a–n**



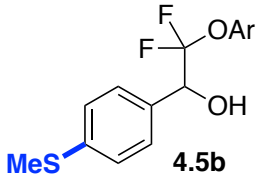
4.5a
74% (16:1)
90 ˚C



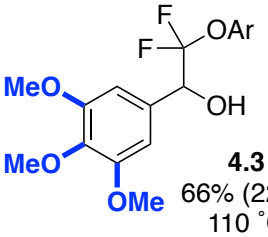
4.5f
54% (21:1)
100 ˚C



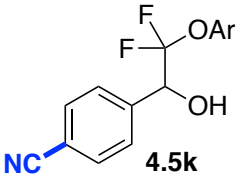
4.5j
43% (9:1)[c]
140 ˚C



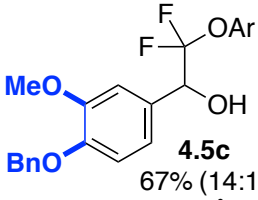
4.5b
48% (25:1)[b]
90 ˚C



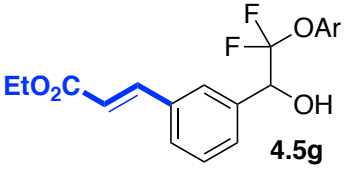
4.3
66% (22:1)
110 ˚C



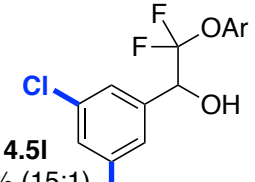
4.5k
41% (12.5:1)
140 ˚C



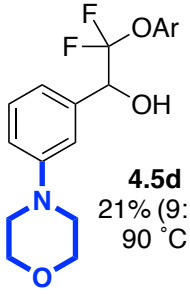
4.5c
67% (14:1)
100 ˚C



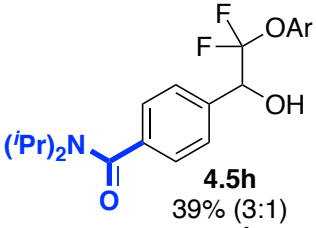
4.5g
50% (9:1)[c]
120 ˚C



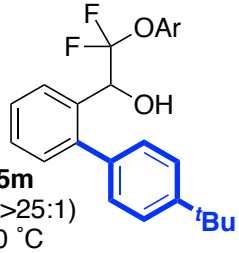
4.5l
44% (15:1)
140 ˚C



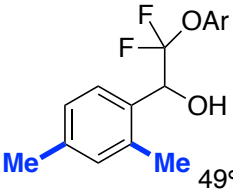
4.5d
21% (9:1)
90 ˚C



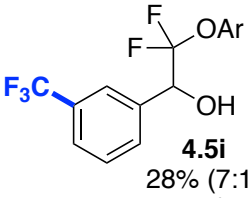
4.5h
39% (3:1)
130 ˚C



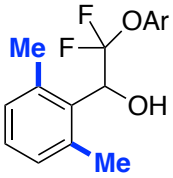
4.5m
57% (>25:1)
100 ˚C



4.5e
49% (16:1)
90 ˚C



4.5i
28% (7:1)
140 ˚C

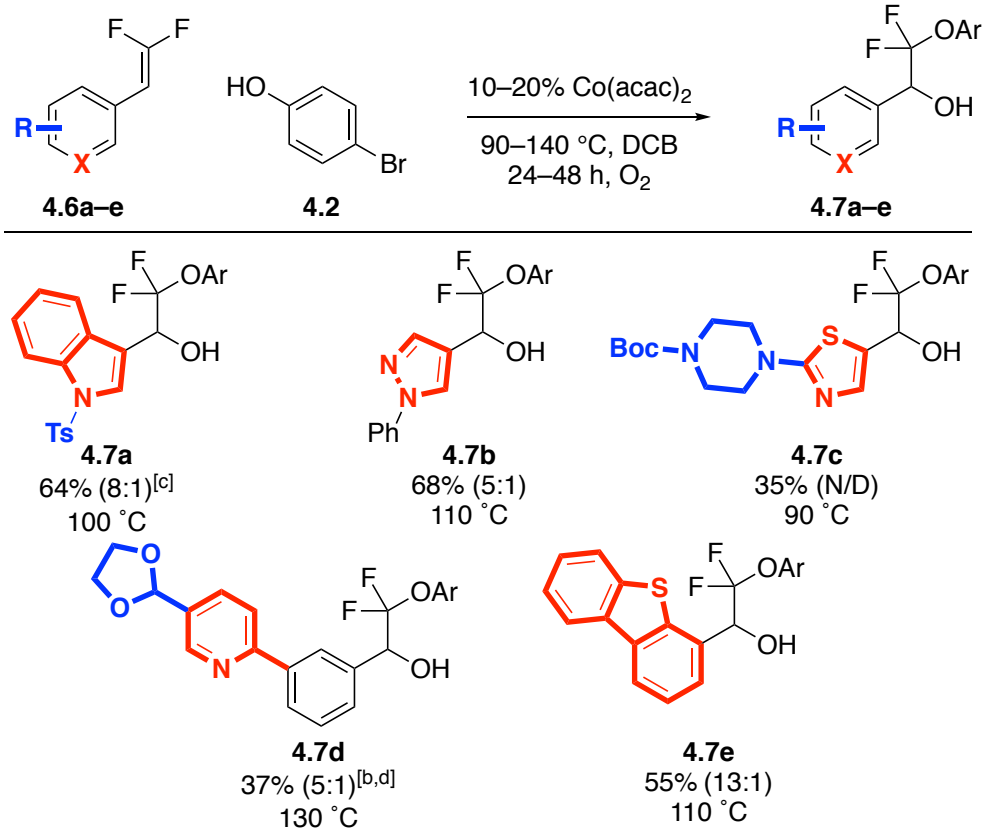


4.5n
0 %

[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 β,β-Difluorostyrenes[a]

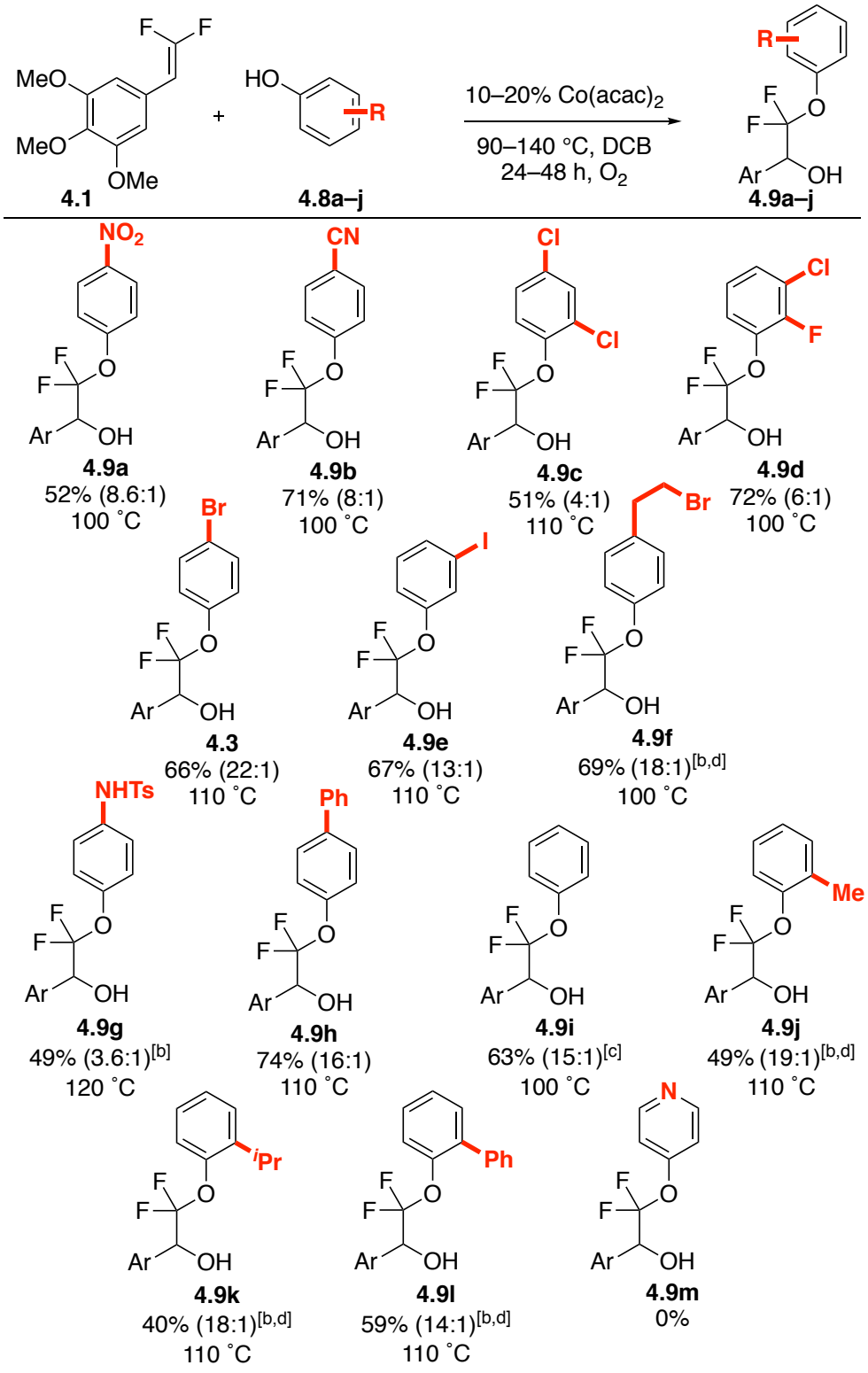


[a] Standard conditions: **4.6a–e** (1.0 equiv., 0.50 mmol), **4.2** (3.0 equiv., 1.5 mmol), DCB (0.25 M, 2.0 mL), $Co(acac)_2$ (10 mol%, 0.050 mmol), temperature as indicated, for 24 h under an O_2 atmosphere. The selectivity of alcohol:ketone was determined by ^{19}F NMR analysis of the reaction mixture 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, 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]



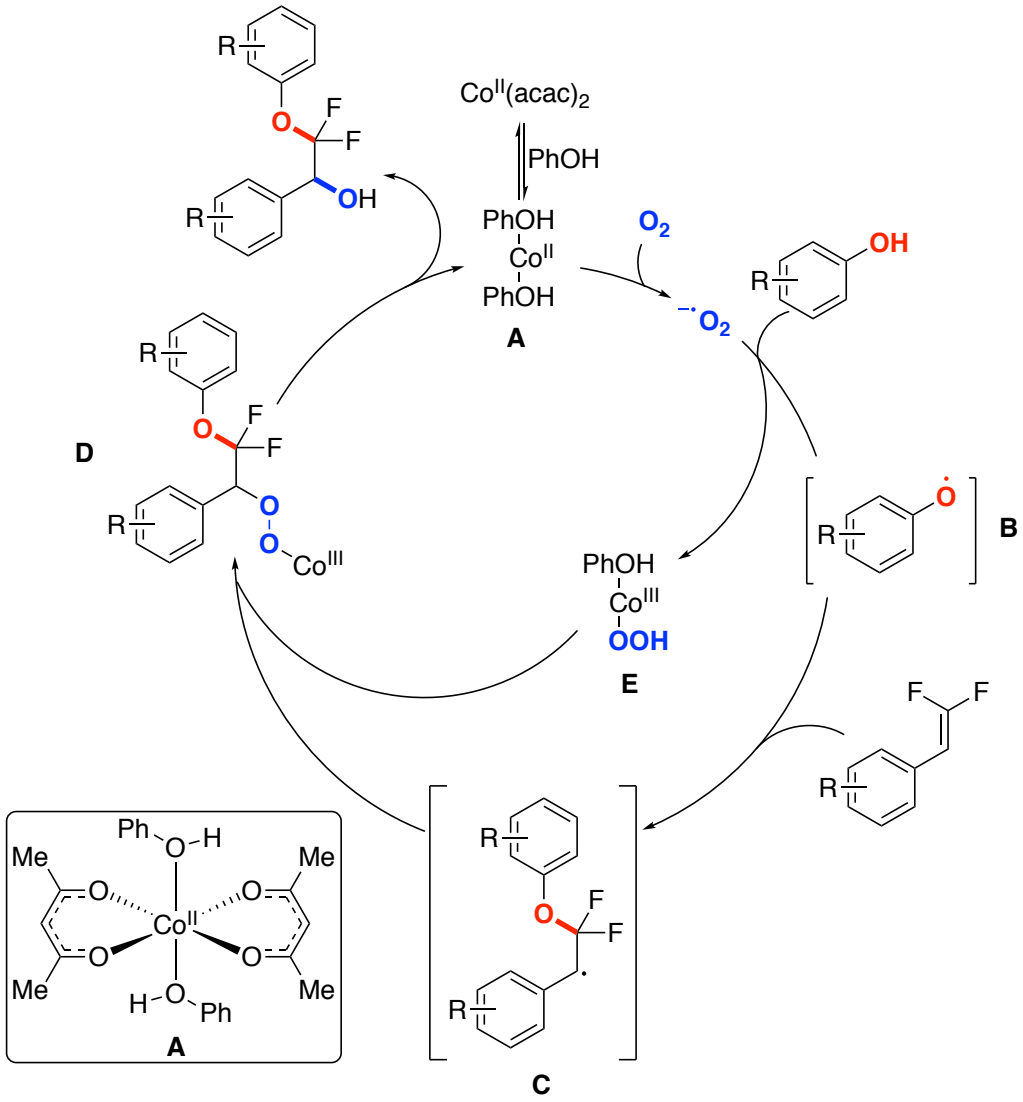
[a] Standard conditions: **4.1** (1.0 equiv., 0.50 mmol), **4.8a–j** (3.0 equiv., 1.5 mmol), DCB (0.25 M, 2.0 mL), $Co(acac)_2$ (10%, 0.050 mmol), temperature as indicated, for 24 h under an O_2 atmosphere. The selectivity of alcohol:ketone was determined by ^{19}F NMR analysis of the reaction mixture 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 phenoxyl 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•$^-$),[36] which subsequently abstracts H• from phenol to generate PhO• (**B**) and a peroxide anion (HO_2^-).[37] 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.[4a, 4b, 38] The anticipated oxidation of **C** by O_2[39] or Cobalt-bound peroxide anion[27b, 40] 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).[27b, 36b] 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).[27b]

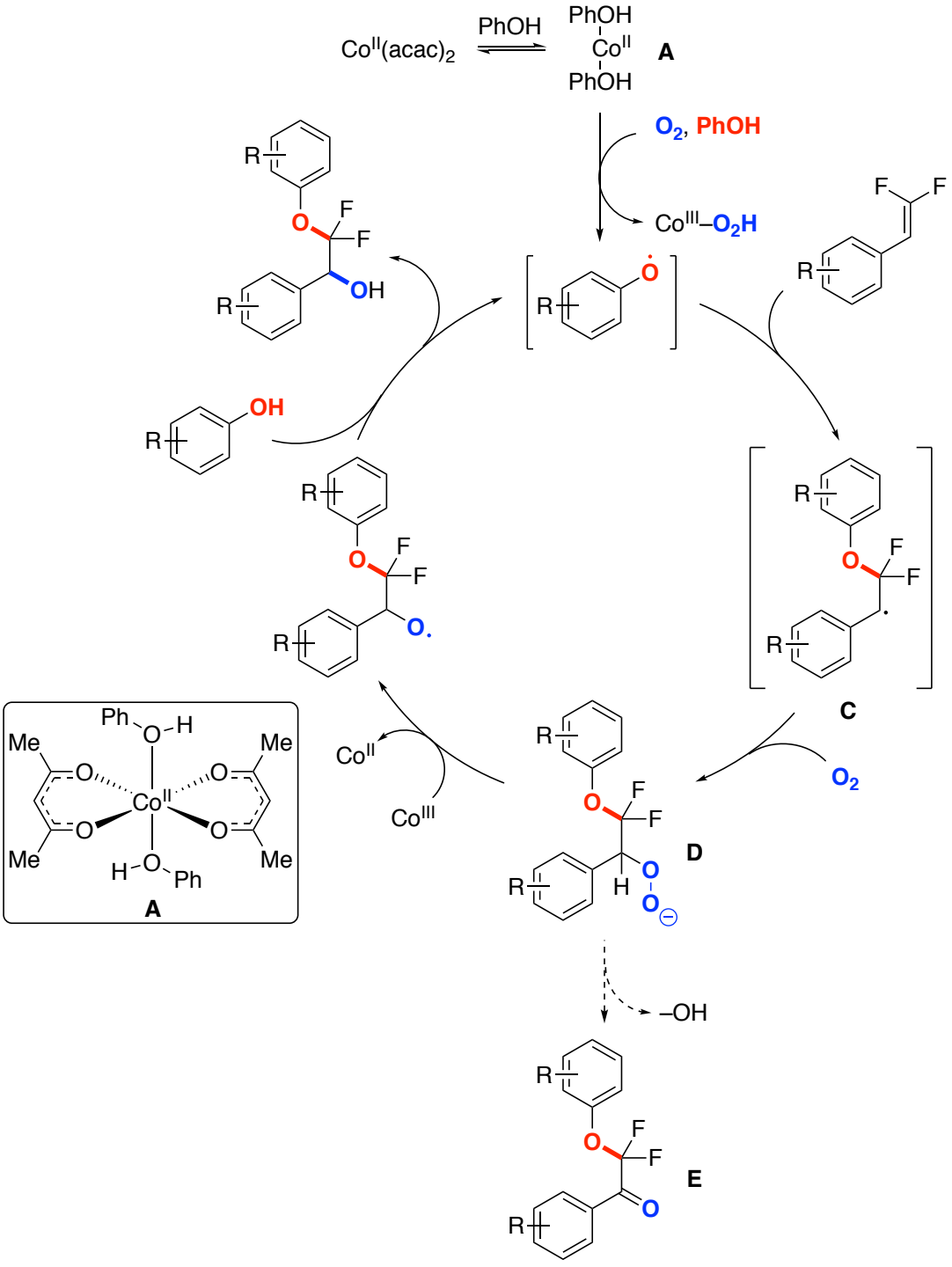
Figure 4-3: Proposed Cobalt-Catalyzed Mechanism



In the second proposed mechanism, Co initiates a radical chain reaction with oxygen and phenol (**Figure 4-4**). Co initiates the reaction by reducing O_2 to generate superoxide radical ($O_2^{\bullet -}$),[36] which subsequently abstracts H• from phenol to generate PhO• (**B**) to initiate the radical chain reaction, and a peroxide anion (HO_2^-).[37] Reaction of PhO• (**B**) with the difluoroalkene generates stabilized benzyl radical **C**. Here the mechanisms

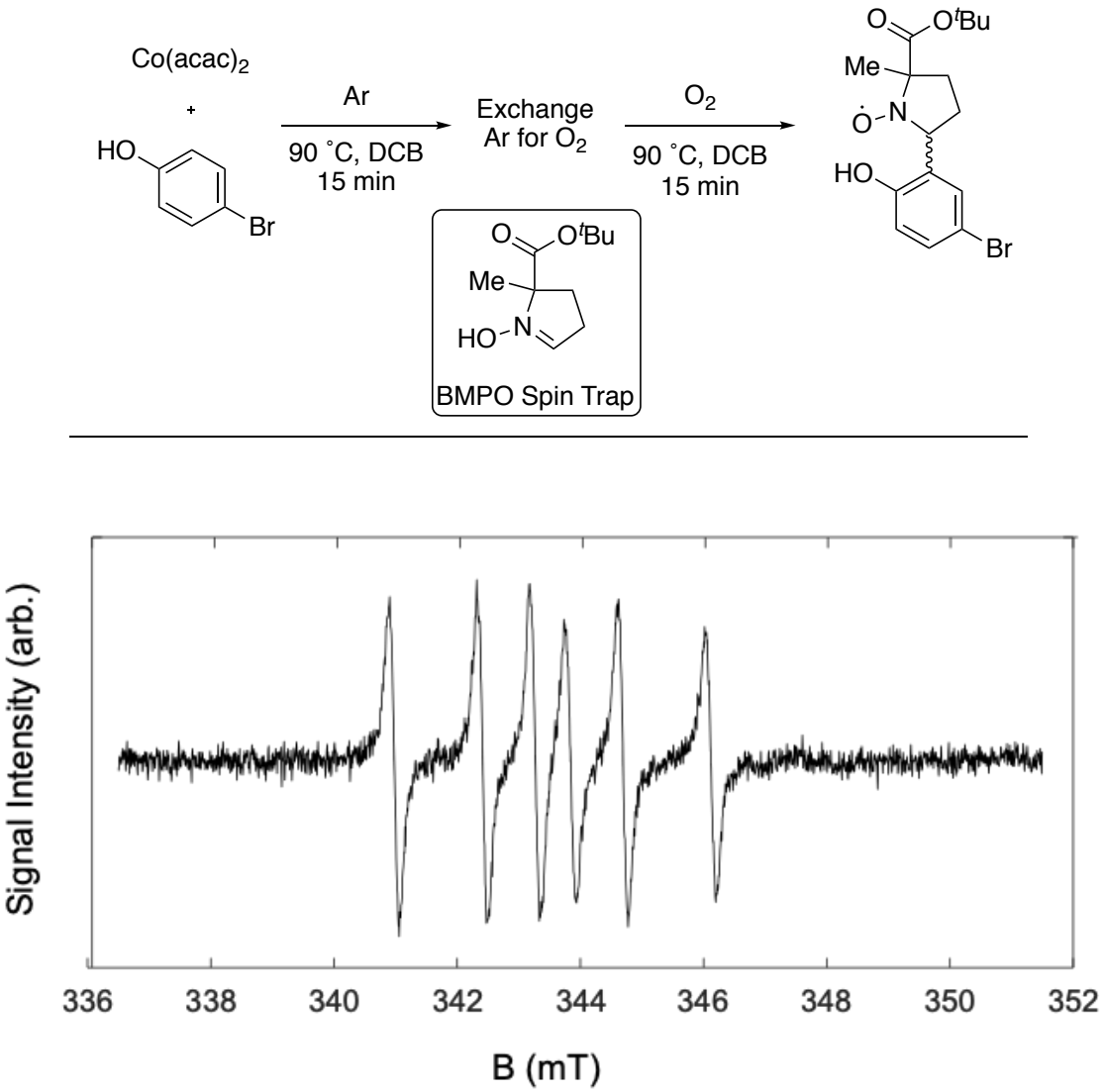
diverge, as **C** oxidizes with O_2 to generate benzylperoxide anion **D**. In what is likely an electron transfer reaction, Co(III) abstracts an electron from benzylperoxide intermediate **D**, which likely undergoes bond homolysis to generate a benzyl alcohol radical, which abstracts a hydrogen radical 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



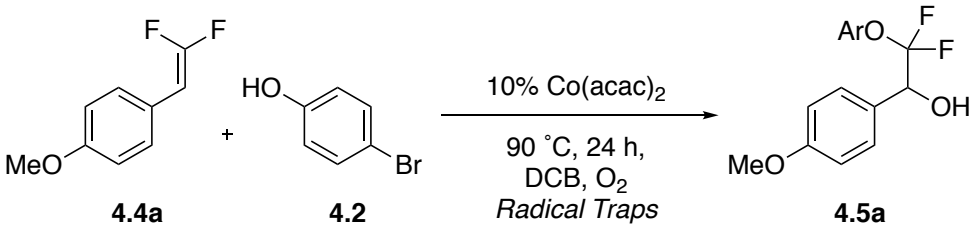
Evidence for early-stage generation of PhO• (**A→B**) derives from a series of electron paramagnetic resonance (EPR) experiments using spin trapping reagents. Specifically, the reaction of Co(II), phenol, O_2 and 5-*tert*-butoxycarbonyl-5-methyl-1-pyrroline-*N*-oxide (BMPO) or 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) generated spin-trapped adducts with EPR spectra (**Figure 4-5A**)[41] consistent with previous reports of Co(II) generating O-based radicals.[42, 43] The EPR spectrum of the phenoxyl 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).[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

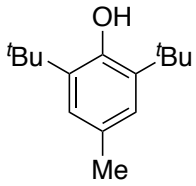
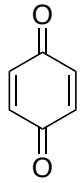
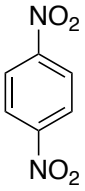


Reaction Conditions: $Co(acac)_2$ (1.0 equiv., 0.10 mmol), **4.2** (3.0 equiv., 0.30 mmol) in 0.80 mL DCB 90 ˚C, for 15 min under an Ar atmosphere, followed by the gas exchange of Ar for O_2, 90 ˚C, for 15 min followed by quenching with BMPO solution.

Table 4-2: Radical Trap Analysis[a]

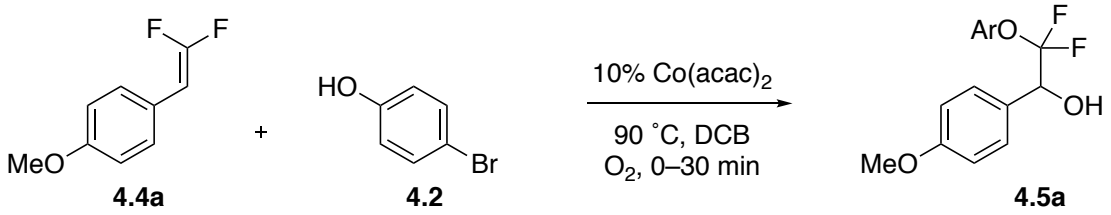


4.4a **4.2** **4.5a**

Radical Trap	*Conv.*	**4.5a**	**4.6a**
	68%	0%	0%
	100%	0%	0%
	92%	54%	5.5%

[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 O_2 atmosphere. The conversion of **4.3a** and the yield of **4.5a** and **4.6a** was determined by ^{19}F 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[a]



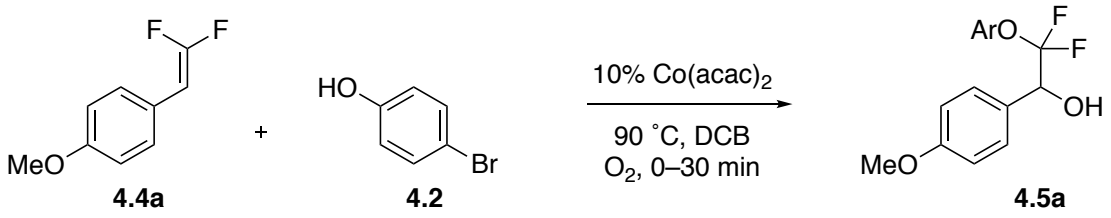
4.4a **4.2** **4.5a**

4.2 Equiv.	k_{obs} (GC–FID)
1.0	0.0040
1.33	0.0050
1.67	0.0070
2.0	0.0080
2.5	0.0090
3.0	0.010
5.0	0.0120

[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]

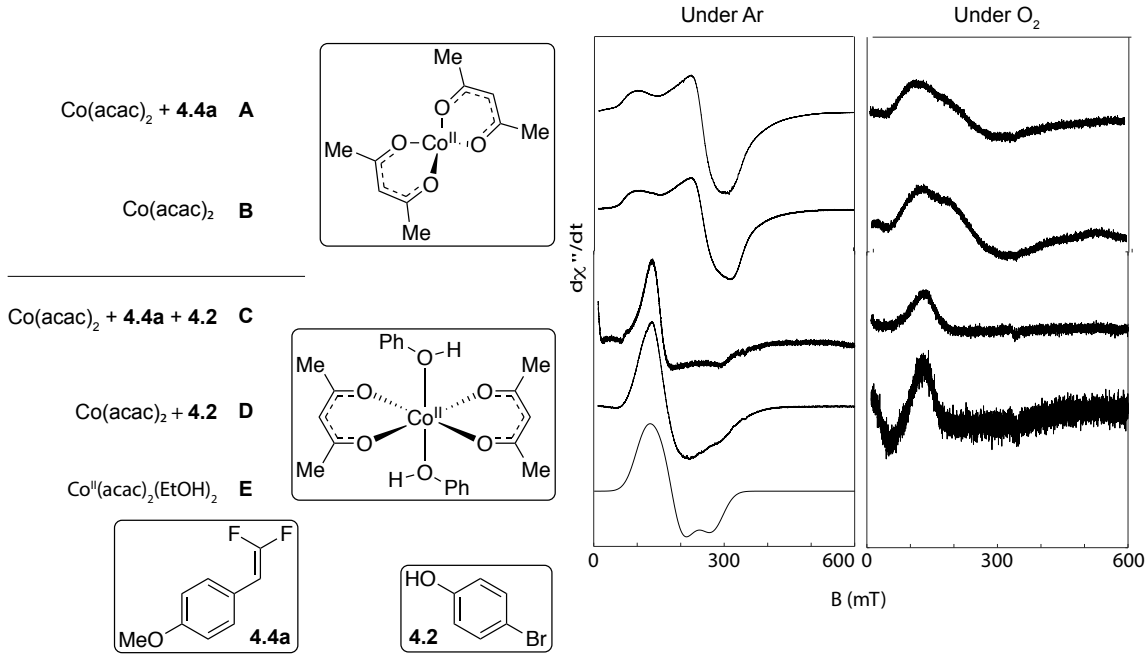


4.4a **4.2** **4.5a**

4.4a Equiv.	k_{obs} (GC–FID)
1.0	0.010
3.0	0.011
5.0	0.0060

[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 μL (0.25 mmol) of dodecane.

Figure 4-6: 10 K EPR Analysis of Co Catalytic Center



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[45] for $Co(acac)_2(EtOH)_2$.[42]

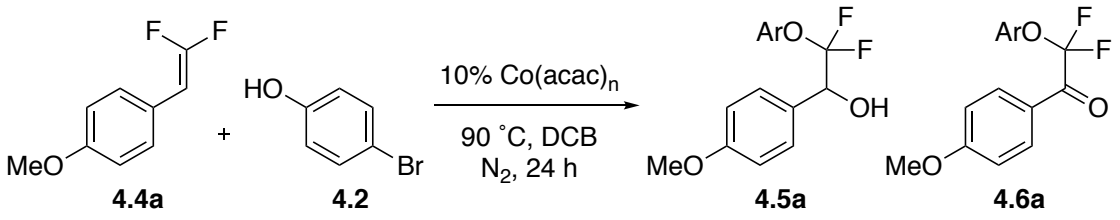
Several pieces of evidence support Co(II) and O_2 playing key roles in initiating the catalytic cycle. First, EPR studies under stoichiometric conditions (Co(II)/O_2/PhOH) suggest the formation of initial Co(II) complex (**A**) bearing two phenolic ligands and two acetylacetonate ligands in an octahedral complex[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).[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).[36] This pre-catalytic 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.[36-37] Supporting this theory, in the absence of O_2, 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)/O_2/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 O_2 also participates in activating the phenol[36a] to generate phenoxyl radical (**B**) prior to reaction with the *gem*-difluoroalkene to generate benzyl radical (**C**).

Scheme 4-7: Reaction in the Absence of O_2[a]



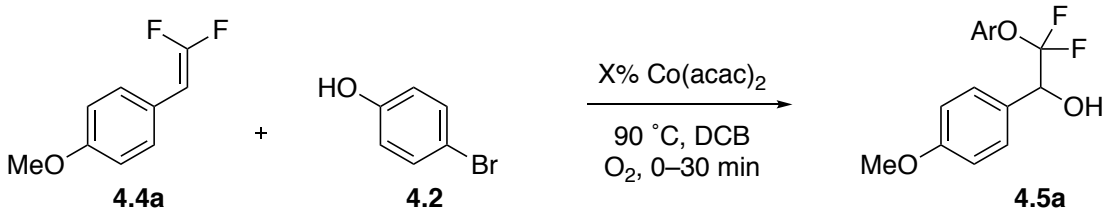
4.4a **4.2** **4.5a** **4.6a**

Co	**4.4a** Conv	**4.5a** Yield	**4.6a** Yield
$Co(acac)_2$	40%	0%	0%
$Co(acac)_3$	40%	0%	0%

[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]



4.4a **4.2** **4.5a**

% $Co(acac)_2$	k_{obs} (GC–FID)
0.050	0.010
0.10	0.0090
0.20	0.010
0.30	0.0080
0.40	0.0080
0.50	0.0060

[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 O_2, which abstracts a hydrogen radical from phenol to form a phenoxyl radical. This phenoxyl 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

1. (a) Zhang, X.; Cao, S., Recent advances in the synthesis and CF functionalization of gem-difluoroalkenes. *Tetrahedron Lett.* **2017,** *58* (5), 375-392; (b) Orsi, D. L.; Altman, R. A., Exploiting the unusual effects of fluorine in methodology. *Chem. Commun.* **2017,** *53* (53), 7168-7181.

2. (a) Orsi, D. L.; Easley, B. J.; Lick, A. M.; Altman, R. A., Base Catalysis Enables Access to alpha,alpha-Difluoroalkylthioethers. *Org. Lett.* **2017,** *19* (7), 1570-1573; (b) Qiao, Y.; Si, T.; Yang, M. H.; Altman, R. A., Metal-free trifluoromethylation of aromatic and heteroaromatic aldehydes and ketones. *J. Org. Chem.* **2014,** *79* (15), 7122-31; (c) Orsi, D. L.; Yadav, M. R.; Altman, R. A., Organocatalytic strategy for hydrophenolation of gem-difluoroalkenes. *Tetrahedron* **2019**.

3. (a) Yokota, M.; Fujita, D.; Ichikawa, J., Activation of 1,1-difluoro-1-alkenes with a transition-metal complex: palladium(II)-catalyzed Friedel-Crafts-type cyclization of 4,4-(difluorohomoallyl)arenes. *Org. Lett.* **2007,** *9* (22), 4639-42; (b) Yu, L.; Tang, M. L.; Si, C. M.; Meng, Z.; Liang, Y.; Han, J.; Sun, X., Zinc-Mediated Decarboxylative Alkylation of Gem-difluoroalkenes. *Org. Lett.* **2018,** *20* (15), 4579-4583; (c) Yang, L.; Ji, W. W.; Lin, E.; Li, J. L.; Fan, W. X.; Li, Q.; Wang, H., Synthesis of Alkylated Monofluoroalkenes via Fe-Catalyzed Defluorinative Cross-Coupling of Donor Alkenes with gem-Difluoroalkenes. *Org. Lett.* **2018,** *20* (7), 1924-1927; (d) Tan, D. H.; Lin, E.; Ji, W. W.; Zeng, Y. F.; Fan, W. X.; Li, Q. J.; Gao, H.; Wang, H. G., Copper-Catalyzed Stereoselective Defluorinative Borylation and Silylation of gem-Difluoroalkenes. *Adv. Synth. Catal.* **2018,** *360* (5), 1032-

1037; (e) Zhang, J.; Dai, W.; Liu, Q.; Cao, S., Cu-Catalyzed Stereoselective Borylation of gem-Difluoroalkenes with B2pin2. *Org. Lett.* **2017,** *19* (12), 3283-3286; (f) Zell, D.; Dhawa, U.; Muller, V.; Bursch, M.; Grimme, S.; Ackermann, L., C-F/C-H Functionalization by Manganese(I) Catalysis: Expedient (Per)Fluoro-Allylations and Alkenylations. *Acs Catal* **2017,** *7* (6), 4209-4213; (g) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T., Copper-Catalyzed Regioselective Monodefluoroborylation of Polyfluoroalkenes en Route to Diverse Fluoroalkenes. *J. Am. Chem. Soc.* **2017,** *139* (36), 12855-12862; (h) Lu, X.; Wang, Y.; Zhang, B.; Pi, J. J.; Wang, X. X.; Gong, T. J.; Xiao, B.; Fu, Y., Nickel-Catalyzed Defluorinative Reductive Cross-Coupling of gem-Difluoroalkenes with Unactivated Secondary and Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2017,** *139* (36), 12632-12637; (i) Li, J.; Lefebvre, Q.; Yang, H.; Zhao, Y.; Fu, H., Visible light photocatalytic decarboxylative monofluoroalkenylation of alpha-amino acids with gem-difluoroalkenes. *Chem. Commun.* **2017,** *53* (74), 10299-10302; (j) Kong, L.; Liu, B.; Zhou, X.; Wang, F.; Li, X., Rhodium(iii)-catalyzed regio- and stereoselective benzylic alpha-fluoroalkenylation with gem-difluorostyrenes. *Chem. Commun.* **2017,** *53* (74), 10326-10329; (k) Watabe, Y.; Kanazawa, K.; Fujita, T.; Ichikawa, J., Nickel-Catalyzed Hydroalkenylation of Alkynes through C-F Bond Activation: Synthesis of 2-Fluoro-1,3-dienes. *Synthesis-Stuttgart* **2017,** *49* (16), 3569-3575; (l) Cai, S. H.; Ye, L.; Wang, D. X.; Wang, Y. Q.; Lai, L. J.; Zhu, C.; Feng, C.; Loh, T. P., Manganese-catalyzed synthesis of monofluoroalkenes via C-H activation and C-F cleavage. *Chem. Commun.* **2017,** *53* (62), 8731-8734; (m) Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S., Monofluoroalkenylation of Dimethylamino Compounds through Radical-Radical Cross-Coupling. *Angew. Chem. Int. Ed. Engl.* **2016,** *55* (32), 9416-21; (n) Thornbury, R. T.;

Toste, F. D., Palladium-Catalyzed Defluorinative Coupling of 1-Aryl-2,2-Difluoroalkenes and Boronic Acids: Stereoselective Synthesis of Monofluorostilbenes. *Angew. Chem. Int. Ed. Engl.* **2016,** *55* (38), 11629-32; (o) Kong, L.; Zhou, X.; Li, X., Cobalt(III)-Catalyzed Regio- and Stereoselective alpha-Fluoroalkenylation of Arenes with gem-Difluorostyrenes. *Org. Lett.* **2016,** *18* (24), 6320-6323; (p) Dai, W.; Shi, H.; Zhao, X.; Cao, S., Sterically Controlled Cu-Catalyzed or Transition-Metal-Free Cross-Coupling of gem-Difluoroalkenes with Tertiary, Secondary, and Primary Alkyl Grignard Reagents. *Org. Lett.* **2016,** *18* (17), 4284-7; (q) Xiong, Y.; Huang, T.; Ji, X.; Wu, J.; Cao, S., Nickel-catalyzed Suzuki-Miyaura type cross-coupling reactions of (2,2-difluorovinyl)benzene derivatives with arylboronic acids. *Org Biomol Chem* **2015,** *13* (27), 7389-92; (r) Tian, P.; Feng, C.; Loh, T. P., Rhodium-catalysed C(sp(2))-C(sp(2)) bond formation via C-H/C-F activation. *Nat Commun* **2015,** *6*, 7472.

4. (a) Gao, B.; Zhao, Y.; Hu, J., AgF-mediated fluorinative cross-coupling of two olefins: facile access to alpha-CF3 alkenes and beta-CF3 ketones. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (2), 638-42; (b) Gao, B.; Zhao, Y.; Ni, C.; Hu, J., AgF-mediated fluorinative homocoupling of gem-difluoroalkenes. *Org. Lett.* **2014,** *16* (1), 102-5; (c) Zhang, B.; Zhang, X.; Hao, J.; Yang, C., Palladium-Catalyzed Direct Approach to α-Trifluoromethyl Alcohols by Selective Hydroxylfluorination of gem-Difluoroalkenes. *Eur. J. Org. Chem.* **2018,** *2018* (36), 5007-5015; (d) Tang, H. J.; Lin, L. Z.; Feng, C.; Loh, T. P., Palladium-Catalyzed Fluoroarylation of gem-Difluoroalkenes. *Angew. Chem. Int. Ed. Engl.* **2017,** *56* (33), 9872-9876; (e) Tian, P.; Wang, C. Q.; Cai, S. H.; Song, S.; Ye, L.; Feng, C.; Loh, T. P., F(-) Nucleophilic-Addition-Induced Allylic Alkylation. *J. Am. Chem.*

Soc. **2016,** *138* (49), 15869-15872; (f) Tang, H. J.; Zhang, Y. F.; Jiang, Y. W.; Feng, C., F(-) Nucleophilic-Addition-Induced [3 + 2] Annulation: Direct Access to CF3-Substituted Indenes. *Org. Lett.* **2018,** *20* (17), 5190-5193.

5. Vela, J.; Smith, J. M.; Yu, Y.; Ketterer, N. A.; Flaschenriem, C. J.; Lachicotte, R. J.; Holland, P. L., Synthesis and reactivity of low-coordinate iron(II) fluoride complexes and their use in the catalytic hydrodefluorination of fluorocarbons. *J. Am. Chem. Soc.* **2005,** *127* (21), 7857-70.

6. (a) Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S., Base-Free Hiyama Coupling Reaction via a Group 10 Metal Fluoride Intermediate Generated by C-F Bond Activation. *Organometallics* **2014,** *33* (14), 3669-3672; (b) Ohashi, M.; Saijo, H.; Shibata, M.; Ogoshi, S., Palladium-Catalyzed Base-Free Suzuki-Miyaura Coupling Reactions of Fluorinated Alkenes and Arenes via a Palladium Fluoride Key Intermediate. *Eur. J. Org. Chem.* **2013,** *2013* (3), 443-447; (c) Ohashi, M.; Kambara, T.; Hatanaka, T.; Saijo, H.; Doi, R.; Ogoshi, S., Palladium-catalyzed coupling reactions of tetrafluoroethylene with arylzinc compounds. *J. Am. Chem. Soc.* **2011,** *133* (10), 3256-9.

7. (a) Dai, W. P.; Zhang, X. X.; Zhang, J.; Lin, Y. Y.; Cao, S., Synthesis of Exocyclic Trisubstituted Alkenes via Nickel-Catalyzed Kumada-Type Cross-Coupling Reaction of gem-Difluoroalkenes with Di-Grignard Reagents. *Adv. Synth. Catal.* **2016,** *358* (2), 183-187; (b) Dai, W.; Xiao, J.; Jin, G.; Wu, J.; Cao, S., Palladium- and nickel-catalyzed Kumada cross-coupling reactions of gem-difluoroalkenes and monofluoroalkenes with Grignard reagents. *J. Org. Chem.* **2014,** *79* (21), 10537-46.

8. Senaweera, S.; Weaver, J. D., Photocatalytic C-F Reduction and Functionalization. *Aldrichimica Acta* **2016,** *49* (3), 45-54.

9. (a) Yamada, S.; Shimoji, K.; Takahashi, T.; Konno, T.; Ishihara, T., An effective preparation of sulfonyl- or sulfinyl-substituted fluorinated alkenes and their stereoselective addition-elimination reactions with organocuprates. *Chem Asian J* **2010,** *5* (8), 1846-53; (b) Yamada, S.; Noma, M.; Hondo, K.; Konno, T.; Ishihara, T., Preparation and Addition–Elimination Reactions of Benzyl a,b,b-Trifluoroacrylate. A New Stereoselective Approach to (*Z*)-b-Substituted a,b-Difluoroacrylates. *J. Org. Chem.* **2008,** *73*, 522–8; (c) Yamada, S.; Noma, M.; Konno, T.; Ishihara, T.; Yamanaka, H., Novel synthesis of (Z)-difluoroacrylates via a highly stereoselective addition-elimination reaction. *Org. Lett.* **2006,** *8* (5), 843-5; (d) Zhang, X.; Dai, W.; Wu, W.; Cao, S., Copper-Catalyzed Coupling Cyclization of gem-Difluoroalkenes with Activated Methylene Carbonyl Compounds: Facile Domino Access to Polysubstituted Furans. *Org. Lett.* **2015,** *17* (11), 2708-11; (e) Kojima, R.; Kubota, K.; Ito, H., Stereodivergent hydrodefluorination of gem-difluoroalkenes: selective synthesis of (Z)- and (E)-monofluoroalkenes. *Chem. Commun.* **2017,** *53* (77), 10688-10691; (f) Sakaguchi, H.; Ohashi, M.; Ogoshi, S., Fluorinated Vinylsilanes from the Copper-Catalyzed Defluorosilylation of Fluoroalkene Feedstocks. *Angew. Chem. Int. Ed. Engl.* **2018,** *57* (1), 328-332.

10. Kikushima, K.; Sakaguchi, H.; Saijo, H.; Ohashi, M.; Ogoshi, S., Copper-mediated One-pot Synthesis of Trifluorostyrene Derivatives from Tetrafluoroethylene and Arylboronate. *Chem. Lett.* **2015,** *44* (7), 1019-1021.

11. Hu, J.; Zhao, Y.; Shi, Z., Highly tunable multi-borylation of gem-difluoroalkenes via copper catalysis. *Nature Catalysis* **2018,** *1* (11), 860-869.

12. Liu, H.; Ge, L.; Wang, D. X.; Chen, N.; Feng, C., Photoredox-Coupled F-Nucleophilic Addition: Allylation of gem-Difluoroalkenes. *Angew. Chem. Int. Ed. Engl.* **2019,** *58* (12), 3918-3922.

13. Yang, L.; Fan, W. X.; Lin, E.; Tan, D. H.; Li, Q.; Wang, H., Synthesis of alpha-CF3 and alpha-CF2H amines via the aminofluorination of fluorinated alkenes. *Chem. Commun.* **2018,** *54* (46), 5907-5910.

14. (a) Ujwaldev, S. M.; Sindhu, K. S.; Thankachan, A. P.; Anilkumar, G., Recent developments and perspectives in the ruthenium-catalyzed olefin epoxidation. *Tetrahedron* **2016,** *72* (41), 6175-6190; (b) Krishnan, K. K.; Thomas, A. M.; Sindhu, K. S.; Anilkumar, G., Recent advances and perspectives in the manganese-catalysed epoxidation reactions. *Tetrahedron* **2016,** *72* (1), 1-16; (c) Hussain, H.; Al-Harrasi, A.; Green, I. R.; Ahmed, I.; Abbas, G.; Rehman, N. U., meta-Chloroperbenzoic acid (mCPBA): a versatile reagent in organic synthesis. *RSC Adv.* **2014,** *4* (25), 12882-12917.

15. (a) Souto, J. A.; Stockman, R. A.; Ley, S. V., Development of a flow method for the hydroboration/oxidation of olefins. *Org Biomol Chem* **2015,** *13* (13), 3871-7; (b) Whiting, A.; Chen, J.-B., Recent Advances in Copper-Catalyzed Asymmetric Hydroboration of Electron-Deficient Alkenes: Methodologies and Mechanism. *Synthesis* **2018,** *50* (19), 3843-3861; (c) Zhang, F.; Du, P.; Chen, J.; Wang, H.; Luo, Q.; Wan, X., Co-catalyzed synthesis of 1,4-dicarbonyl compounds using TBHP oxidant. *Org. Lett.* **2014,** *16* (7),

1932-5; (d) Kanth, J. V. B.; Brown, H. C., Hydroboration. 97. Synthesis of New Exceptional Chloroborane−Lewis Base Adducts for Hydroboration. Dioxane−Monochloroborane as a Superior Reagent for the Selective Hydroboration of Terminal Alkenes†. *The Journal of Organic Chemistry* **2001,** *66* (16), 5359-5365.

16. Takacs, J.; Jiang, X.-t., The Wacker Reaction and Related Alkene Oxidation Reactions. *Curr. Org. Chem.* **2003,** *7* (4), 369-396.

17. (a) Sharpless, K. B.; Lauer, R. F., Selenium dioxide oxidation of olefins. Evidence for the intermediacy of allylseleninic acids. *J. Am. Chem. Soc.* **1972,** *94* (20), 7154-7155; (b) Jensen, H. P.; Sharpless, K. B., Selenium dioxide oxidation of d-limonene. Reinvestigation. *The Journal of Organic Chemistry* **1975,** *40* (2), 264-265; (c) Garcia-Cabeza, A. L.; Marin-Barrios, R.; Moreno-Dorado, F. J.; Ortega, M. J.; Massanet, G. M.; Guerra, F. M., Allylic oxidation of alkenes catalyzed by a copper-aluminum mixed oxide. *Org. Lett.* **2014,** *16* (6), 1598-601; (d) Nakada, M.; Nakamura, A., Allylic Oxidations in Natural Product Synthesis. *Synthesis* **2013,** *45* (11), 1421-1451; (e) Bayeh, L.; Le, P. Q.; Tambar, U. K., Catalytic allylic oxidation of internal alkenes to a multifunctional chiral building block. *Nature* **2017,** *547* (7662), 196-200.

18. Fisher, T. J.; Dussault, P. H., Alkene ozonolysis. *Tetrahedron* **2017,** *73* (30), 4233-4258.

19. (a) Bataille, C. J.; Donohoe, T. J., Osmium-free direct syn-dihydroxylation of alkenes. *Chem. Soc. Rev.* **2011,** *40* (1), 114-28; (b) Wang, C., Vicinal anti-Dioxygenation of Alkenes. *Asian J. Org. Chem.* **2018,** *7* (3), 509-521; (c) Bag, R.; De, P. B.; Pradhan,

S.; Punniyamurthy, T., Recent Advances in Radical Dioxygenation of Olefins. *Eur. J. Org. Chem.* **2017,** *2017* (37), 5424-5438; (d) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B., Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994,** *94* (8), 2483-2547.

20. Aertker, K.; Rama, R. J.; Opalach, J.; Muniz, K., Vicinal Difunctionalization of Alkenes under Iodine(III) Catalysis involving Lewis Base Adducts. *Adv. Synth. Catal.* **2017,** *359* (8), 1290-1294.

21. (a) Morimoto, T.; Hirano, M.; Echigoya, K.; Sato, T., Oxidation by cobalt(III) acetate. Part 10. Effects of ring substituents on the product distributions in the oxidation of β-methylstyrenes by cobalt(III) acetate in acetic acid. *J. Chem. Soc., Perkin Trans. 2* **1986,** (8), 1205-1209; (b) Hirano, M.; Morimoto, T., Oxidation by cobalt(III) acetate. Part 6. A novel synthesis of the glycol monoacetates from aromatic olefins in wet acetic acid. *J Chem Soc Perk T 2* **1984,** (6), 1033–1036; (c) Hirano, M.; Kitamura, E.; Morimoto, T., Oxidation by cobalt(III) acetate. Part 2. Oxidation of styrene in acetic acid. *J Chem Soc Perk T 2* **1980,** *4* (4), 569–573.

22. (a) Schroeder, M., Osmium tetraoxide cis hydroxylation of unsaturated substrates. *Chem. Rev.* **1980,** *80* (2), 187-213; (b) Donohoe, T. J.; Harris, R. M.; Butterworth, S.; Burrows, J. N.; Cowley, A.; Parker, J. S., New osmium-based reagent for the dihydroxylation of alkenes. *J. Org. Chem.* **2006,** *71* (12), 4481-9.

23. Azizi, N.; Khajeh-Amiri, A.; Ghafuri, H.; Bolourtchian, M., LiOH-Catalyzed Simple Ring Opening of Epoxides Under Solvent-Free Conditions. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2010,** *185* (7), 1550-1557.

24. (a) Szermerski, M.; Melesina, J.; Wichapong, K.; Loppenberg, M.; Jose, J.; Sippl, W.; Holl, R., Synthesis, biological evaluation and molecular docking studies of benzyloxyacetohydroxamic acids as LpxC inhibitors. *Bioorg. Med. Chem.* **2014,** *22* (3), 1016-28; (b) Lipka, E.; Vaccher, M. P.; Vaccher, C.; Len, C., Enantiomerical excess determination, purification and biological evaluation of (3S) and (3R) alpha,beta-butenolide analogues of isobenzofuranone. *Bioorg. Med. Chem. Lett.* **2005,** *15* (3), 501-4; (c) Miyakoshi, H.; Miyahara, S.; Yokogawa, T.; Endoh, K.; Muto, T.; Yano, W.; Wakasa, T.; Ueno, H.; Chong, K. T.; Taguchi, J.; Nomura, M.; Takao, Y.; Fujioka, A.; Hashimoto, A.; Itou, K.; Yamamura, K.; Shuto, S.; Nagasawa, H.; Fukuoka, M., 1,2,3-Triazole-containing uracil derivatives with excellent pharmacokinetics as a novel class of potent human deoxyuridine triphosphatase inhibitors. *J. Med. Chem.* **2012,** *55* (14), 6427-37; (d) Ye, S.; Loll, B.; Berger, A. A.; Mulow, U.; Alings, C.; Wahl, M. C.; Koksch, B., Fluorine teams up with water to restore inhibitor activity to mutant BPTI. *Chem Sci* **2015,** *6* (9), 5246-5254; (e) Lee, A. L.; Ley, S. V., The synthesis of the anti-malarial natural product polysphorin and analogues using polymer-supported reagents and scavengers. *Org. Biomol. Chem.* **2003,** *1* (22), 3957-3966.

25. (a) Sekar, G.; Naidu, A.; Ganapathy, D., Copper(I)-Catalyzed Intramolecular Caryl-O Bond-Forming Cyclization for the Synthesis of 1,4-Benzodioxines and Its Application in the Total Synthesis of Sweetening Isovanillins. *Synthesis* **2010,** *2010* (20), 3509-3519; (b) Kang, Y. B.; Gade, L. H., Triflic acid catalyzed oxidative lactonization and diacetoxylation of alkenes using peroxyacids as oxidants. *J. Org. Chem.* **2012,** *77* (3), 1610-5.

26. (a) Reddi, R. N.; Prasad, P. K.; Sudalai, A., I2-catalyzed regioselective oxo- and hydroxy-acyloxylation of alkenes and enol ethers: a facile access to alpha-acyloxyketones, esters, and diol derivatives. *Org. Lett.* **2014,** *16* (21), 5674-7; (b) Xue, Q. C.; Xie, J.; Xu, P.; Hu, K. D.; Cheng, Y. X.; Zhu, C. J., Metal-Free, n-Bu4NI-Catalyzed Regioselective Difunctionalization of Unactivated Alkenes. *Acs Catal* **2013,** *3* (6), 1365-1368.

27. (a) Xia, X. F.; Zhu, S. L.; Gu, Z.; Wang, H.; Li, W.; Liu, X.; Liang, Y. M., Catalyst-controlled dioxygenation of olefins: an approach to peroxides, alcohols, and ketones. *J. Org. Chem.* **2015,** *80* (11), 5572-80; (b) Lu, Q.; Liu, Z.; Luo, Y.; Zhang, G.; Huang, Z.; Wang, H.; Liu, C.; Miller, J. T.; Lei, A., Copper-/Cobalt-Catalyzed Highly Selective Radical Dioxygenation of Alkenes. *Org. Lett.* **2015,** *17* (14), 3402-5; (c) Giglio, B. C.; Schmidt, V. A.; Alexanian, E. J., Metal-free, aerobic dioxygenation of alkenes using simple hydroxamic acid derivatives. *J. Am. Chem. Soc.* **2011,** *133* (34), 13320-2; (d) Schmidt, V. A.; Alexanian, E. J., Metal-free, aerobic dioxygenation of alkenes using hydroxamic acids. *Angew. Chem. Int. Ed. Engl.* **2010,** *49* (26), 4491-4.

28. Luo, C.; Bandar, J. S., Superbase-Catalyzed anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes. *J. Am. Chem. Soc.* **2018,** *140* (10), 3547-3550.

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)

Hayashi, S.-i.; Nakai, T.; Ishikawa, N., DEFLUORINATION REACTIONS OFgem-DIFLUORO- AND MONOFLUOROOLEFINS. NOVEL METHODS FOR ONE-CARBON HOMOLOGATIONS OF CARBONYL COMPOUNDS LEADING TO ALDEHYDES, CARBOXYLIC ACIDS, AND ESTERS. *Chem. Lett.* **1980,** *9* (6), 651-654.

30. (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015,** *58* (21), 8315-59; (b) Spahn, V.; Del Vecchio, G.; Labuz, D.; Rodriguez-Gaztelumendi, A.; Massaly, N.; Temp, J.; Durmaz, V.; Sabri, P.; Reidelbach, M.; Machelska, H.; Weber, M.; Stein, C., A nontoxic pain killer designed by modeling of pathological receptor conformations. *Science* **2017,** *355* (6328), 966-969.

31. (a) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Muller, K., Fluorination Patterning: A Study of Structural Motifs That Impact Physicochemical Properties of Relevance to Drug Discovery. *J. Med. Chem.* **2015,** *58* (22), 9041-60; (b) 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.

32. Bégué, J.-P.; Bonnet-Delpon, D., *Bioorganic and Medicinal Chemistry of Fluorine*. Wiley-VCH:Weinheim: 2008.

33. (a) Hunter, L., The C-F bond as a conformational tool in organic and biological chemistry. *Beilstein J Org Chem* **2010,** *6*, 38; (b) Thiehoff, C.; Rey, Y. P.; Gilmour, R., The Fluorine Gauche Effect: A Brief History. *Isr. J. Chem.* **2017,** *57* (1-2), 92-100.

34. (a) Xing, L.; Keefer, C.; Brown, M. E., Fluorine multipolar interaction: Toward elucidating its energetics in binding recognition. *J. Fluorine Chem.* **2017,** *198*, 47-53; (b) Muller, K.; Faeh, C.; Diederich, F., Fluorine in pharmaceuticals: looking beyond intuition. *Science* **2007,** *317* (5846), 1881-6; (c) Olsen, J. A.; Banner, D. W.; Seiler, P.; Obst Sander, U.; D'Arcy, A.; Stihle, M.; Muller, K.; Diederich, F., A fluorine scan of thrombin inhibitors to map the fluorophilicity/fluorophobicity of an enzyme active site: evidence for C-F...C=O interactions. *Angew. Chem. Int. Ed. Engl.* **2003,** *42* (22), 2507-11; (d) Paulini, R.; Muller, K.; Diederich, F., Orthogonal multipolar interactions in structural chemistry and biology. *Angew. Chem. Int. Ed. Engl.* **2005,** *44* (12), 1788-805.

35. (a) Martone, R. L.; Zhou, H.; Atchison, K.; Comery, T.; Xu, J. Z.; Huang, X.; Gong, X.; Jin, M.; Kreft, A.; Harrison, B.; Mayer, S. C.; Aschmies, S.; Gonzales, C.; Zaleska, M. M.; Riddell, D. R.; Wagner, E.; Lu, P.; Sun, S. C.; Sonnenberg-Reines, J.; Oganesian, A.; Adkins, K.; Leach, M. W.; Clarke, D. W.; Huryn, D.; Abou-Gharbia, M.; Magolda, R.; Bard, J.; Frick, G.; Raje, S.; Forlow, S. B.; Balliet, C.; Burczynski, M. E.; Reinhart, P. H.; Wan, H. I.; Pangalos, M. N.; Jacobsen, J. S., Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease. *J. Pharmacol. Exp. Ther.* **2009,** *331* (2), 598-608; (b) Mayer, S. C.; Kreft, A. F.; Harrison, B.; Abou-Gharbia, M.; Antane, M.; Aschmies, S.; Atchison, K.; Chlenov, M.; Cole, D. C.; Comery, T.; Diamantidis, G.; Ellingboe, J.; Fan,

K.; Galante, R.; Gonzales, C.; Ho, D. M.; Hoke, M. E.; Hu, Y.; Huryn, D.; Jain, U.; Jin, M.; Kremer, K.; Kubrak, D.; Lin, M.; Lu, P.; Magolda, R.; Martone, R.; Moore, W.; Oganesian, A.; Pangalos, M. N.; Porte, A.; Reinhart, P.; Resnick, L.; Riddell, D. R.; Sonnenberg-Reines, J.; Stock, J. R.; Sun, S. C.; Wagner, E.; Wang, T.; Woller, K.; Xu, Z.; Zaleska, M. M.; Zeldis, J.; Zhang, M.; Zhou, H.; Jacobsen, J. S., Discovery of begacestat, a Notch-1-sparing gamma-secretase inhibitor for the treatment of Alzheimer's disease. *J. Med. Chem.* **2008,** *51* (23), 7348-51.

36. (a) Wang, Y. H.; Goldsmith, Z. K.; Schneider, P. E.; Anson, C. W.; Gerken, J. B.; Ghosh, S.; Hammes-Schiffer, S.; Stahl, S. S., Kinetic and Mechanistic Characterization of Low-Overpotential, H2O2-Selective Reduction of O2 Catalyzed by N2O2-Ligated Cobalt Complexes. *J. Am. Chem. Soc.* **2018,** *140* (34), 10890-10899; (b) Ma, X.; Herzon, S. B., Synthesis of Ketones and Esters from Heteroatom-Functionalized Alkenes by Cobalt-Mediated Hydrogen Atom Transfer. *J. Org. Chem.* **2016,** *81* (19), 8673-8695.

37. (a) Zhang, H.; Guo, L. H.; Wang, D.; Zhao, L.; Wan, B., Light-induced efficient molecular oxygen activation on a Cu(II)-grafted TiO2/graphene photocatalyst for phenol degradation. *ACS Appl Mater Interfaces* **2015,** *7* (3), 1816-23; (b) Zabik, N. L.; Anwar, S.; Ziu, I.; Martic-Milne, S., Electrochemical reactivity of bulky-phenols with superoxide anion radical. *Electrochim. Acta* **2019,** *296*, 174-180; (c) Rene, A.; Abasq, M. L.; Hauchard, D.; Hapiot, P., How do phenolic compounds react toward superoxide ion? A simple electrochemical method for evaluating antioxidant capacity. *Anal. Chem.* **2010,** *82* (20), 8703-10; (d) Peng, Z.; Chen, Y.; Bruce, P. G.; Xu, Y., Direct Detection of the Superoxide Anion as a Stable Intermediate in the Electroreduction of Oxygen in a Non-Aqueous

Electrolyte Containing Phenol as a Proton Source. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (28), 8165-8; (e) Ma, D.; Zhong, J.; Li, J.; Burda, C.; Duan, R., Preparation and photocatalytic performance of MWCNTs/BiOCl: Evidence for the superoxide radical participation in the degradation mechanism of phenol. *Appl. Surf. Sci.* **2019,** *480*, 395-403; (f) Chen, Y.; Zhang, X.; Feng, S., Contribution of the Excited Triplet State of Humic Acid and Superoxide Radical Anion to Generation and Elimination of Phenoxyl Radical. *Environmental Science & Technology* **2018,** *52* (15), 8283-8291; (g) Aboul-Enein, H. Y.; Kruk, I.; Kladna, A.; Lichszteld, K.; Michalska, T., Scavenging effects of phenolic compounds on reactive oxygen species. *Biopolymers* **2007,** *86* (3), 222-30.

38. (a) Suda, M., Radical addition reactions on 1,1-difluoro-1-olefins. *Tetrahedron Lett.* **1981,** *22* (25), 2395-2396; (b) Frost, A. B.; Brambilla, M.; Exner, R. M.; Tredwell, M., Synthesis and Derivatization of 1,1-[(18) F]Difluorinated Alkenes. *Angew. Chem. Int. Ed. Engl.* **2019,** *58* (2), 472-476; (c) Chen, L. S., Free-radical initiated addition of carbon tetrachloride to fluoro olefins. *J. Fluorine Chem.* **1990,** *47* (2), 261-272; (d) Hu, J.; Yang, Y.; Lou, Z.; Ni, C.; Hu, J., Fluoro-Hydroxylation of gem-Difluoroalkenes: Synthesis of 18 O-labeled α-CF3 Alcohols. *Chin. J. Chem .* **2018,** *36* (12), 1202-1208.

39. (a) Melone, L.; Franchi, P.; Lucarini, M.; Punta, C., Sunlight Induced Oxidative Photoactivation ofN-Hydroxyphthalimide Mediated by Naphthalene Imides. *Adv. Synth. Catal.* **2013,** *355* (16), 3210-3220; (b) Tokuyasu, T.; Kunikawa, S.; McCullough, K. J.; Masuyama, A.; Nojima, M., Synthesis of cyclic peroxides by chemo- and regioselective peroxidation of dienes with Co(II)/O2/Et3SiH. *J. Org. Chem.* **2005,** *70* (1), 251-60; (c) Toribio, P. P.; Gimeno-Gargallo, A.; Capel-Sanchez, M. C.; de Frutos, M. P.; Campos-

Martin, J. M.; Fierro, J. L. G., Ethylbenzene oxidation to its hydroperoxide in the presence of N-hydroxyimides and minute amounts of sodium hydroxide. *Applied Catalysis A: General* **2009,** *363* (1-2), 32-39; (d) Dobras, G.; Orlińska, B., Aerobic oxidation of alkylaromatic hydrocarbons to hydroperoxides catalysed by N -hydroxyimides in ionic liquids as solvents. *Applied Catalysis A: General* **2018,** *561*, 59-67.

40. (a) Santamaria, J.; Jroundi, R.; Rigaudy, J., Electron transfer activation. Hydroperoxide intermediates in a novel and selective procedure for benzylic oxidations. *Tetrahedron Lett.* **1989,** *30* (35), 4677-4680; (b) Wang, H.; Chen, C.; Liu, W.; Zhu, Z., Difunctionalization of alkenes with iodine and tert-butyl hydroperoxide (TBHP) at room temperature for the synthesis of 1-(tert-butylperoxy)-2-iodoethanes. *Beilstein J Org Chem* **2017,** *13*, 2023-2027; (c) Liu, W.; Li, Y.; Liu, K.; Li, Z., Iron-catalyzed carbonylation-peroxidation of alkenes with aldehydes and hydroperoxides. *J. Am. Chem. Soc.* **2011,** *133* (28), 10756-9; (d) Schweitzer-Chaput, B.; Demaerel, J.; Engler, H.; Klussmann, M., Acid-catalyzed oxidative radical addition of ketones to olefins. *Angew. Chem. Int. Ed. Engl.* **2014,** *53* (33), 8737-40; (e) Cheng, J. K.; Loh, T. P., Copper- and cobalt-catalyzed direct coupling of sp(3) alpha-carbon of alcohols with alkenes and hydroperoxides. *J. Am. Chem. Soc.* **2015,** *137* (1), 42-5.

41. Sokolova, R.; Tarabek, J.; Papouskova, B.; Kocabova, J.; Fiedler, J.; Vacek, J.; Marhol, P.; Vavrikova, E.; Kren, V., Oxidation of the Flavonolignan Silybin. In situ EPR Evidence of the Spin-Trapped Silybin Radical. *Electrochim. Acta* **2016,** *205*, 118-123.

42. Pietrzyk, P.; Srebro, M.; Radon, M.; Sojka, Z.; Michalak, A., Spin ground state and magnetic properties of cobalt(II): relativistic DFT calculations guided by EPR measurements of bis(2,4-acetylacetonate)cobalt(II)-based complexes. *J. Phys. Chem. A* **2011,** *115* (11), 2316-24.

43. (a) Kuppusamy, R.; Muralirajan, K.; Cheng, C.-H., Cobalt(III)-Catalyzed [5 + 1] Annulation for 2H-Chromenes Synthesis via Vinylic C–H Activation and Intramolecular Nucleophilic Addition. *Acs Catal* **2016,** *6* (6), 3909-3913; (b) Vinck, E.; Murphy, D. M.; Fallis, I. A.; Strevens, R. R.; Van Doorslaer, S., Formation of a cobalt(III)-phenoxyl radical complex by acetic acid promoted aerobic oxidation of a Co(II)salen complex. *Inorg. Chem.* **2010,** *49* (5), 2083-92.

44. Teixeira, M. C.; Telo, J. P.; Duarte, N. F.; Sa-Correia, I., The herbicide 2,4-dichlorophenoxyacetic acid induces the generation of free-radicals and associated oxidative stress responses in yeast. *Biochem. Biophys. Res. Commun.* **2004,** *324* (3), 1101-7.

45. Stoll, S.; Schweiger, A., EasySpin, a comprehensive software package for spectral simulation and analysis in EPR. *J Magn Reson* **2006,** *178* (1), 42-55.

Chapter 4 Appendix

Experimental Procedures and Spectra for Compounds in Chapter 4

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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 α,α,α–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.

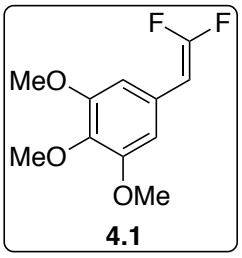
Unless otherwise noted, reagents were purchased from commercial sources and used as received. Cobalt(II) 2,4-pentanedionate [$Co(acac)_2$] was purchased from Alfa Aesar. 1,2–Dichlorobenzene (DCB, anhydrous, 99+%) and *N*-methylpyrrolidine (NMP, anhydrous) were purchased from Sigma Aldrich. Solvents, 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: α,α,α-trifluorotoluene (TFT), sodium sulfate (Na_2SO_4), magnesium sulfate ($MgSO_4$), ethyl acetate (EtOAc), diethyl ether (Et_2O), ammonium chloride (NH_4Cl), ^{n}butyl lithium (^{n}BuLi), sodium hydroxide (NaOH), room temperature (R.T.), ^{t}butyl carbonate anhydride (Boc_2O), potassium carbonate (K_2CO_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 (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 ($CHCl_3$: 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 ($CDCl_3$: δ = 77.2 ppm; DMSO: δ = 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, d = 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

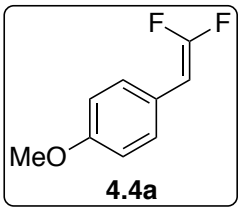
ionization (ESI) on a Waters LCT Premier^{TM} mass spectrometer or by atmospheric-pressure chemical ionization (APCI-hexane/PhMe) on a Waters Q-Tof Premier^{TM}, for which sample plus near mass internal exact mass standard were dissolved in hexane, and hexane or PhMe/hexane were used as ionization solvent. 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



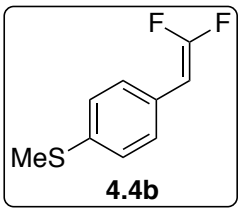
4.1

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.



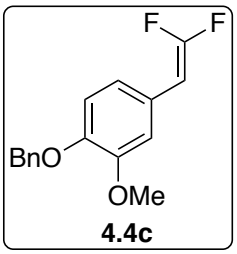
4.4a

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.



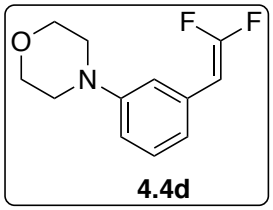
4.4b

(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.



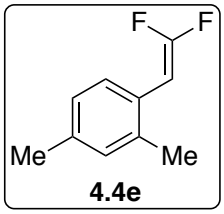
4.4c

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.



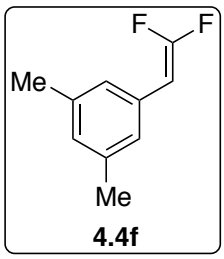
4.4d

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.



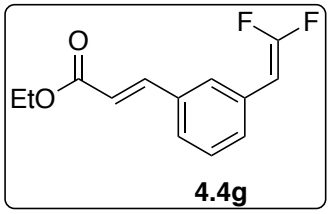
4.4e

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.



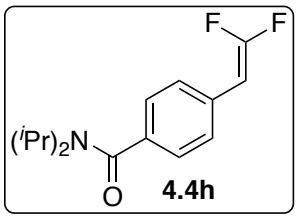
4.4f

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.



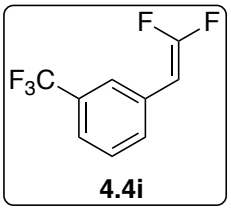
4.4g

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.



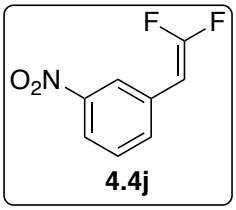
4.4h

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.



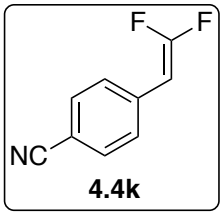
4.4i

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.



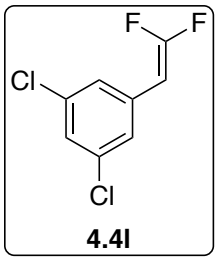
4.4j

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.



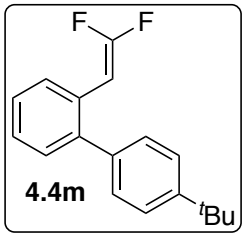
4.4k

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.



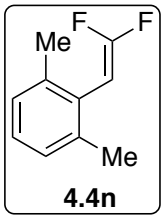
4.4l

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.



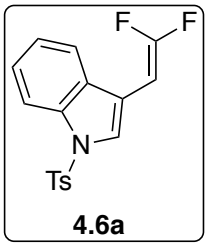
4.4m

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.



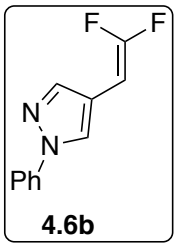
4.4n

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.



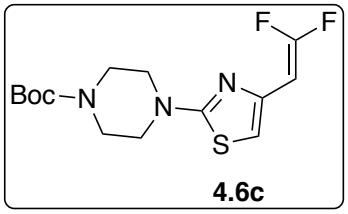
4.6a

3-(2,2-difluorovinyl)-1-tosyl-1*H*-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.



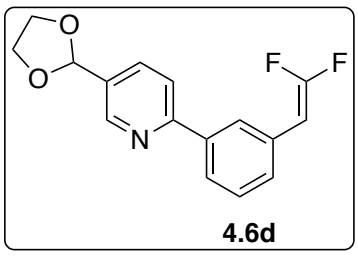
4.6b

4-(2,2-difluorovinyl)-1-phenyl-1*H*-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.



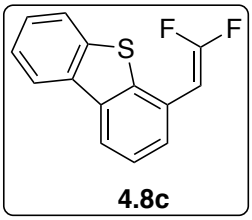
4.6c

***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.



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.



4.8c

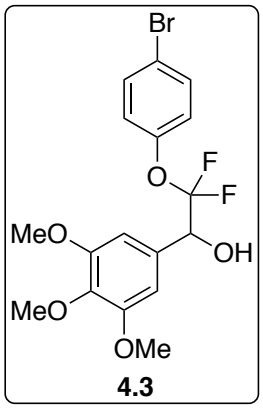
4-(2,2-difluorovinyl)dibenzo[*b*,*d*]thiophene (4.6e): Compound **4.6e** corresponds to compound **2.7d** in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.

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 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.

Preparation and Characterization of Compounds in Table 4-1



4.3

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 °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 **4.3** as a yellow solid (MP = 93–95 °C).

^{1}H NMR (400 MHz, $CDCl_3$): 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)

^{13}C NMR (126 MHz, $CDCl_3$): 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

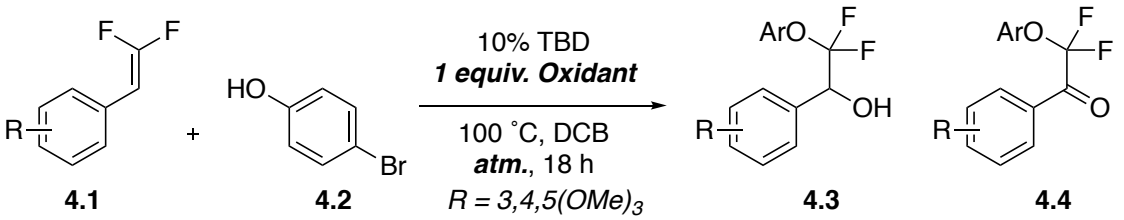
^{19}F NMR (376 MHz, $CDCl_3$): δ –81.65 (dd, *J* = 141.05, 6.98 Hz, 1 F), –82.16 (dd, *J* = 140.99, 7.23 Hz, 1 F)

IR (film): 3450, 2939, 1595, 1508, 1485, 1464, 1422, 1326, 1253, 1129, 1068, 1011, 829, 750, 710 cm^{-1}

HRMS (ESI+): calc. for $C_{17}H_{17}BrF_2O_5$ (M+) 418.0227, found 418.0212, 3.6 ppm.

Optimization of Reaction Conditions:

Table SI-4-1: Reactions with Oxidants:



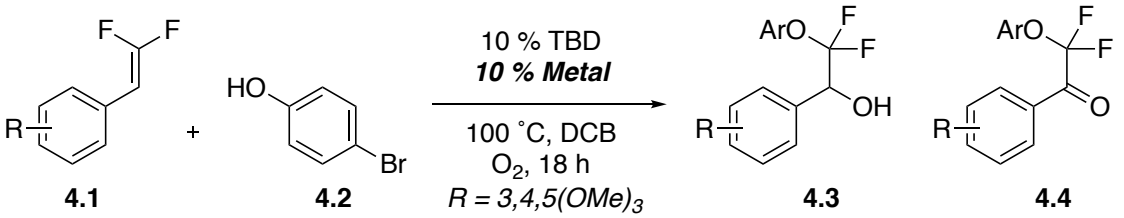
4.1 **4.2** **4.3** **4.4**

Oxidant	Atmosphere	**4.1**	**4.3**	**4.4**
MnO_2	O_2	0	0	0
$K_2S_2O_8$	O_2	15	23	15
$KMnO_4$	O_2	38	13	9
Oxone	O_2	48	5	1
DMP	O_2	16	14	9
NMO	O_2	53	3	7
IBX	O_2	27	35	15
$K_2S_2O_8$	air	21	8	0
$KMnO_4$	air	46	0	0
mCPBA	air	23	0	0
IBX	air	61	0	0
H_2O_2 (30 %)	air	40	11	6
^{t}BuOOH	air	34	0	0
Iodopentoxide	air	trace	trace	trace
Cumene Hydroperoxide	air	28	3	1
$(^t\text{BuO})_2$	air	40	trace	1.5
H_2O_2-Urea	air	39	6	6
Oxone	air	37	0	0
DMP*	air	36	0	0
NMO	air	67	0	0

* = Reacted on addition at room temperature

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:

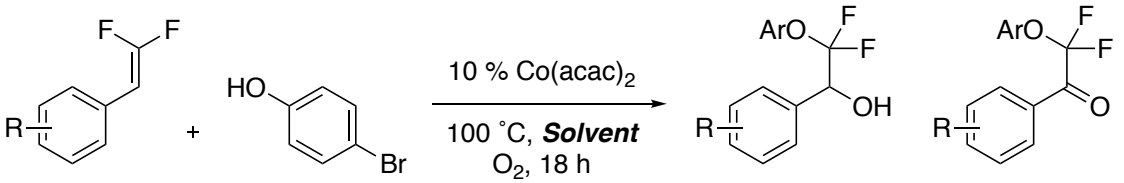


4.1 **4.2** **4.3** **4.4**

Metal	**4.1**	**4.3**	**4.4**
$Pd(OAc)_2$	5	38	26
$Pd_2(dba)_3$	5	47	17
$FeCl_3$	4	38	23
$Fe(OAc)_2$	5	41	35
CuCl	4	24	23
$Cu(OAc)_2$	0	30	33
$AuCl_3$	0	0	0
Ag_2CO_3	10	43	24
$AgNO_3$	5	32	27
$[Ir(cod)Cl]_2$	26	30	22
$RhCl_3–H_2O$	6	46	29
$Co(acac)_2$	6	74	13

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:



4.1 **4.2** **4.3** **4.4**

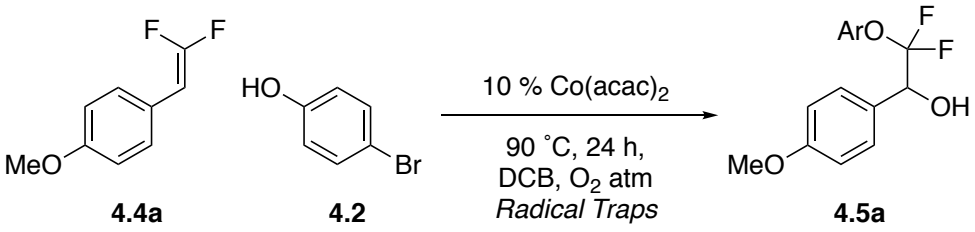
Solvent	**4.1**	**4.3**	**4.4**
DCB	7	63	5
H_2O	35	32	1
IPA	64	7	0.5
1,4-Dioxane	61	5	0
MeCN	45	20	2
DMF	55	15	5
PhMe	28	55	2
DMSO	49	9	5

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.

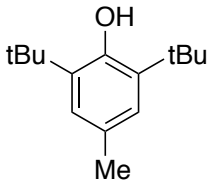
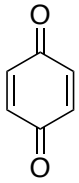
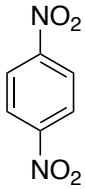
Experimental Procedures for Mechanistic Determination:

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:



4.4a **4.2** **4.5a**

Radical Trap	*Conv.*	***4.5a***	***4.6a***
	68 %	0 %	0 %
	100 %	0 %	0 %
	92 %	54 %	5.5 %

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

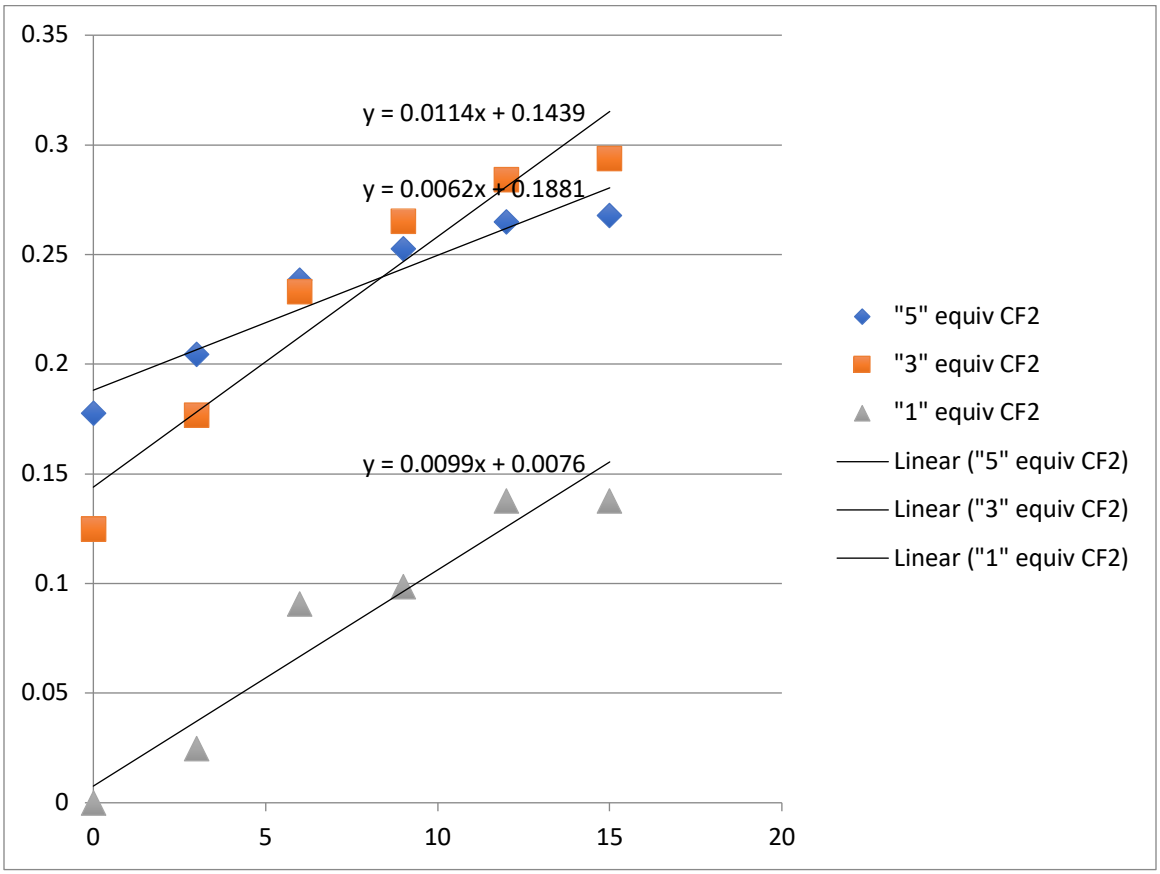


Figure SI-4-2: Phenol Kinetics:

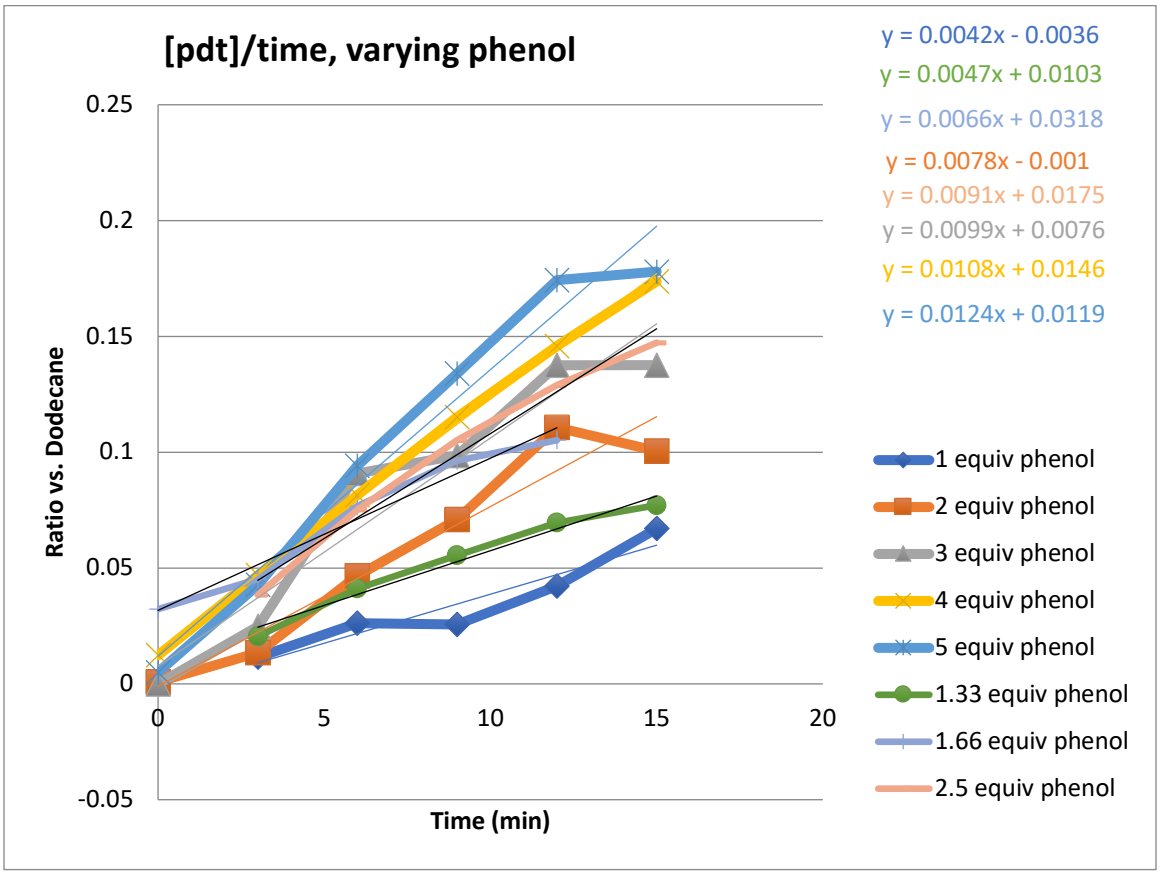
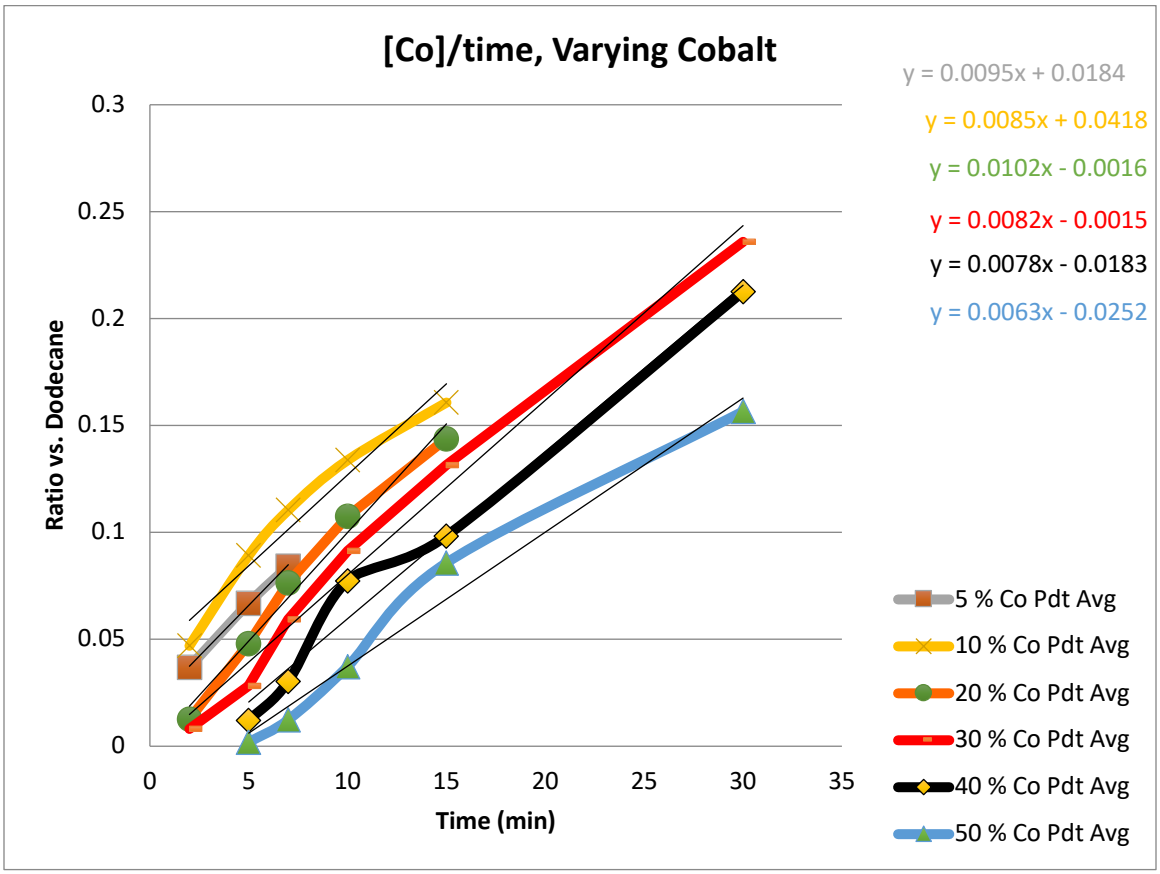


Figure SI-4-3: Cobalt Kinetics



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

(1.0 mL) 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.

Reacting $Co(acac)_2$ and 4.4a under O_2: Following General Procedure A, in an oven-dried one dram vial compound **4.4a** (0.043 g, 0.25 mmol) was reacted with $Co(acac)_2$ (0.064 g, 0.25 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.

Reacting $Co(acac)_2$ and 4-bromophenol under O_2: Following General Procedure A, in an oven-dried one dram vial of 4-bromophenol (0.13 g, 0.75 mmol) was reacted with $Co(acac)_2$ (0.064 g, 0.25 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.

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:

Table S1-4-6: EPR Parameters of Spectral Types Observed, 10 K

Spectrum ID	g-values	Line Width	Experiments
A	7, 2.5, 2.5	75	Co(II) and Ar C(II) and **4.4a** and Ar
B	5, 3, 2	150	Co(II) and O_2 C(II) and **4.4a** and O_2

C	5.8, 3.8, 2.5	50	Co(II), **4.2**, and Ar Co(II), **4.2**, **4.4a**, and Ar
D	4.5, 2	75	Co(II), **4.2**, and O_2 Co(II), **4.2**, **4.4a**, and O_2

Table SI-4-7: Summary of EPR Parameters for Full Dipolar Zero-Field-Splitting Hamiltonian

	Spectrum A/B	Spectrum C/D
S	3/2	3/2
G	2.2	2.2
Nucleus	Co	Co
A (MHz)	0	0
Line Width	100	100
D (MHz)	500,000	500,000
E (MHz)	166,667	0

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 O_2, 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 N_2. 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 O_2, 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 °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 13). Then Ar was exchanged for O_2, 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 14). 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 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

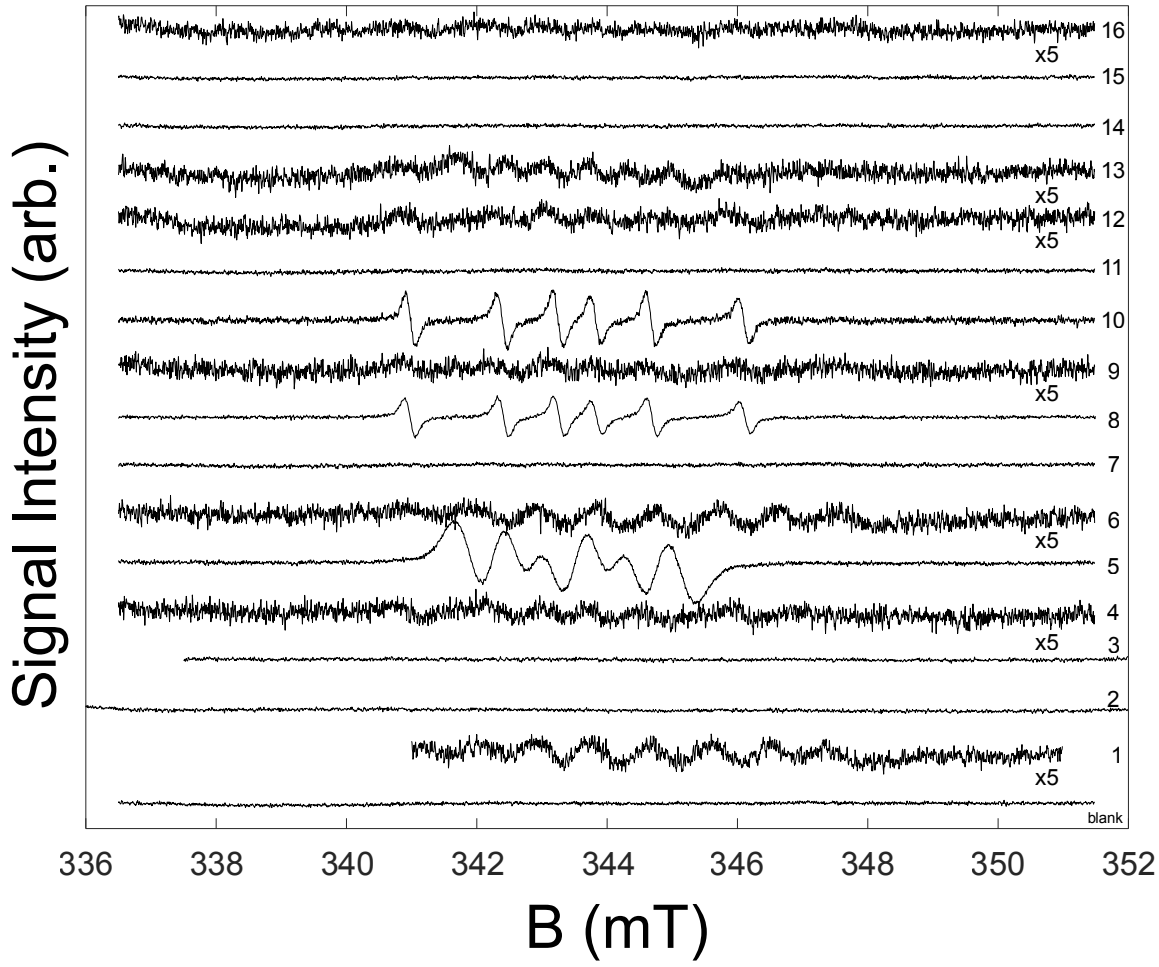
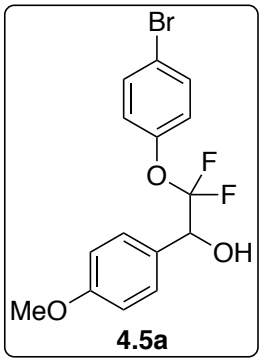


Table SI-4-8: Spectral Simulation Parameters for Spectrum 5			
Center Field (mT)	344		
Sweep Width (mT)	15		
Microwave Frequenct (GHz)	9.6426		
G	2.0055		

A (MHz)	1 – ^{14}N	35.3525 (1.2615 mT)	N = 1
	2 – ^{1}H	20.0400 (0.6161 mT)	N = 1
lwpp (mT)	0.45		

Table SI-4-9: Spectral Simulation Parameters for Spectrum 8			
Center Field (mT)	344		
Sweep Width (mT)	15		
Microwave Frequency (GHz)	9.6433		
G	2.0055		
A (MHz)	1 –	39.2349 (1.40 mT)	N = 1
	2 – ^{1}H	64.4574 (2.30 mT)	N = 1
lwpp (mT)	0.45		

Experimental Procedures and Characterization of Compounds in Scheme 4-4:



4.5a

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).

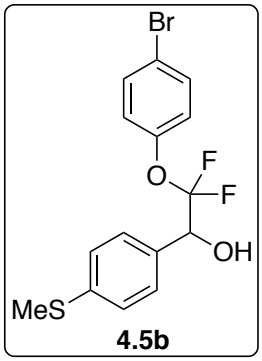
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.64 Hz, 2 H), 7.44–7.41 (m, 2 H), 7.01 (d, *J* = 8.91 Hz, 2 H), 6.96–6.92 (m, 2H), 5.04 (td, *J* = 7.18, 4.29 Hz, 1 H), 3.83 (s, 3 H), 2.57 (d, *J* = 4.27 Hz, 1 H)

^{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, 1305, 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 $C_{15}H_{13}BrF_2O_3Cl$ (M+Cl) 392.9705, found 392.9709, 1.0 ppm.



4.5b

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)

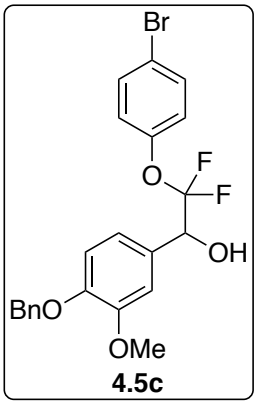
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (t, *J* = 8.70 Hz, 4 H), 7.28 (d, *J* = 8.49 Hz, 2 H), 7.01 (d, *J* = 8.40 Hz, 2 H), 5.04 (t, *J* = 7.06 Hz, 1 H), 2.83 (bs, 1 H), 2.50 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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

^{19}F NMR (376 MHz, $CDCl_3$): δ –82.27 (dd, *J* = 19.13, 7.12 Hz, 2 F)

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^{-1}

HRMS (ESI–): calc. for $C_{15}H_{13}BrF_2O_2SCl$ (M+Cl) 408.9476, found 408.9482, 1.5 ppm.



4.5c

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 **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 $Co(acac)_2$ 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 **4.5c** as a light orange solid (MP = 87–88 °C)

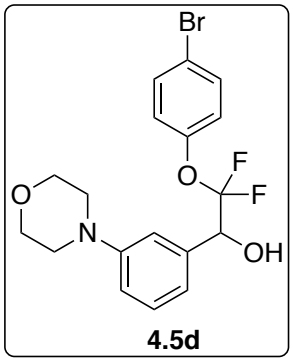
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (td, *J* = 7.21, 6.81, 1.94 Hz, 4 H), 7.41–7.34 (m, 2 H), 7.34–7.28 (m, 1 H), 7.11 (d, *J* = 1.93 Hz, 1 H), 7.06–6.96 (m, 3 H), 6.89 (d, *J* = 8.29 Hz, 1 H), 5.17 (s, 2 H), 5.00 (t, *J* = 7.12 Hz, 1 H), 3.90 (s, 3H), 2.83 (bs, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{22}H_{19}BrF_2O_4K$ (M+K) 503.0072, found 503.0078, 1.2 ppm.



4.5d

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

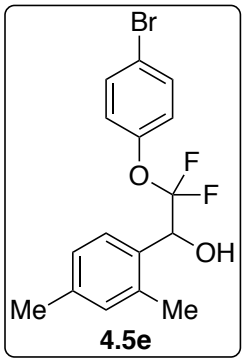
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.86 Hz, 2 H), 7.31 (t, *J* = 7.92 Hz, 1 H), 7.10 (t, *J* = 2.00 Hz, 1 H), 7.04 (d, *J* = 7.93 Hz, 1 H), 7.01 (d, *J* = 8.62 Hz, 2 H), 6.94 (ddd, *J* = 8.26, 2.55, 0.96, 1 H), 5.04 (t, *J* = 7.24 Hz, 1 H), 3.88–3.85 (m, 4 H), 3.20–3.17 (m, 4 H), 2.72 (d, *J* = 3.57 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{18}H_{19}BrF_2NO_3$ (M+H) 414.0516, found 414.0521, 1.2 ppm.



4.5e

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

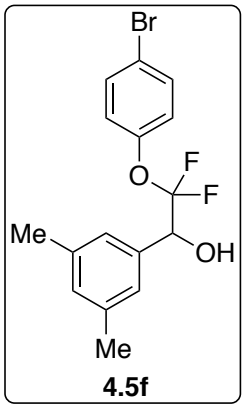
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.96 Hz, 1 H), 7.43 (d, *J* = 8.90 Hz, 2 H), 7.11 (d, *J* = 8.24 Hz, 1 H), 7.04 (d, *J* = 2.23 Hz, 2 H), 7.02 (s, 1 H), 5.35 (td, *J* = 7.18, 3.79 Hz, 1 H), 2.85 (d, *J* = 4.35 Hz, 1 H), 2.40 (s, 3 H), 2.35 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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}F NMR (376 MHz, $CDCl_3$): 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 $C_{16}H_{15}BrF_2O_2Cl$ (M+Cl) 390.9912, found 390.9920, 2.0 ppm.



4.5f

2-(4-bromophenoxy)-1-(3,5-dimethylphenyl)-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)

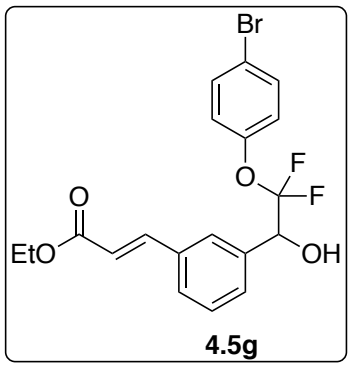
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.88 Hz, 2 H), 7.16 (bs, 2 H), 7.04 (bs, 2 H), 7.02 (bs, 1 H), 5.00 (t, *J* = 7.25 Hz, 1 H), 2.74 (bs, 1 H), 2.36 (s, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{16}H_{15}BrF_2O_2Cl$ (M+Cl) 390.9912, found 390.9921, 2.3 ppm.



4.5g

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_2CO_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

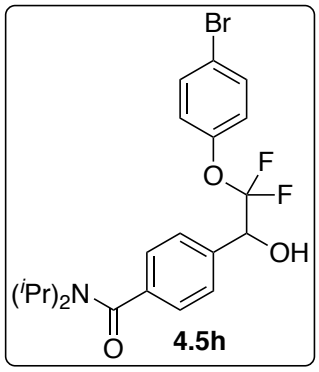
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 16.16 Hz, 2 H), 7.56 (d, *J* = 7.42 Hz, 1 H), 7.52 (dt, *J* = 7.88, 1.47 Hz, 1 H), 7.42–7.38 (m, 3 H), 6.98 (m, 2 H), 6.45 (d, *J* = 16.02 Hz, 1 H), 5.10 (t *J* = 7.05 Hz, 1 H), 4.25 (q, *J* = 7.11 Hz, 2 H), 3.53 (bs, 1 H), 1.32 (t, *J* = 7.13 Hz, 3 H)

^{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, $CDCl_3$): δ –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 $C_{19}H_{17}BrF_2O_4Cl$ (M+Cl) 460.9967, found 460.9999, 6.9 ppm.



4.5h

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)

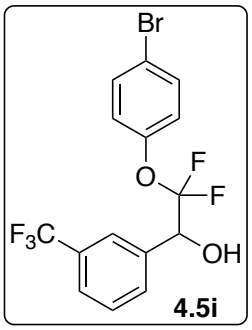
^{1}H NMR (500 MHz, DMSO-D_6, 60 °C): δ 7.57 (dd, *J* = 8.45, 3.06 Hz, 4 H), 7.29 (d, *J* = 7.74 Hz, 2 H), 7.08 (d, *J* = 8.34 Hz, 2 H), 6.51 (d, *J* = 5.64 Hz, 1 H), 5.10 (q, *J* = 7.08 Hz, 1 H), 3.66–3.63 (m, 2 H), 1.28 (bs, 12 H)

^{13}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

^{19}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 $C_{21}H_{24}BrF_2NO_3Na$ (M+Na) 478.0805, found 478.0813, 1.7 ppm.



4.5i

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

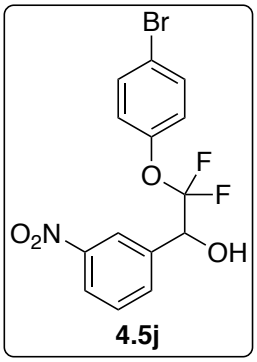
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 7.45 – 7.37 (m, 2 H), 7.06 – 6.91 (m, 2 H), 5.15 (td, *J* = 7.0, 3.6 Hz, 1 H), 2.81 (d, *J* = 4.0 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{15}H_{10}BrF_5O_2Cl$ (M+Cl) 430.9478, found 430.9504, 2.6 ppm.



4.5j

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.

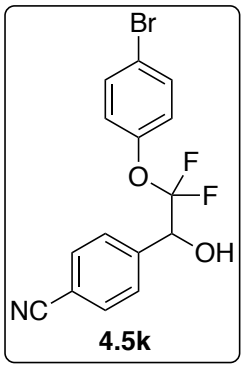
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (t, *J* = 1.89 Hz, 1 H), 8.27 (ddd, *J* = 6.22, 2.30, 1.09 Hz, 1 H), 7.91 (d, *J* = 7.82 Hz, 1 H), 7.61 (t, *J* = 7.99 Hz, 1 H), 7.45 (d, *J* = 8.88 Hz, 2 H), 7.00 (d, *J* = 9.03 Hz, 2 H), 5.23 (td, *J* = 6.90, 3.91 Hz, 1 H), 2.91 (d, *J* = 3.95 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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, $CDCl_3$): δ –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 $C_{14}H_{10}BrF_2NO_4Cl$ (M+Cl) 407.9450, found 407.9453, 0.7 ppm.



4.5k

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_2CO_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).

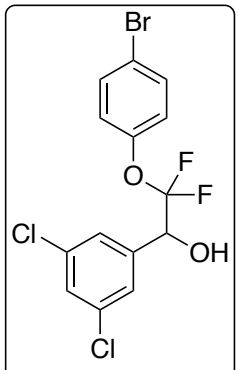
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.57 (m, 4 H), 7.41 – 7.32 (m, 2 H), 6.91 (d, *J* = 9.0 Hz, 1 H), 5.10 (td, *J* = 6.9, 3.5 Hz, 2 H), 2.91 (d, *J* = 4.0 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{15}H_{10}BrF_2NO_2Cl$ (M+Cl) 387.9557, found 387.9583, 2.6 ppm.



4.5l

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.

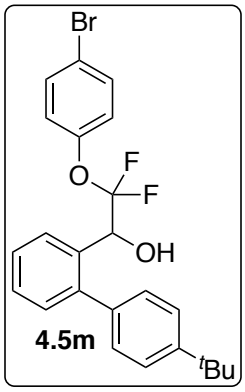
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 5.4, 3.5 Hz, 4 H), 7.42 (t, *J* = 1.9 Hz, 1 H), 7.12 – 6.96 (m, 2 H), 5.07 (td, *J* = 6.8, 3.7 Hz, 1 H), 2.85 (d, *J* = 4.0 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{14}H_9BrCl_3F_2O_2$ (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.

^{1}H NMR (400 MHz, $CDCl_3$): 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)

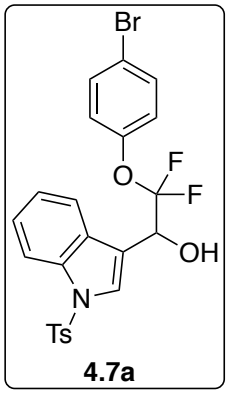
^{13}C NMR (126 MHz, $CDCl_3$): δ 150.7, 149.1, 141.3, 137.9, 135.8, 132.5, 128.8, 127.8, 126.9, 126.5, 126.4, 125.9, 123.6, 122.5 (t, *J* = 272.36 Hz), 119.0, 74.5 (t, *J* = 31.35 Hz), 34.7, 31.5

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{24}H_{24}BrF_2O_2$ (M+H) 461.0928, found 461.1971, 2.0 ppm.

Experimental Procedures and Characterization of Compounds in Scheme 4-5:



4.7a

2-(4-bromophenoxy)-2,2-difluoro-1-(1-tosyl-1*H*-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 $Co(acac)_2$ 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).

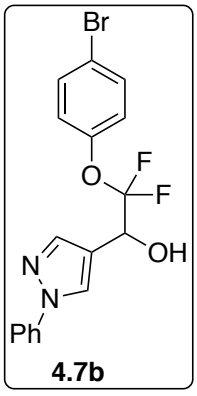
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dt, *J* = 8.49, 0.88 Hz), 1 H), 7.77 (d, *J* = 8.53 Hz, 3 H), 7.73 (d, *J* = 7.75 Hz, 1 H), 7.45–7.41 (m, 2 H), 7.34 (ddd, *J* = 8.38, 7.16, 1.28 Hz, 1 H), 7.28–7.24 (m, 1 H), 7.21 (d, *J* = 7.65 Hz, 2 H), 6.98 (dd, *J* = 8.76, 1.07 Hz, 2 H), 5.35 (td, *J* = 6.73, 4.53 Hz, 1 H), 2.68 (d, *J* = 4.95 Hz, 1 H), 2.34 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{23}H_{18}F_2NO_4S$ (M–) 520.0030, found 520.0041, 2.1 ppm.



4.7b

2-(4-bromophenoxy)-2,2-difluoro-1-(1-phenyl-1*H*-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)

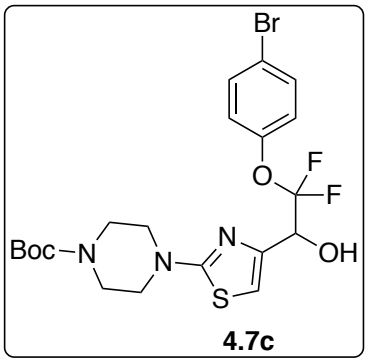
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1 H), 7.82 (s, 1 H), 7.65 (d, *J* = 7.51 Hz, 2 H), 7.43 (dd, *J* = 8.90, 7.22 Hz, 4 H), 7.29 (t, *J* = 7.45 Hz, 1 H), 7.04 (d, *J* = 8.57 Hz, 2 H), 5.16 (td, *J* = 6.91, 3.91 Hz, 1 H), 3.59 (d, *J* = 5.46 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{14}BrF_2N_2O_2$ (M+H) 395.0207, found 395.0220, 3.3 ppm.



4.7c

***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_2CO_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).

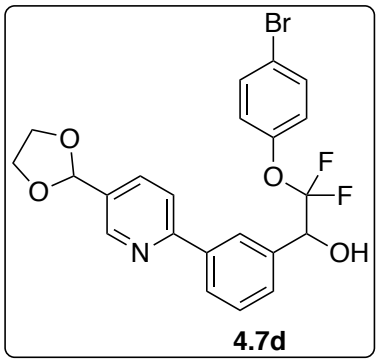
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.69 Hz, 2 H), 7.23 (d, *J* = 0.68 Hz, 1 H), 7.06 (d, *J* = 8.62 Hz, 2 H), 5.19 (t, *J* = 6.29 Hz, 1 H), 3.54 (dd, *J* = 6.43, 3.50 Hz, 4 H), 3.47 (td, *J* = 5.10, 1.76 Hz, 4 H), 1.47 (s, 9 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{20}H_{25}BrF_2N_3O_4S$ (M+H) 520.0717, found 520.0735, 3.5 ppm.



4.7d

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).

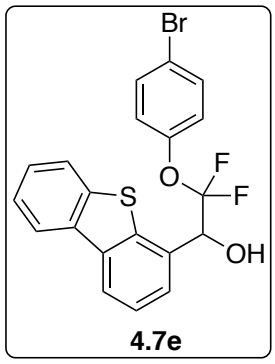
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 2.14 Hz,1 H), 8.09 (t, *J* = 1.72 Hz, 1 H), 7.92 (dt, *J* = 7.85, 1.47 Hz, 1 H), 7.86 (dd, *J* = 8.19, 2.21 Hz, 1 H), 7.72 (dd, *J* = 8.05, 0.85 Hz, 1 H), 7.59 (d, *J* = 7.70 Hz, 1 H), 7.46 (t, *J* = 7.74 Hz, 1 H), 7.39 (d, *J* = 8.69 Hz, 2 H), 6.98 (d, *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, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{22}H_{19}BrF_2NO_4$ (M+H) 478.0466, found 478.0448, 3.8 ppm.



4.7e

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)

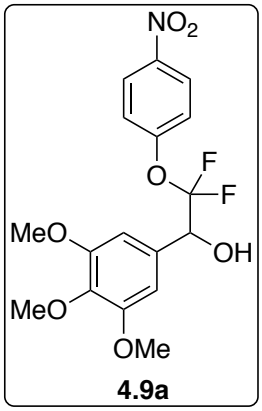
^{13}C NMR (126 MHz, $CDCl_3$): δ 149.0 (d, *J* = 3.01 Hz), 139.5, 139.2, 136.4, 135.3, 132.5, 129.9, 127.1, 126.2, 124.7, 124.6, 123.4, 122.7, 122.3, 121.7, 118.9, 73.7 (t, *J* = 32.23 Hz)

^{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 $C_{20}H_{13}BrF_2O_2SCl$ (M+Cl) 468.9476, found 468.9471, 1.1 ppm.

Experimental Procedures and Characterization of Compounds in Scheme 4-6:



4.9a

2,2-difluoro-2-(4-nitrophenoxy)-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).

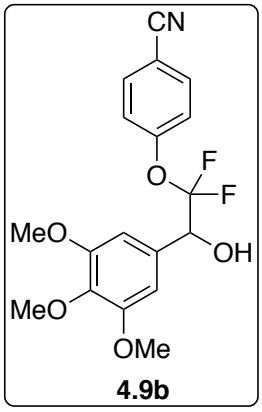
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 9.19 Hz, 2 H), 7.30 (d, *J* = 9.27 Hz, 2 H), 6.77 (s, 2 H), 5.07 (td, *J* = 7.19, 4.02 Hz, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 2.73 (d, *J* = 4.03 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.0 (d, *J* = 1.57 Hz), 153.4, 145.2, 138.9 (d, *J* = 1.59 Hz), 130.3, 125.5, 122.6 (t, *J* = 275.02 Hz), 121.5 (d, *J* = 1.64 Hz), 105.0, 74.4 (t, *J* = 31.34 Hz), 61.0, 56.4

^{19}F NMR (376 MHz, $CDCl_3$): δ –82.02 (dd, *J* = 139.86, 7.08 Hz, 1 F), –82.44 (dd, *J* = 139.86, 7.43 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 $C_{17}H_{17}F_2NO_7Na$ (M+Na) 408.0871, found 408.0874, 0.7 ppm.



4.9b

4-(1,1-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_2CO_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).

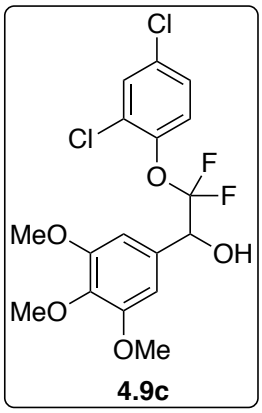
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.77 Hz, 2 H), 7.26 (d, *J* = 8.80 Hz, 2 H), 6.77 (s, 2 H), 5.06 (td, *J* = 7.22, 4.04 Hz, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 2.67 (d, *J* = 4.05 Hz)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{18}H_{18}BrF_2NO_3K$ (M+K) 404.0712, found 404.0717, 1.2 ppm.



4.9c

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.

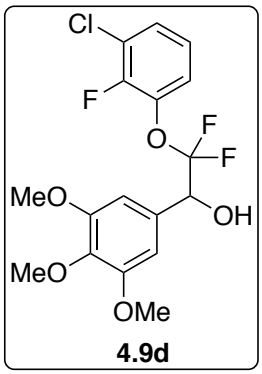
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 2.43 Hz, 1 H), 7.28–7.25 (m ,1 H), 7.21 (dd, *J* = 8.81, 2.42 Hz, 1 H), 6.79 (s, 2 H), 5.09 (t, *J* = 7.27 Hz, 1 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.89 (bs, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{16}Cl_2F_2O_5K$ (M+K) 446.9980, found 446.9998, 4.0 ppm.



4.9d

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).

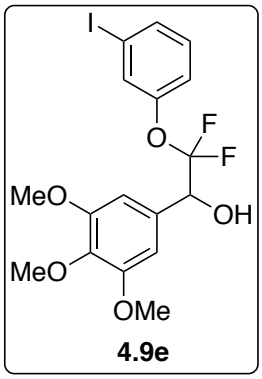
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (ddd, *J* = 8.08, 6.36, 1.61 Hz, 1 H), 7.18 (ddd, *J* = 8.52, 6.62, 1.30 Hz, 1 H), 7.01 (td, *J* = 8.26, 1.86 Hz, 1 H), 6.77 (s, 2 H), 5.07 (t, *J* = 7.23 Hz, 1 H), 3.85 (s, 6 H), 3.84 (s, 3 H), 3.42 (bs, 1 H)

^{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 $C_{17}H_{17}ClF_3O_5$ (M+H) 393.0717, found 393.0734, 1.7 mmu.



4.9e

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).

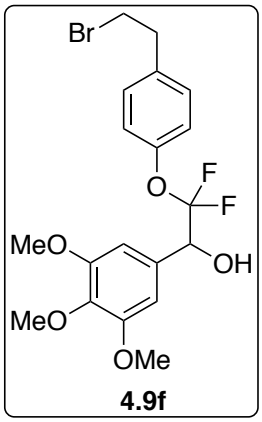
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dt, *J* = 7.82, 1.28 Hz, 1 H), 7.51 (t, *J* = 1.90 Hz, 1 H), 7.13 (ddd, *J* = 8.34, 2.23, 1.03 Hz, 1 H), 7.06 (t, *J* = 8.00 Hz, 1 H), 6.77 (s, 2 H), 5.02 (td, *J* = 7.14, 3.90 Hz, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 2.67 (d, *J* = 3.26 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{17}H_{17}F_2IO_5Cl$ (M+Cl) 500.9777, found 500.9782, 1.0 ppm.



4.9f

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 $Co(acac)_2$ 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.

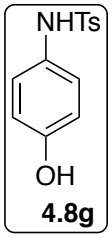
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.56 Hz, 2 H), 7.08 (d, *J* = 8.21 Hz, 2 H), 6.77 (s, 2 H), 5.02 (td, *J* = 7.24, 3.11 Hz, 1 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.54 (t, *J* = 7.49 Hz, 2 H), 3.12 (t, *J* = 7.47 Hz, 2 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): δ –81.56 (dd, *J* = 141.41, 7.45 Hz, 1 F), –81.99 (dd, *J* = 141.40, 7.81 Hz, 1 F)

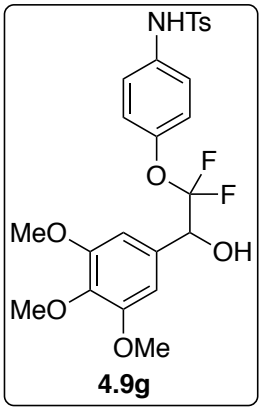
IR (film): 3446, 2939, 2839, 2250, 1758, 1593, 1507, 1462, 1421, 1325, 1235, 1200, 1125, 1064, 1019, 1002, 910, 831, 809, 764, 751, 731, 697, 646, 551, 531 cm^{-1}

HRMS (ESI–): calc. for $C_{19}H_{21}BrF_2O_5Cl$ (M+Cl) 481.0229, found 481.0247, 3.7 ppm.



4.8g

***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_2SO_4, dried *in vacuo*, and purified by flash chromatography (30–50% EtOAc in Hexanes) to provide 3.05 g (83% yield) of desired product **4.8g** as a pale yellow solid; ^{1}H NMR matched the previously reported spectrum.[2]



4.9g

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).

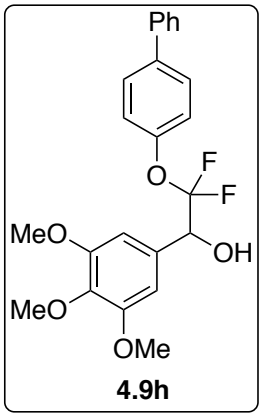
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.27 Hz, 2 H), 7.19 (d, *J* = 7.78 Hz, 2 H), 7.16 (bs, 1 H), 7.02–6.96 (m, 4 H), 6.74 (s, 2 H), 4.98 (t, *J* = 6.94 Hz, 1 H), 3.84 (s, 9 H), 3.10 (bs, 1 H), 2.35 (s, 3 H)

^{13}C (126 MHz, $CDCl_3$): δ 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{24}H_{25}F_2NO_7SNa$ (M+Na) 532.1218, found 532.1227, 1.7 ppm.



4.9h

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.

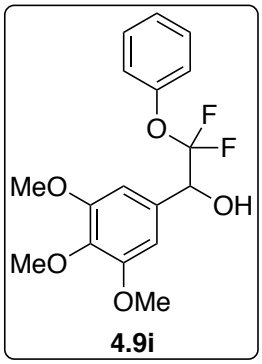
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.54 Hz, 4 H), 7.43 (t, *J* = 7.50 Hz, 2 H), 7.37–7.33 (m, 1 H), 7.22 (dd, *J* = 8.65, 0.91 Hz, 2 H), 6.81 (s, 2 H), 5.06 (td, *J* = 7.09, 3.94 Hz, 1 H), 3.90 (s, 6 H), 3.88 (s, 3 H), 2.90 (d, *J* = 4.01 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{23}H_{22}F_2O_5Na$ (M+Na) 439.1333, found 439.1344, 2.5 ppm.



4.9i

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).

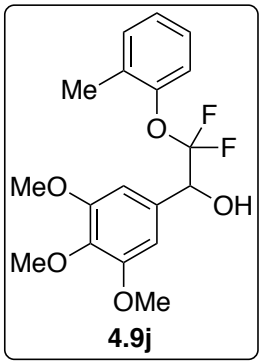
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 8.53, 7.23 Hz, 2 H), 7.20 (t, *J* = 7.42 Hz, 1 H), 7.14 (d, *J* = 7.18 Hz, 2 H), 6.78 (s, 2 H), 5.03 (ddd, *J* = 9.10, 6.73, 2.85 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.07 (d, *J* = 3.91 Hz, 1 H)

^{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 $C_{17}H_{19}F_2O_5$ (M+H) 341.1201, found 341.1195, 1.8 ppm.



4.9j

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.

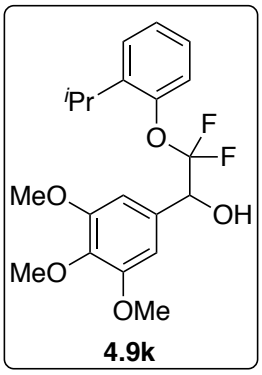
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.07 (m, 4 H), 6.80 (s, 2 H), 5.07 (dd, *J* = 7.79, 5.83 Hz, 1 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.93 (bs, 1 H), 2.05 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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, 1507, 1492, 1461, 1421, 1325, 1251, 1234, 1178, 1125, 1062, 1003, 922, 844, 819, 787, 745, 712, 694, 660, 559, 527 cm^{-1}

HRMS (ESI+): calc. for $C_{18}H_{20}F_2O_5Na$ (M+Na) 377.1177, found 377.1179, 0.5 ppm.



4.9k

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.

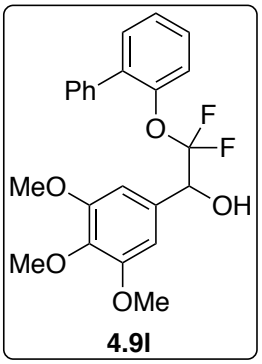
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dt, *J* = 7.74, 2.51 Hz, 2 H), 7.15 (ddd, *J* = 8.03, 5.34, 2.08 Hz, 2 H), 6.81 (s, 2 H), 5.09 (dt, *J* = 8.66, 4.45 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 2.82 (p, *J* = 6.92 Hz, 1 H), 2.74 (d, *J* = 3.95 Hz, 1 H), 1.03 (dd, *J* = 6.92, 1.01 Hz, 6 H)

^{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}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{20}H_{24}F_2O_5Cl$ (M+Cl) 417.1280, found 417.1280, 0.0 ppm.



4.9l

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, $CDCl_3$): δ 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, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{23}H_{22}F_2O_5K$ (M+K) 455.1072, found 455.1076, 0.9 ppm.

References:

1. Chechik, V.; Carter, E.; Murphy, D., *Electron Paramagnetic Resonance*. Oxford University Press: 2016.

2. Chen, K.; Liu, S.; Wang, D.; Hao, W.-J.; Zhou, P.; Tu, S.-J.; Jiang, B., Silver/Scandium-Cocatalyzed Bicyclization of β-Alkynyl Ketones Leading to Benzo[c]xanthenes and Naphtho[1,2-b]benzofurans. *The Journal of Organic Chemistry* **2017,** *82* (21), 11524-11530.

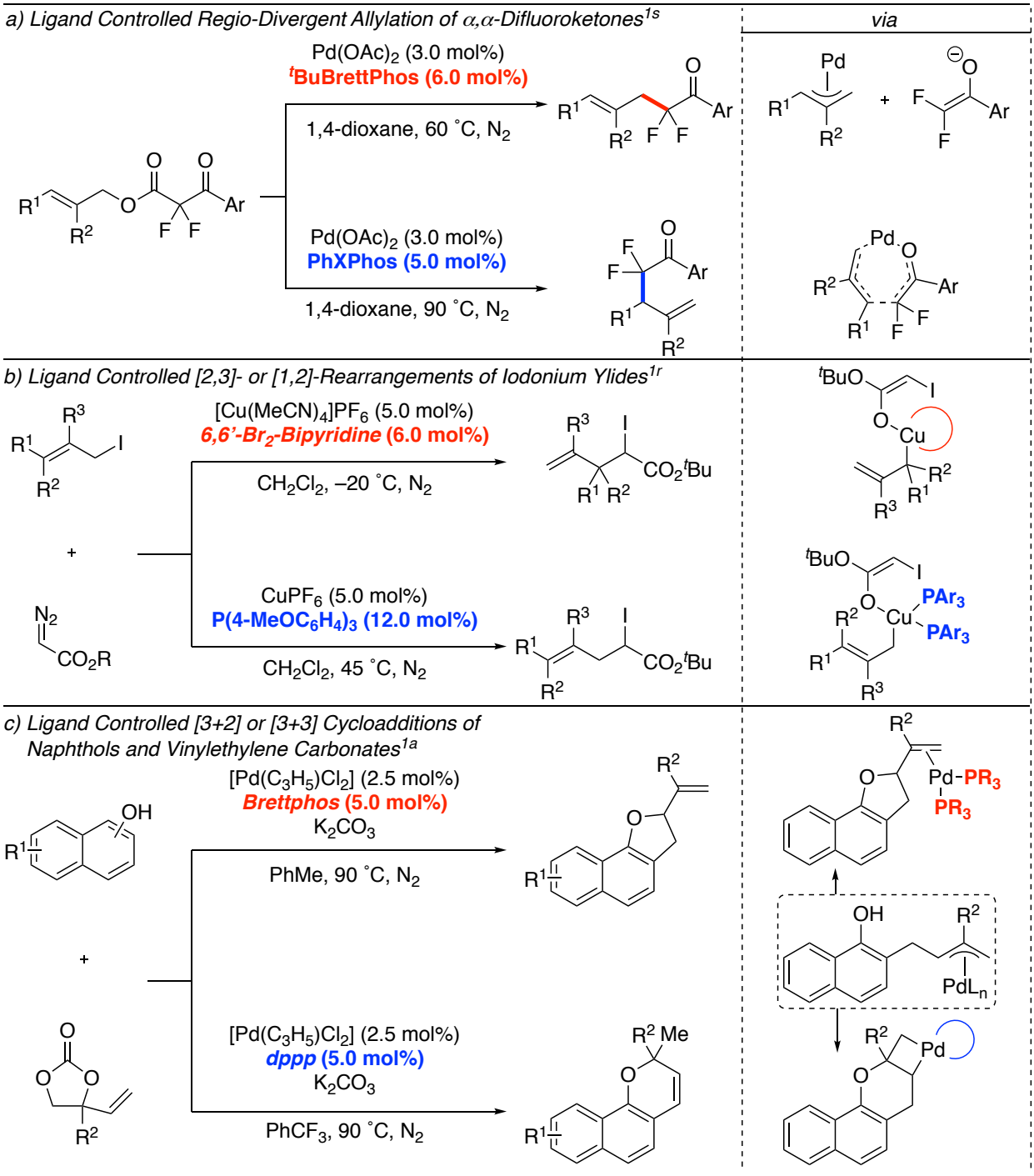
Chapter 5 – Ongoing Metal-Catalyzed Dioxygenation Reactions of *gem*-Difluoroalkenes

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.

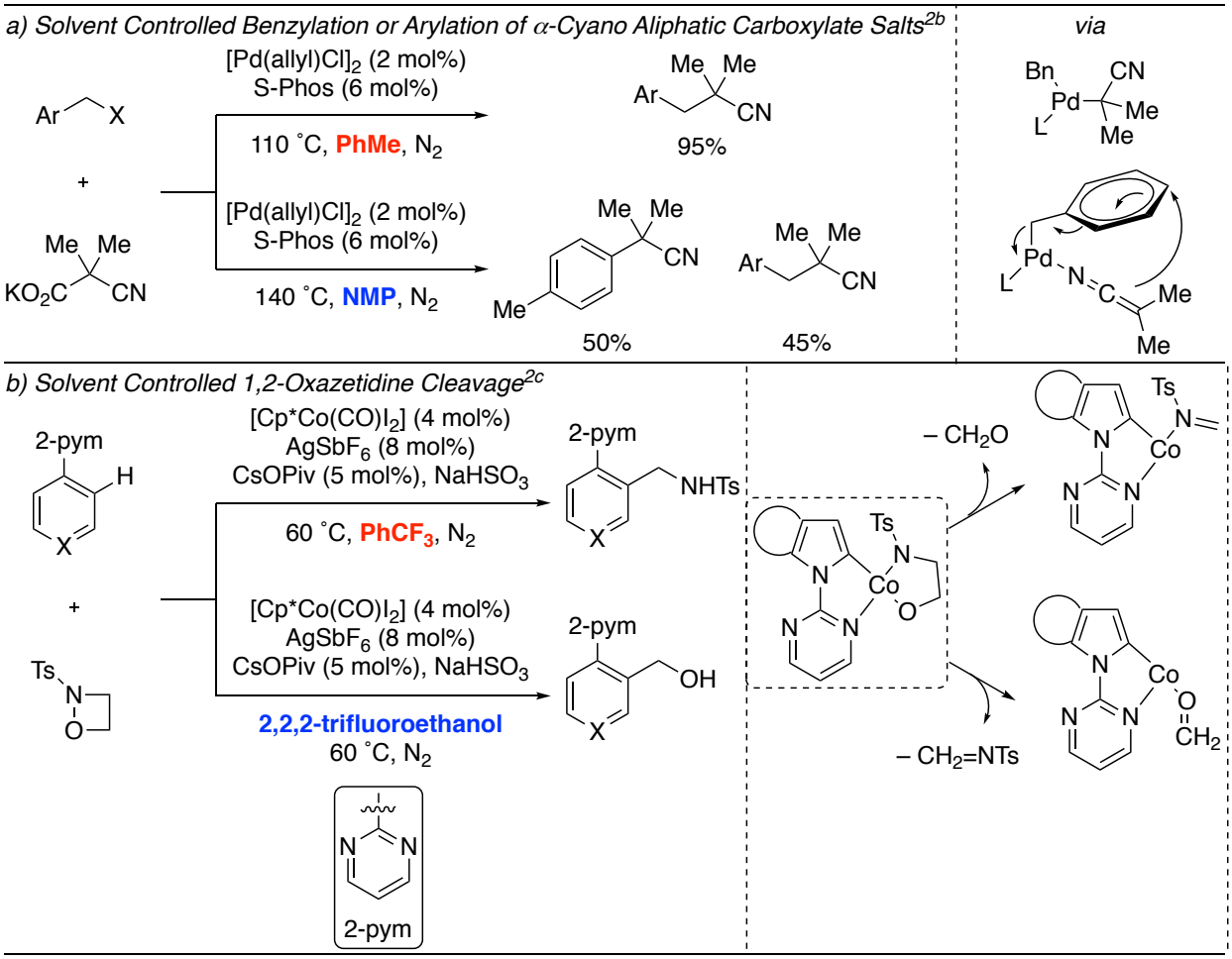
Tunable, divergent catalyst systems are becoming more common, especially as C–H functionalization and directed reactions are developed. Often these divergent systems utilize distinct ligands to control the regioselectivity of transition metal catalyzed reactions.[1] For example, in the Pd-catalyzed decarboxylative 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**).[1s] 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**).[1r] 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**).[1a]

Scheme 5-1: Ligand Controlled Divergent Reactions



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.[2] 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**).[2b] 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**).[2c]

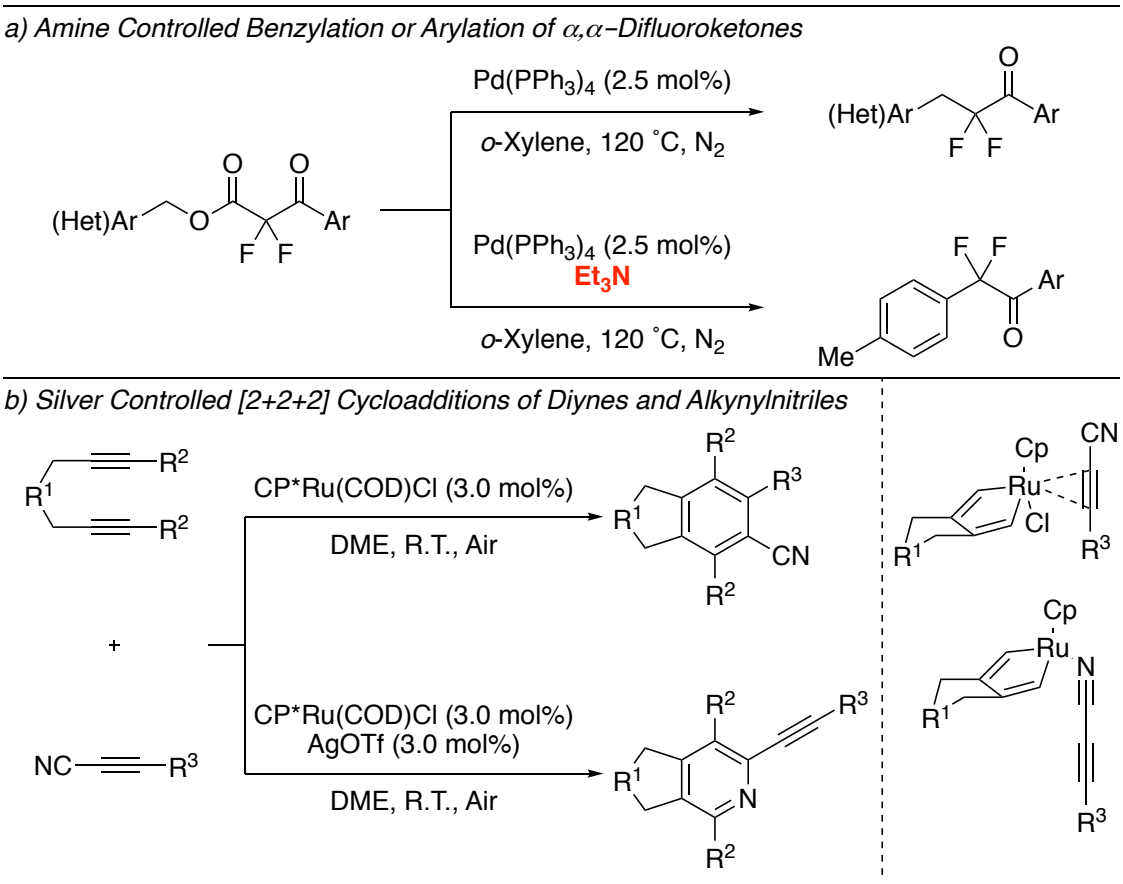
Scheme 5-2: Solvent Controlled Divergent Reactions



A third strategy uses additives, such as an exogenous base or acid, to control the reaction outcome.[3] For instance, the addition of amine bases to the decarboxylative benzylation reaction of α,α-difluoroketones controls the whether the nucleophile attacks the benzyl position or adds to the aryl ring of the benzyl electrophile (**Scheme 5-3a**).[4] In a Ru-catalyzed [2+2+2] cycloaddition, a silver additive controls whether the reaction forms benzonitrile or pyridyl products (**Scheme 5-3b**).[3f] 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 η^1 binding event through the nitrile nitrogen, an η^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



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.[5] 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.[6] Many oxidative difunctionalization reactions of alkenes provide access to alcohol or ether derived products,[5-7] through strategies such as epoxidation-nucleophilic addition[7e, 8] or dihydroxylation[5, 9] reactions. However, few alkene difunctionalization reactions selectively functionalize each terminus of an alkene with two different oxygen functional groups in a single step.[10] Such an unsymmetric difunctionalization typically requires two or more steps[8b, 8c, 9c-g] or provides a regioisomeric mixture of difunctionalized products.[7a-c]

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 β-phenoxy-β,β-difluorobenzyl alcohol or ketone products, and a Cu-based catalyst system to selectively provide β-phenoxy-β,β-difluorobenzyl ketones.

5.2. Platinum Catalysis to Access β-Phenoxy-β,β-Difluorobenzyl Alcohols

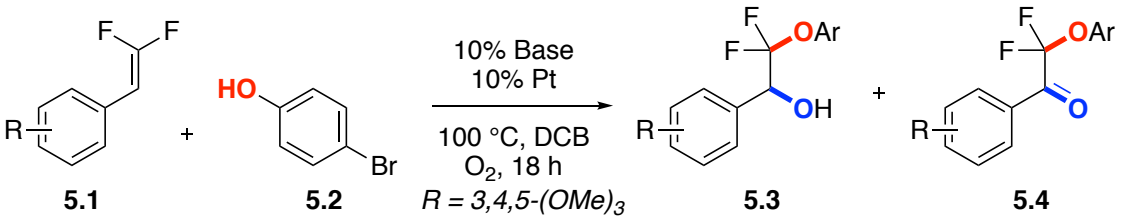
The catalytic addition of phenol to *gem*-difluoroalkenes using a platinum-based catalyst system provides similar reactivity to Co-based catalyst systems. In the presence of a basic additive, Pt(0)- and Pt(IV)-based precatalysts both selectively accessed the β-phenoxy-β,β-difluorobenzyl alcohol product (**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 β-phenoxy-β,β-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 $Pt(PPh_3)_4$ 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 $Pt(PPh_3)_4$, required a phosphine-based ligand to provide consistent results. Gratifyingly, use of PPh_3 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



5.1 **5.2** **5.3** **5.4**

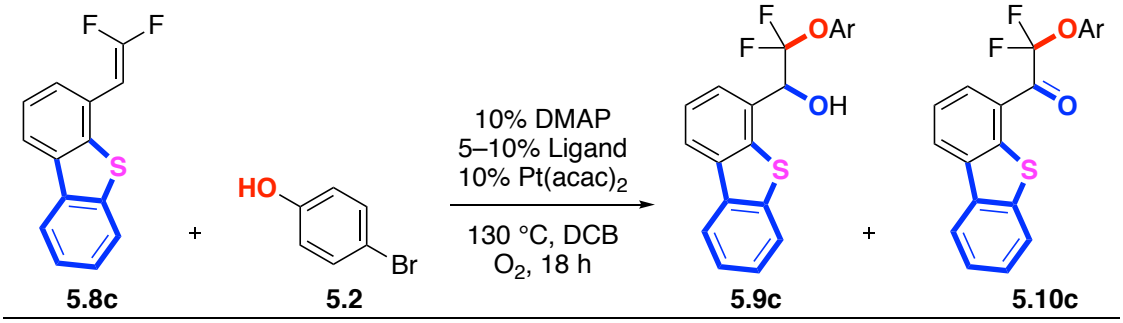
Entry	Metal	Base	Solvent	Conv.[b]	5.3[b]	5.4[b]
1	PtO_2	TBD	DCB	98	68	15
2	$Pt(PPh_3)_4$	TBD	DCB	95	66	7
3	PtO_2	–	DCB	84	10	5
4	$Pt(PPh_3)_4$	–	DCB	85	1	8
5[c]	PtO_2	–	DCB	34	1	0
6[c]	$Pt(PPh_3)_4$	Et_3N	DCB	87	1	8
7	$Pt(PPh_3)_4$	2,6-Lutidine	DCB	92	1	8
8	$Pt(PPh_3)_4$	Imidazole	DCB	94	72	12
9	$Pt(PPh_3)_4$	DABCO	DCB	90	67	7
10	$Pt(PPh_3)_4$	DBU	DCB	87	1	10
11	$Pt(PPh_3)_4$	DMAP	DCB	94	85	3
12	$Pt(PPh_3)_4$	DMAP	H_2O	87	28	1
13	$Pt(PPh_3)_4$	DMAP	IPA	34	0	0
14	$Pt(PPh_3)_4$	DMAP	1,4-Dioxane	38	1	0
15	$Pt(PPh_3)_4$	DMAP	MeCN	47	0	0
16	$Pt(PPh_3)_4$	DMAP	DMF	56	1	1
17	$Pt(PPh_3)_4$	DMAP	DMSO	77	0	2
18	$Pt(PPh_3)_4$	DMAP	PhMe	78	40	1
19	$Pt_2(dba)_3$	DMAP	DCB	83	32	10
20	$Pt(acac)_2$	DMAP	DCB	95	74	3
21[d]	$Pt(acac)_2$	DMAP	DCB	95	76	5
22[e]	$Pt(acac)_2$	DMAP	DCB	90	65	4
23[f]	$Pt(acac)_2$	DMAP	DCB	79	48	5

[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), $Pt(PPh_3)_4$ (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 α,α,α-trifluorotoluene

(TFT). [c] N_2 atmosphere. [d] 10% PPh_3. [e] 20% PPh_3. [f] 40% PPh_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_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_3 [1:1 with $Pt(acac)_2$] 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 $Pt(acac)_2$] 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% $Pt(acac)_2$, ligated with either 10% PPh_3 or 5% bidentate phosphine, with a 10% DMAP co-catalyst, in DCB at 100 ˚C for 24 h under an O_2 atmosphere.

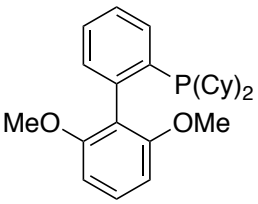
Table 5-2: Ligand Screening of Pt-Catalyzed Addition of Phenols to *gem*-Difluoroalkenes



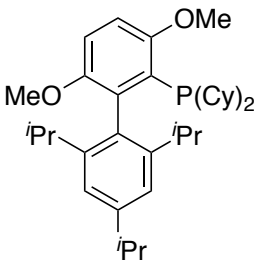
5.8c **5.2** **5.9c** **5.10c**

Entry	Ligand (%)	Conv.[b]	5.9a[b]	5.10a[b]
1	PPh_3 (10%)	90	71	4
2	$OPPh_3$ (10%)	81	78	9
3	PCy_3 (10%)	67	58	3
4	$P(4\text{-}CF_3Ph)_3$ (10%)	88	73	6
5	SPhos (10%)	84	65	8
6	BrettPhos (10%)	82	69	8
7	^{t}Bu-XPhos (10%)	82	62	14
8	Xantphos (5%)	81	68	3
9	DPPE (5%)	91	84	4
10	DPPF (5%)	85	64	17
11	Bipyridine (5%)	89	33	35
12	Phenanthroline (5%)	86	52	35
13	BINAP (5%)	85	74	8

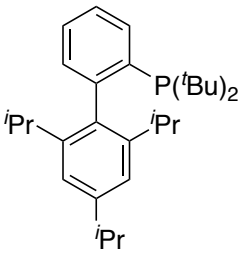
SPhos



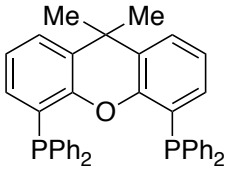
BrettPhos



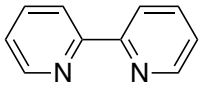
^{t}Bu-XPhos



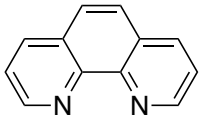
Xantphos



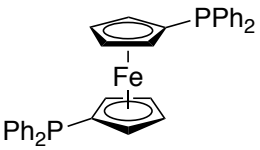
Bipyridine



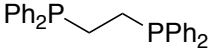
Phenanthroline



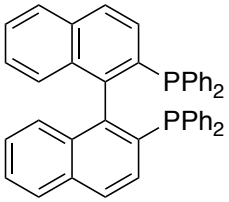
DPPF



DPPE



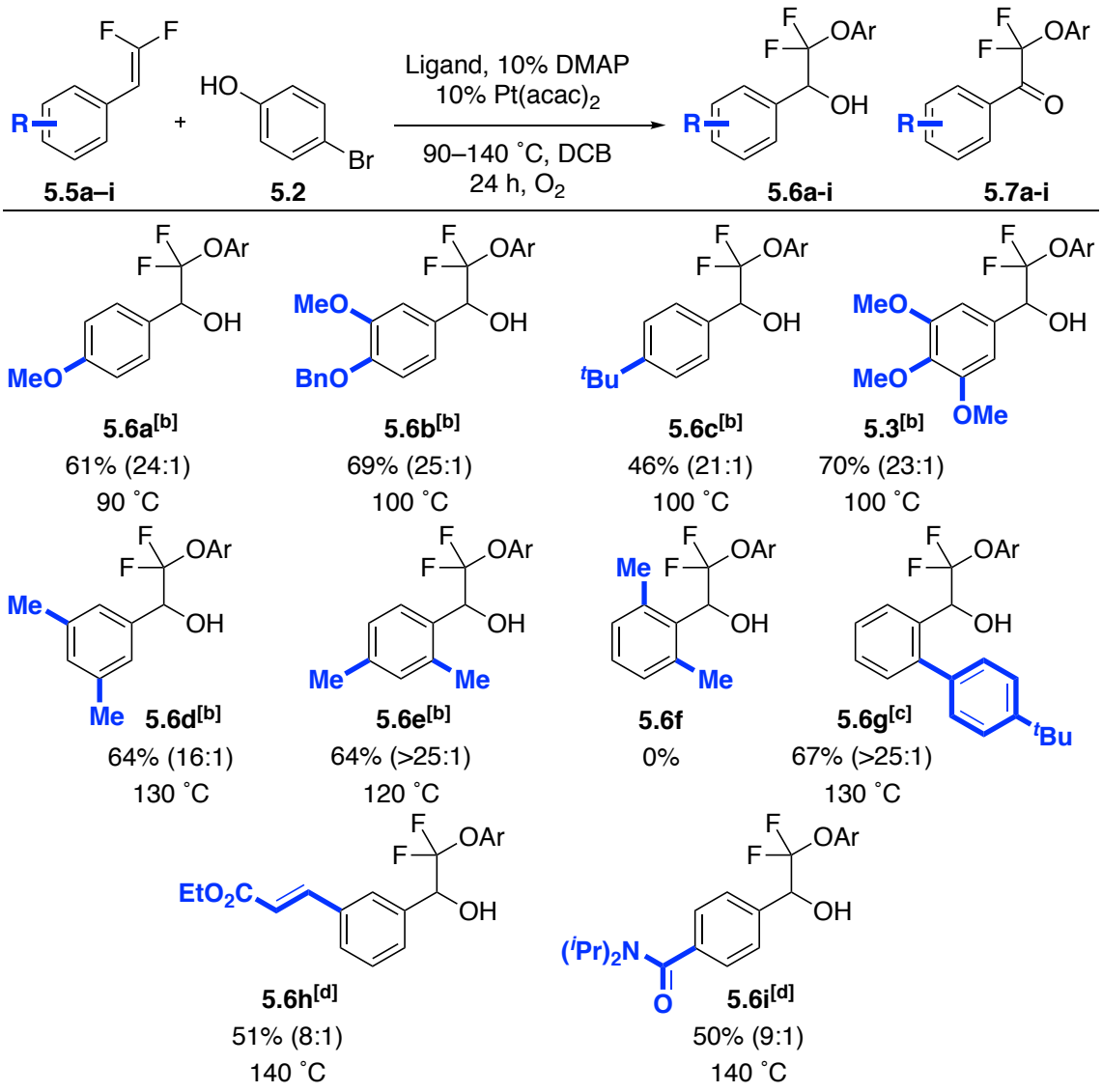
BINAP



[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), $Pt(PPh_3)_4$ (10 mol%, 0.010 mmol), 130 ˚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. **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-Me_2 substituted difluoroalkene failed to react (**5.6f**).

Scheme 5-4: Scope of *gem*-Difluoroalkenes in Pt-Catalyzed Addition / Oxidation of Phenols[a]

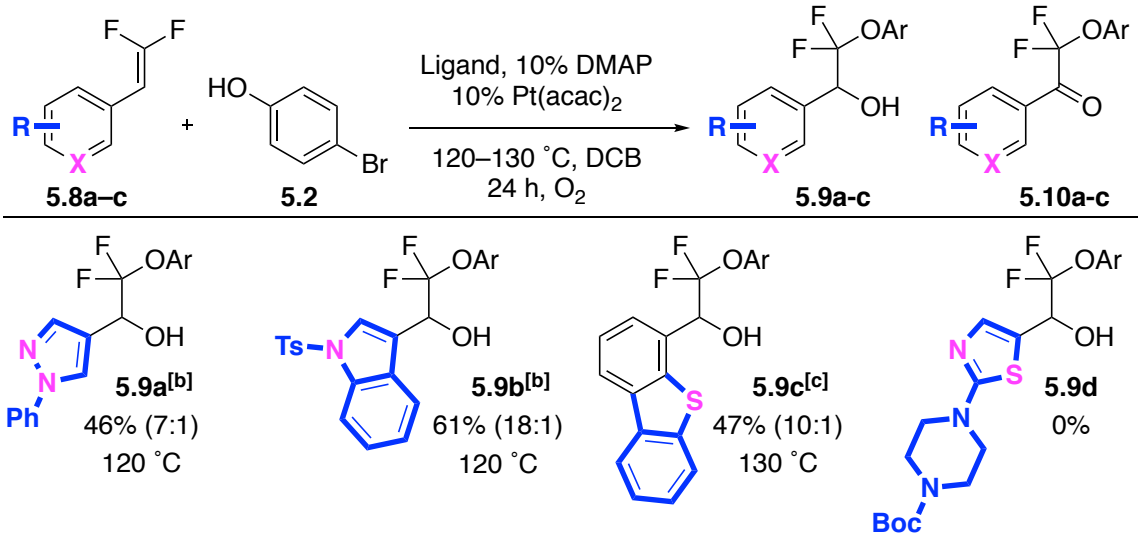


[a] Standard conditions: **5.5a–n** (1.0 equiv., 0.50 mmol), **5.2** (3.0 equiv., 1.5 mmol), DMAP (10 mol%, 0.050 mmol), Ligand (5–10 mol%, 0.025–0.050 mmol), DCB (0.25 M, 2.0 mL), $Pt(acac)_2$ (10 mol%, 0.050 mmol), temperature as indicated, for 24 h under an O_2 atmosphere. The selectivity of alcohol:ketone 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] PPh_3 (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**).

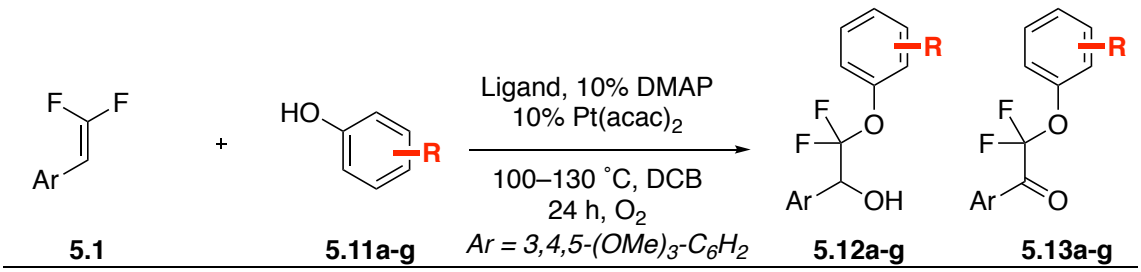
Scheme 5-5: Scope of Heteroaryl *gem*-Difluoroalkenes in Pt-Catalyzed Addition / Oxidation of Phenols[a]



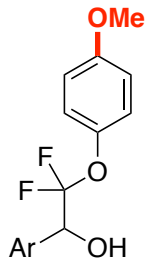
[a] Standard conditions: **5.8a–d** (1.0 equiv., 0.50 mmol), **5.2** (3.0 equiv., 1.5 mmol), DMAP (10 mol%, 0.050 mmol), Ligand (5–10 mol%, 0.050 mmol), DCB (0.25 M, 2.0 mL), $Pt(acac)_2$ (10 mol%, 0.050 mmol), temperature as indicated, for 24 h under an O_2 atmosphere. The selectivity of alcohol:ketone 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.

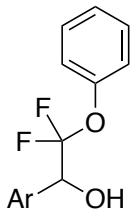
Scheme 5-6: Scope of Phenol Nucleophiles in Pt-Catalyzed Addition / Oxidation to *gem*-Difluoroalkenes[a]



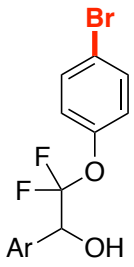
5.1 **5.11a-g** **5.12a-g** **5.13a-g**



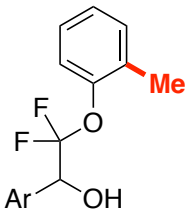
5.12a[b]
68% (>25:1)
120 ˚C



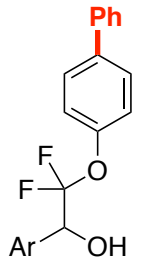
5.12b[c]
50% (24:1)
130 ˚C



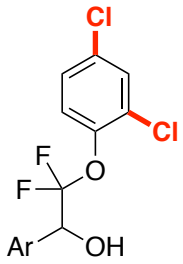
5.3[b]
70% (23:1)
130 ˚C



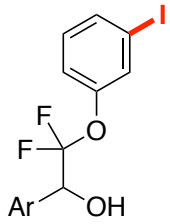
5.12c[c]
39% (>25:1)
130 ˚C



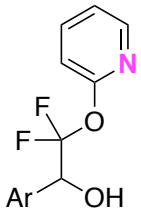
5.12d[b]
65% (>25:1)
120 ˚C



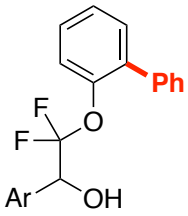
5.12e[b]
61% (11:1)
100 ˚C



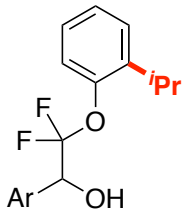
5.12f[b]
63% (>25:1)
100 ˚C



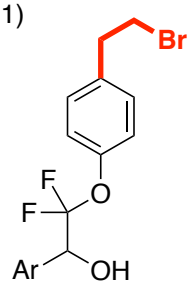
5.12g[d]
79% (20:1)
120 ˚C



5.12h[c]
50% (15:1)
130 ˚C



5.12i[c]
47% (>25:1)
130 ˚C

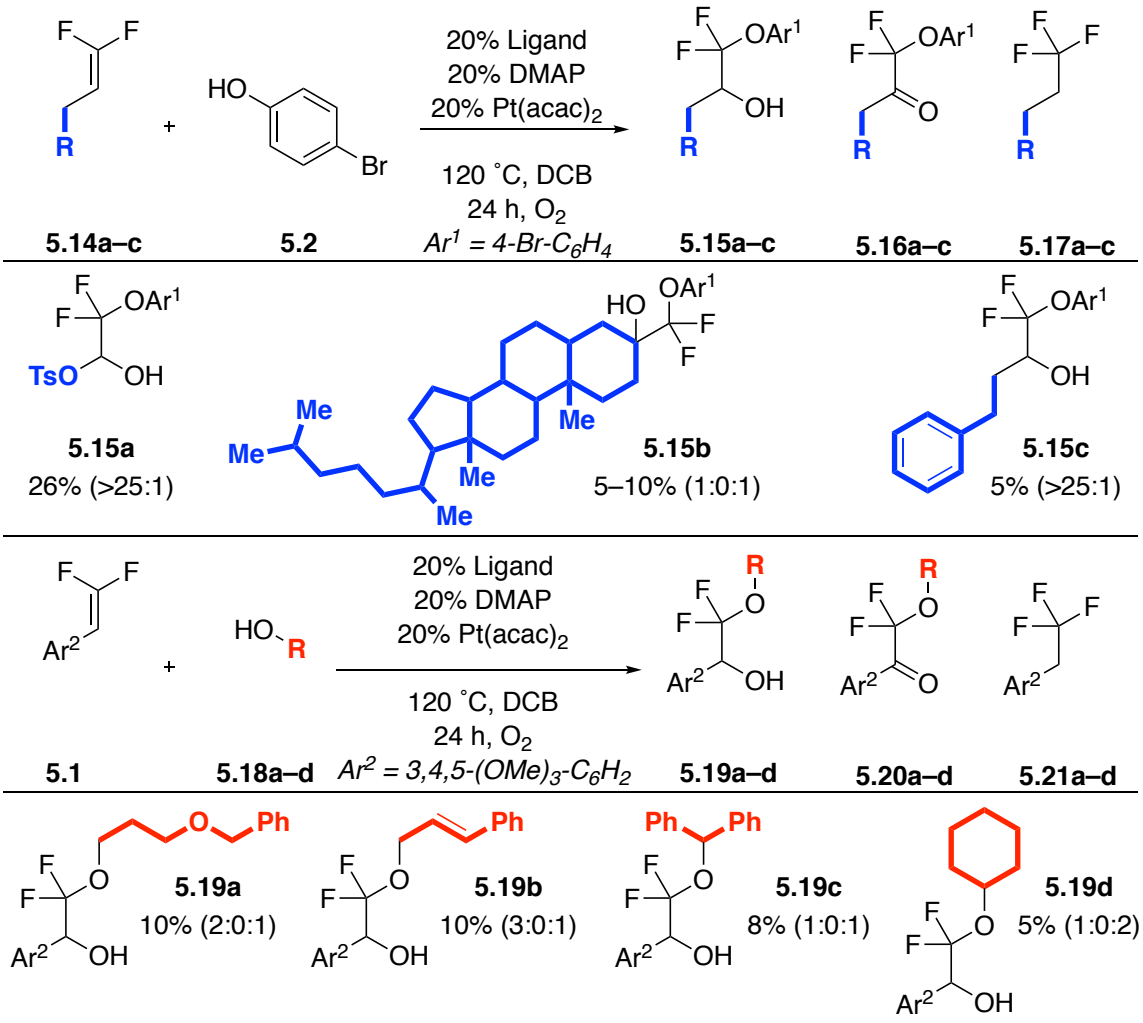


5.12j[b]
46% (7:1)
120 ˚C

[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]



[a] Standard conditions: **5.1** or **5.14a–c** (1.0 equiv., 0.10 mmol), **5.2** or **5.18a–d** (3.0 equiv., 0.30 mmol), DMAP (20 mol%, 0.020 mmol), PPh_3 (20 mol%, 0.020 mmol), DCB (0.25 M, 0.40 mL), $Pt(acac)_2$ (20 mol%, 0.020 mmol), 120 ˚C, for 24 h under an O_2 atmosphere. The yield and selectivity of **5.15**:**5.16**:**5.17** or **5.19**:**5.20**:**5.21** was determined by ^{19}F NMR analysis of the crude reaction mixture, standardized with 10 μL (0.080 mmol) of TFT, and the selectivity is reported in parentheses.

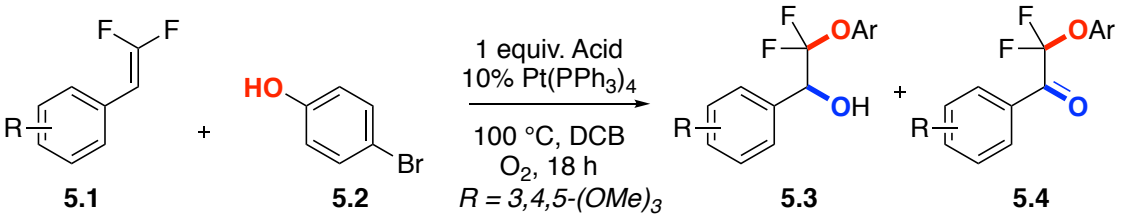
5.3. Mechanistic Considerations

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 phenoxide 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]



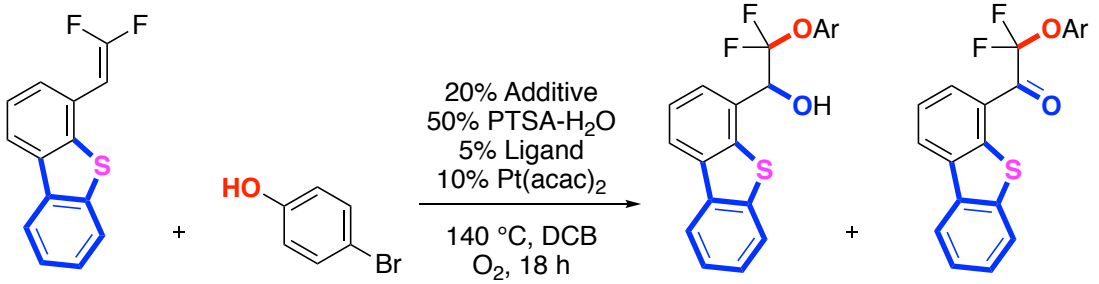
5.1 **5.2** **5.3** **5.4**

Entry	Acid	Conv.[b]	5.3[b]	5.4[b]
1	H_2SO_4	79	0	0
2	AcOH	72	40	8
3	TFA	92	0	8
4	Proline	25	1	0
5	PTSA-H_2O	>99	0	14
6	MsOH	>99	0	10
7	SDS	60	0	2
8	Isoquinoline-5-SO_4	40	16	5
9[c]	PTSA-H_2O	76	0	18
10[d]	PTSA-H_2O	57	0	8
11[e]	PTSA-H_2O	52	5	12
12[c,f]	PTSA-H_2O	76	0	31
13[c,f]	4-NH_2-C_6H_4-SO_3H	60	0	4
14[c,f]	4-Cl-C_6H_4-SO_3H	12	trace	18
15[c,f]	C_6H_5-SO_3H	80	11	23
16[c,f]	2,4-Me_2-C_6H_3-SO_3H	84	9	23

[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),[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.

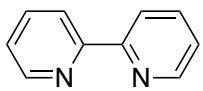
Table 5-4: Initial Discovery of Cu-Catalyzed Addition / Oxidation of Phenols to *gem*-Difluoroalkenes to Provide β-Phenoxy-β,β-Difluorobenzyl Ketones[a]



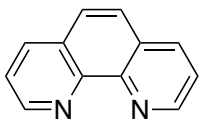
5.8c + **5.2** → **5.9c** + **5.10c**

Entry	Additive	Ligand	Conv.[b]	5.9c[b]	5.10c[b]
1	–	Bipyridine	89	0	48
2	–	Phenanthroline	82	0	44
3	–	Terpyridine	89	0	45
4	$CuCl_2$	PPh_3	>99	0	30
5	$CuCl_2$	Bipyridine	84	0	51
6	$CuCl_2$	Phenanthroline	80	0	66
7	$CuCl_2$	Terpyridine	89	0	66
8	$CuCl_2$	Bipyridine	81	0	48
9	$CuCl_2$	Phenanthroline	81	0	49
10	$CuCl_2$	Terpyridine	81	0	64
11[c,d]	$CuCl_2$	Terpyridine	84	14	64

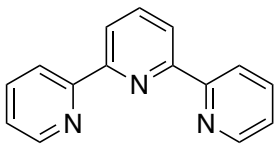
Bipyridine



Phenanthroline



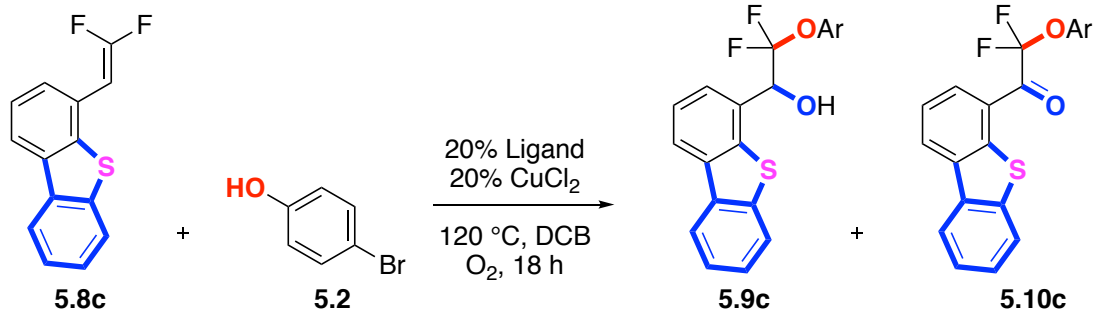
Terpyridine



[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), $Pt(PPh_3)_4$ (10 mol%, 0.010 mmol), 140 ˚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] 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% $CuCl_2$ ligated with 20% terpyridine in 95:5 DCB:DMSO at 100 ˚C in an O_2 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[a]



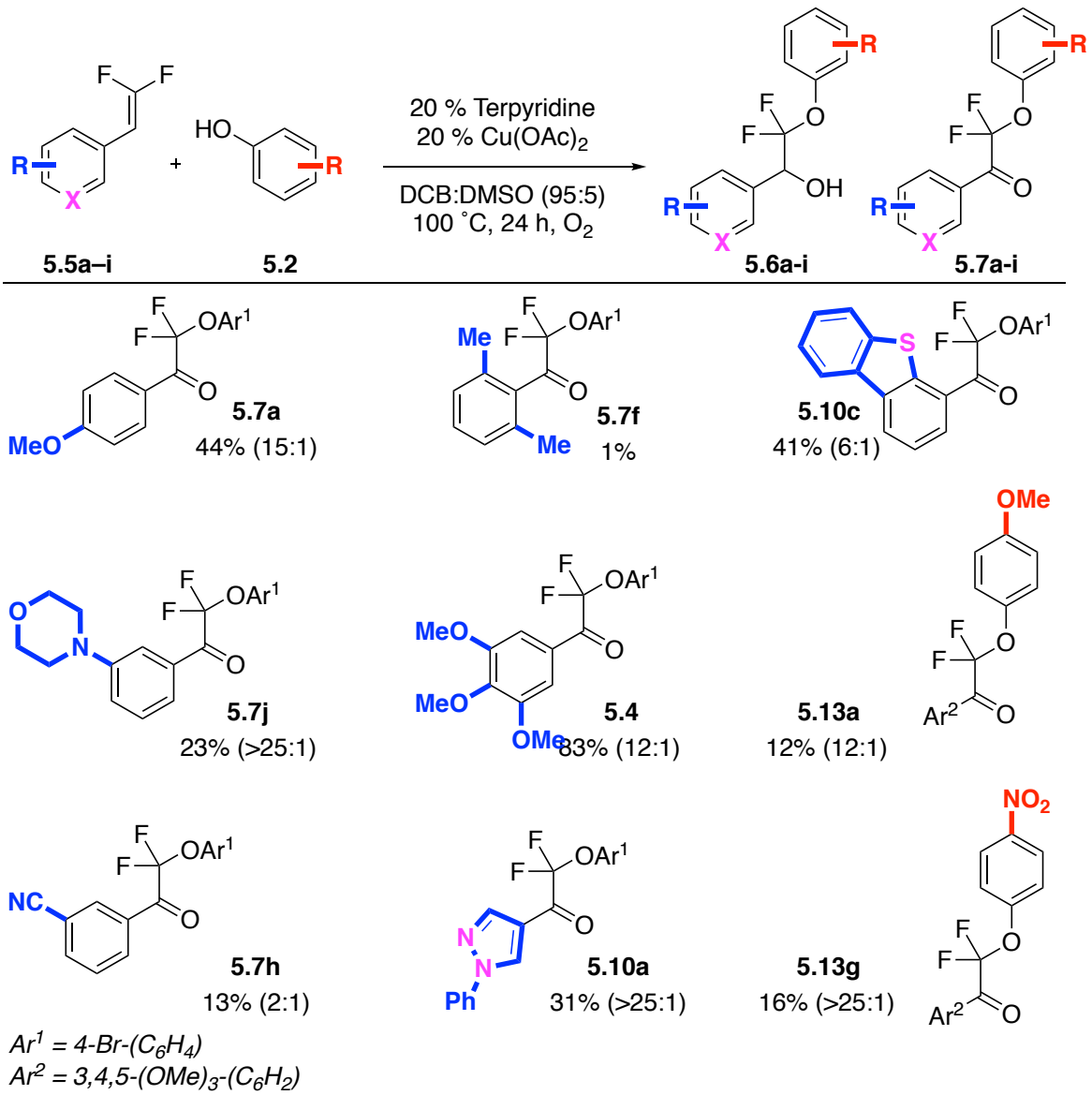
5.8c **5.2** **5.9c** **5.10c**

Entry	Metal	Ligand	Solvent	Conv.[b]	5.9c[b]	5.10c[b]
1	$CuCl_2$	Bipyridine	DCB	75	16	68
2	$CuCl_2$	Phenanthroline	DCB	81	18	76
3	$CuCl_2$	Terpyridine	DCB	76	16	69
4	$CuSO_4$	Terpyridine	DCB	89	10	74
5	$Cu(OAc)_2$	Terpyridine	DCB	80	11	79
6	$Cu(OAc)_2$	Phenanthroline	DCB	82	8	60
7	$Cu(OAc)_2$	Bathophenanthroline	DCB	75	9	56
8	$Cu(OAc)_2$	Me_4-Phenanthroline	DCB	91	10	48
9	$Cu(OAc)_2$	$(OMe)_2$-Phenanthroline	DCB	82	13	68
10	$CuCl_2$	Phenanthroline	PhMe	80	10	45
11	$CuCl_2$	Phenanthroline	DMF	44	0	14
12	$CuCl_2$	Phenanthroline	DMSO	40	0	13
13	$CuCl_2$	Phenanthroline	Diglyme	67	0	28
14[c]	$Cu(OAc)_2$	Terpyridine	3:1 DCB:Diglyme	94	18	81
15[c]	$Cu(OAc)_2$	Terpyridine	3:1 DCB:DMSO	61	0	45
16[c,d]	$Cu(OAc)_2$	Terpyridine	95:5 DCB:DMSO	>99	7	83
17[c,d]	$Cu(OAc)_2$	Terpyridine	3:1 DCB:DMSO	87	2	65

[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 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] 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[a]



[a] 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 mol%, 0.020 mmol), DCB (0.38 mL), DMSO (0.020 mL), 100 ˚C, for 24 h under an O_2 atmosphere. Yield of **5.7**, **5.10**, or **5.12** and selectivity versus **5.6**, **5.9**, or **5.11** determined by ^{19}F 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**.

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 O_2 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 β-phenoxy-β,β-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 β-phenoxy-β,β-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

1. (a) Xia, Y.; Bao, Q. F.; Li, Y.; Wang, L. J.; Zhang, B. S.; Liu, H. C.; Liang, Y. M., Ligand-controlled regiodivergent pi-allyl palladium catalysis enables a switch between [3+2] and [3+3] cycloadditions. *Chem Commun (Camb)* **2019**; (b) Li, X.; Wu, H.; Wu, Z.; Huang, G., Mechanism and Origins of Regioselectivity of Copper-Catalyzed Borocyanation of 2-Aryl-Substituted 1,3-Dienes: A Computational Study. *J. Org. Chem.* **2019**; (c) Ye, Y.; Kim, S. T.; Jeong, J.; Baik, M. H.; Buchwald, S. L., CuH-Catalyzed Enantioselective Alkylation of Indole Derivatives with Ligand-Controlled Regiodivergence. *J. Am. Chem. Soc.* **2019,** *141* (9), 3901-3909; (d) Yang, J.; Wang, C.; Sun, Y.; Man, X.; Li, J.; Sun, F., Ligand-controlled iridium-catalyzed semihydrogenation of alkynes with ethanol: highly stereoselective synthesis of E- and Z-alkenes. *Chem Commun (Camb)* **2019,** *55* (13), 1903-1906; (e) Deng, L.; Kleij, A. W.; Yang, W., Diversity-Orientated Stereoselective Synthesis through Pd-Catalyzed Switchable Decarboxylative C-N/C-S Bond Formation in Allylic Surrogates. *Chemistry* **2018,** *24* (72), 19156-19161; (f) Zhang, S.; Yamamoto, Y.; Bao, M., Palladium-Catalyzed Ligand-Controlled Regioselective Nucleophilic Aromatic Substitution of 1-(Chloromethyl)naphthalenes with Arylacetonitriles. *J. Org. Chem.* **2018,** *83* (22), 13981-13990; (g) Jadhav, P. D.; Lu, X.; Liu, R.-S., Gold-Catalyzed [5+2]- and [5+1]-Annulations between Ynamides and 1,2-Benzisoxazoles with Ligand-Controlled Chemoselectivity. *Acs Catal* **2018,** *8* (10), 9697-9701; (h) Ming, J.; Hayashi, T., Rhodium-Catalyzed Arylzincation of Alkynes: Ligand Control of 1,4-Migration Selectivity. *Org. Lett.* **2018,** *20* (19), 6188-6192; (i) Li, X.-D.; Xia, S.-M.; Chen, K.-H.; Liu, X.-F.; Li, H.-R.; He, L.-N., Copper catalysis: ligand-controlled

selective N-methylation or N-formylation of amines with CO2 and phenylsilane. *Green Chemistry* **2018,** *20* (21), 4853-4858; (j) Kato, K.; Kusakabe, T.; Ariyama, T.; Sato, K.; Funatogawa, M.; Lee, D.; Takahashi, K., Pd(II)-Catalyzed Ligand-Controlled Synthesis of 2,3-Dihydroisoxazole-4-carboxylates and Bis(2,3-dihydroisoxazol-4-yl)methanones. *Heterocycles* **2016,** *93* (2); (k) Ogiwara, Y.; Sakurai, Y.; Hattori, H.; Sakai, N., Palladium-Catalyzed Reductive Conversion of Acyl Fluorides via Ligand-Controlled Decarbonylation. *Org. Lett.* **2018,** *20* (14), 4204-4208; (l) Ding, D.; Zhu, G.; Jiang, X., Ligand-Controlled Palladium(II)-Catalyzed Regiodivergent Carbonylation of Alkynes: Syntheses of Indolo[3,2-c]coumarins and Benzofuro[3,2-c]quinolinones. *Angew. Chem. Int. Ed. Engl.* **2018,** *57* (29), 9028-9032; (m) Wang, F.; Wang, D.; Zhou, Y.; Liang, L.; Lu, R.; Chen, P.; Lin, Z.; Liu, G., Divergent Synthesis of CF3 -Substituted Allenyl Nitriles by Ligand-Controlled Radical 1,2- and 1,4-Addition to 1,3-Enynes. *Angew. Chem. Int. Ed. Engl.* **2018,** *57* (24), 7140-7145; (n) Yu, B.; Yang, K. F.; Bai, X. F.; Cao, J.; Zheng, Z. J.; Cui, Y. M.; Xu, Z.; Li, L.; Xu, L. W., Ligand-Controlled Inversion of Diastereo- and Enantioselectivity in Silver-Catalyzed Azomethine Ylide-Imine Cycloaddition of Glycine Aldimino Esters with Imines. *Org. Lett.* **2018,** *20* (9), 2551-2554; (o) Wu, C. Y.; Zhang, Y. F.; Xu, M. H., Ligand-Controlled Rhodium-Catalyzed Site-Selective Asymmetric Addition of Arylboronic Acids to alpha,beta-Unsaturated Cyclic N-Sulfonyl Ketimines. *Org. Lett.* **2018,** *20* (7), 1789-1793; (p) Chatupheeraphat, A.; Liao, H.-H.; Srimontree, W.; Guo, L.; Minenkov, Y.; Poater, A.; Cavallo, L.; Rueping, M., Ligand-Controlled Chemoselective C(acyl)–O Bond vs C(aryl)–C Bond Activation of Aromatic Esters in Nickel Catalyzed C(sp2)–C(sp3) Cross-Couplings. *J. Am. Chem. Soc.* **2018,** *140* (10), 3724-3735; (q) Meng, Q. Y.; Wang, S.; Huff, G. S.; Konig, B., Ligand-Controlled Regioselective

Hydrocarboxylation of Styrenes with CO2 by Combining Visible Light and Nickel Catalysis. *J. Am. Chem. Soc.* **2018,** *140* (9), 3198-3201; (r) Xu, B.; Tambar, U. K., Ligand-Controlled Regiodivergence in the Copper-Catalyzed [2,3]- and [1,2]-Rearrangements of Iodonium Ylides. *J. Am. Chem. Soc.* **2016,** *138* (37), 12073-6; (s) Yang, M. H.; Orsi, D. L.; Altman, R. A., Ligand-controlled regiodivergent palladium-catalyzed decarboxylative allylation reaction to access alpha,alpha-difluoroketones. *Angew. Chem. Int. Ed. Engl.* **2015,** *54* (8), 2361-5.

2. (a) Cao, M.; Liu, L.; Tang, s.; Peng, Z.; Wang, Y., Palladium-Catalyzed Solvent-Controlled Selective Synthesis of Acyl Isoureas and Imides from Amides, Isocyanides, Alcohols and Carboxylates. *Adv. Synth. Catal.* **2018**; (b) Shang, R.; Huang, Z.; Xiao, X.; Lu, X.; Fu, Y.; Liu, L., β-Aryl Nitrile Construction via Palladium-Catalyzed Decarboxylative Benzylation of α-Cyano Aliphatic Carboxylate Salts. *Adv. Synth. Catal.* **2012**, n/a-n/a; (c) Li, S.; Shi, P.; Liu, R. H.; Hu, X. H.; Loh, T. P., Cobalt-Catalyzed N-O and C-C Bond Cleavage in 1,2-Oxazetidines: Solvent-Controlled C-H Aminomethylation and Hydroxymethylation of Heteroarenes. *Org. Lett.* **2019,** *21* (6), 1602-1606; (d) Li, Y.; Wu, Z.; Ling, Z.; Chen, H.; Zhang, W., Mechanistic study of the solvent-controlled Pd(ii)-catalyzed chemoselective intermolecular 1,2-aminooxygenation and 1,2-oxyamination of conjugated dienes. *Organic Chemistry Frontiers* **2019,** *6* (4), 486-492; (e) Xu, L.; Chen, J.; Chu, L., Solvent-tuned chemoselective carboazidation and diazidation of alkenes via iron catalysis. *Organic Chemistry Frontiers* **2019,** *6* (4), 512-516; (f) Ma, Y.; Wang, K.; Zhang, D.; Sun, P., Solvent Controlled Transformation between Sulfonyl Hydrazides and Alkynes: Divergent Synthesis of Benzo[b]thiophene-1,1-dioxides and (E)-β-iodo

Vinylsulfones. *Adv. Synth. Catal.* **2019,** *361* (3), 597-602; (g) Viji, M.; Sim, J.; Li, S.; Lee, H.; Oh, K.; Jung, J.-K., Organocatalytic and Regiodivergent Mannich Reaction of Ketones with Benzoxazinones. *Adv. Synth. Catal.* **2018,** *360* (23), 4464-4469; (h) Ramu, G.; Hari Krishna, N.; Pawar, G.; Visweswara Sastry, K. N.; Nanubolu, J. B.; Nagendra Babu, B., Solvent-Controlled, Tunable Domino Reaction of 3-Ylideneoxindoles with in Situ-Generated α-Aryldiazomethanes: A Facile Access to 3-Spirocyclopropyl-2-oxindole and Pyrazoloquinazolinone Scaffolds. *ACS Omega* **2018,** *3* (10), 12349-12360; (i) Yi, W.; Chen, W.; Liu, F.-X.; Zhong, Y.; Wu, D.; Zhou, Z.; Gao, H., Rh(III)-Catalyzed and Solvent-Controlled Chemoselective Synthesis of Chalcone and Benzofuran Frameworks via Synergistic Dual Directing Groups Enabled Regioselective C–H Functionalization: A Combined Experimental and Computational Study. *Acs Catal* **2018,** *8* (10), 9508-9519; (j) Bookser, B. C.; Weinhouse, M. I.; Burns, A. C.; Valiere, A. N.; Valdez, L. J.; Stanczak, P.; Na, J.; Rheingold, A. L.; Moore, C. E.; Dyck, B., Solvent-Controlled, Site-Selective N-Alkylation Reactions of Azolo-Fused Ring Heterocycles at N1-, N2-, and N3-Positions, Including Pyrazolo[3,4- d]pyrimidines, Purines, [1,2,3]Triazolo[4,5]pyridines, and Related Deaza-Compounds. *J. Org. Chem.* **2018,** *83* (12), 6334-6353; (k) Wu, C.; Yoshikai, N., Cobalt-Catalyzed Intramolecular Reactions between a Vinylcyclopropane and an Alkyne: Switchable [5+2] Cycloaddition and Homo-Ene Pathways. *Angew. Chem. Int. Ed. Engl.* **2018,** *57* (22), 6558-6562; (l) Wen, K.; Wu, Z.; Huang, B.; Ling, Z.; Gridnev, I. D.; Zhang, W., Solvent-Controlled Pd(II)-Catalyzed Aerobic Chemoselective Intermolecular 1,2-Aminooxygenation and 1,2-Oxyamination of Conjugated Dienes for the Synthesis of Functionalized 1,4-Benzoxazines. *Org. Lett.* **2018,** *20* (6), 1608-1612; (m) Jia, J.; Yu, A.; Ma, S.; Zhang, Y.; Li, K.; Meng, X., Solvent-Controlled Switchable Domino Reactions of

MBH Carbonate: Synthesis of Benzothiophene Fused alpha-Pyran, 2,3-Dihydrooxepine, and Oxatricyclodecene Derivatives. *Org. Lett.* **2017,** *19* (22), 6084-6087.

3. (a) Gollwitzer, A.; Dietel, T.; Kretschmer, W. P.; Kempe, R., A broadly tunable synthesis of linear alpha-olefins. *Nat Commun* **2017,** *8* (1), 1226; (b) Lai, R.; Wu, X.; Lv, S.; Zhang, C.; He, M.; Chen, Y.; Wang, Q.; Hai, L.; Wu, Y., Synthesis of indoles and quinazolines via additive-controlled selective C-H activation/annulation of N-arylamidines and sulfoxonium ylides. *Chem Commun (Camb)* **2019,** *55* (28), 4039-4042; (c) Peng, J.-B.; Wang, W.-F.; Wu, F.-P.; Ying, J.; Qi, X.; Wu, X.-F., Palladium catalyzed carbonylation of benzyl chlorides: Additive-controlled divergent synthesis of benzyl arylacetates and arylacetic acids. *J. Catal.* **2018,** *368*, 275-278; (d) Panyam, P. K. R.; Sreedharan, R.; Gandhi, T., Synthesis of topologically constrained naphthalimide appended palladium(ii)-N-heterocyclic carbene complexes - insights into additive controlled product selectivity. *Org Biomol Chem* **2018,** *16* (23), 4357-4364; (e) Wang, J. Y.; Wu, P.; Wu, J. L.; Mei, G. J.; Shi, F., Chemodivergent Tandem Cyclizations of 2-Indolylmethanols with Tryptophols: C-N versus C-C Bond Formation. *J. Org. Chem.* **2018,** *83* (11), 5931-5946; (f) Bhatt, D.; Patel, N.; Chowdhury, H.; Bharatam, P. V.; Goswami, A., Additive-Controlled Switchable Selectivity from Cyanobenzenes to 2-Alkynylpyridines: Ruthenium(II)-Catalyzed [2+2+2] Cycloadditions of Diynes and Alkynylnitriles. *Adv. Synth. Catal.* **2018,** *360* (9), 1876-1882.

4. Yang, M. H.; Hunt, J. R.; Sharifi, N.; Altman, R. A., Palladium Catalysis Enables Benzylation of alpha,alpha-Difluoroketone Enolates. *Angew. Chem. Int. Ed. Engl.* **2016,** *55* (31), 9080-3.

5. Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B., Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994,** *94* (8), 2483-2547.

6. Aertker, K.; Rama, R. J.; Opalach, J.; Muniz, K., Vicinal Difunctionalization of Alkenes under Iodine(III) Catalysis involving Lewis Base Adducts. *Adv. Synth. Catal.* **2017,** *359* (8), 1290-1294.

7. (a) Morimoto, T.; Hirano, M.; Echigoya, K.; Sato, T., Oxidation by cobalt(III) acetate. Part 10. Effects of ring substituents on the product distributions in the oxidation of β-methylstyrenes by cobalt(III) acetate in acetic acid. *J. Chem. Soc., Perkin Trans. 2* **1986,** (8), 1205-1209; (b) Hirano, M.; Morimoto, T., Oxidation by cobalt(III) acetate. Part 6. A novel synthesis of the glycol monoacetates from aromatic olefins in wet acetic acid. *J Chem Soc Perk T 2* **1984,** (6), 1033–1036; (c) Hirano, M.; Kitamura, E.; Morimoto, T., Oxidation by cobalt(III) acetate. Part 2. Oxidation of styrene in acetic acid. *J Chem Soc Perk T 2* **1980,** *4* (4), 569–573; (d) Bataille, C. J.; Donohoe, T. J., Osmium-free direct syn-dihydroxylation of alkenes. *Chem. Soc. Rev.* **2011,** *40* (1), 114-28; (e) Wang, C., Vicinal anti-Dioxygenation of Alkenes. *Asian J. Org. Chem.* **2018,** *7* (3), 509-521; (f) Bag, R.; De, P. B.; Pradhan, S.; Punniyamurthy, T., Recent Advances in Radical Dioxygenation of Olefins. *Eur. J. Org. Chem.* **2017,** *2017* (37), 5424-5438.

8. (a) Azizi, N.; Khajeh-Amiri, A.; Ghafuri, H.; Bolourtchian, M., LiOH-Catalyzed Simple Ring Opening of Epoxides Under Solvent-Free Conditions. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2010,** *185* (7), 1550-1557; (b) Sekar, G.; Naidu, A.; Ganapathy, D., Copper(I)-Catalyzed Intramolecular Caryl-O Bond-Forming Cyclization

for the Synthesis of 1,4-Benzodioxines and Its Application in the Total Synthesis of Sweetening Isovanillins. *Synthesis* **2010,** *2010* (20), 3509-3519; (c) Kang, Y. B.; Gade, L. H., Triflic acid catalyzed oxidative lactonization and diacetoxylation of alkenes using peroxyacids as oxidants. *J. Org. Chem.* **2012,** *77* (3), 1610-5.

9. (a) Schroeder, M., Osmium tetraoxide cis hydroxylation of unsaturated substrates. *Chem. Rev.* **1980,** *80* (2), 187-213; (b) Donohoe, T. J.; Harris, R. M.; Butterworth, S.; Burrows, J. N.; Cowley, A.; Parker, J. S., New osmium-based reagent for the dihydroxylation of alkenes. *J. Org. Chem.* **2006,** *71* (12), 4481-9; (c) Szermerski, M.; Melesina, J.; Wichapong, K.; Loppenberg, M.; Jose, J.; Sippl, W.; Holl, R., Synthesis, biological evaluation and molecular docking studies of benzyloxyacetohydroxamic acids as LpxC inhibitors. *Bioorg. Med. Chem.* **2014,** *22* (3), 1016-28; (d) Lipka, E.; Vaccher, M. P.; Vaccher, C.; Len, C., Enantiomerical excess determination, purification and biological evaluation of (3S) and (3R) alpha,beta-butenolide analogues of isobenzofuranone. *Bioorg. Med. Chem. Lett.* **2005,** *15* (3), 501-4; (e) Miyakoshi, H.; Miyahara, S.; Yokogawa, T.; Endoh, K.; Muto, T.; Yano, W.; Wakasa, T.; Ueno, H.; Chong, K. T.; Taguchi, J.; Nomura, M.; Takao, Y.; Fujioka, A.; Hashimoto, A.; Itou, K.; Yamamura, K.; Shuto, S.; Nagasawa, H.; Fukuoka, M., 1,2,3-Triazole-containing uracil derivatives with excellent pharmacokinetics as a novel class of potent human deoxyuridine triphosphatase inhibitors. *J. Med. Chem.* **2012,** *55* (14), 6427-37; (f) Ye, S.; Loll, B.; Berger, A. A.; Mulow, U.; Alings, C.; Wahl, M. C.; Koksch, B., Fluorine teams up with water to restore inhibitor activity to mutant BPTI. *Chem Sci* **2015,** *6* (9), 5246-5254; (g) Lee, A. L.; Ley, S. V., The

synthesis of the anti-malarial natural product polysphorin and analogues using polymer-supported reagents and scavengers. *Org. Biomol. Chem.* **2003,** *1* (22), 3957-3966.

10. (a) Luo, C.; Bandar, J. S., Superbase-Catalyzed anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes. *J. Am. Chem. Soc.* **2018,** *140* (10), 3547-3550; (b) Xia, X. F.; Zhu, S. L.; Gu, Z.; Wang, H.; Li, W.; Liu, X.; Liang, Y. M., Catalyst-controlled dioxygenation of olefins: an approach to peroxides, alcohols, and ketones. *J. Org. Chem.* **2015,** *80* (11), 5572-80; (c) Lu, Q.; Liu, Z.; Luo, Y.; Zhang, G.; Huang, Z.; Wang, H.; Liu, C.; Miller, J. T.; Lei, A., Copper-/Cobalt-Catalyzed Highly Selective Radical Dioxygenation of Alkenes. *Org. Lett.* **2015,** *17* (14), 3402-5; (d) Giglio, B. C.; Schmidt, V. A.; Alexanian, E. J., Metal-free, aerobic dioxygenation of alkenes using simple hydroxamic acid derivatives. *J. Am. Chem. Soc.* **2011,** *133* (34), 13320-2; (e) Schmidt, V. A.; Alexanian, E. J., Metal-free, aerobic dioxygenation of alkenes using hydroxamic acids. *Angew. Chem. Int. Ed. Engl.* **2010,** *49* (26), 4491-4; (f) Reddi, R. N.; Prasad, P. K.; Sudalai, A., I2-catalyzed regioselective oxo- and hydroxy-acyloxylation of alkenes and enol ethers: a facile access to alpha-acyloxyketones, esters, and diol derivatives. *Org. Lett.* **2014,** *16* (21), 5674-7; (g) Xue, Q. C.; Xie, J.; Xu, P.; Hu, K. D.; Cheng, Y. X.; Zhu, C. J., Metal-Free, n-Bu4NI-Catalyzed Regioselective Difunctionalization of Unactivated Alkenes. *Acs Catal* **2013,** *3* (6), 1365-1368.

11. Takacs, J.; Jiang, X.-t., The Wacker Reaction and Related Alkene Oxidation Reactions. *Curr. Org. Chem.* **2003,** *7* (4), 369-396.

Chapter 5 Appendix

Experimental Procedures and Spectra for Compounds in 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 α,α,α–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.

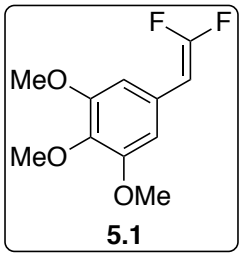
Unless otherwise noted, reagents were purchased from commercial sources and used as received. Cobalt(II) 2,4-pentanedionate [$Co(acac)_2$] was purchased from Alfa Aesar. 1,2–Dichlorobenzene (DCB, anhydrous, 99+%) and *N*-methylpyrrolidine (NMP, anhydrous) were purchased from Sigma Aldrich. Solvents, 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: α,α,α-trifluorotoluene (TFT), sodium sulfate (Na_2SO_4), magnesium sulfate ($MgSO_4$), ethyl acetate (EtOAc), diethyl ether (Et_2O), ammonium chloride (NH_4Cl), *n*butyl lithium (*n*BuLi), sodium hydroxide (NaOH), room temperature (R.T.), *t*butyl carbonate anhydride (Boc_2O), potassium carbonate (K_2CO_3), 1,5,7–triazabicyclo[4.4.0]dec-5-ene (TBD), and hydrochloric acid (HCl).

Proton nuclear magnetic resonance (^1H 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 (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 ($CHCl_3$: 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 ($CDCl_3$: δ = 77.2 ppm; DMSO: δ = 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, δ = doublet, t = triplet, q = quartet, p = pentet,

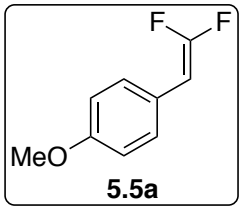
m = multiplet), coupling constant in Hertz (Hz), integration. Electron paramagnetic resonance (EPR) were taken on a Bruker EMXplus EPR spectrometer with an Oxford cryostat. High-resolution mass determinations were obtained either by electrospray ionization (ESI) on a Waters LCT Premier^{TM} mass spectrometer or by atmospheric-pressure chemical ionization (APCI-hexane/PhMe) on a Waters Q-Tof Premier^{TM}, 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



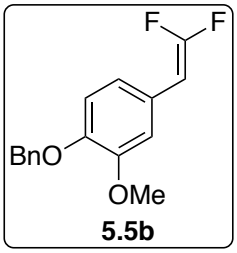
5.1

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.



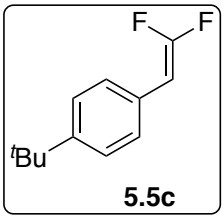
5.5a

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.



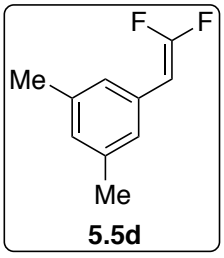
5.5b

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.



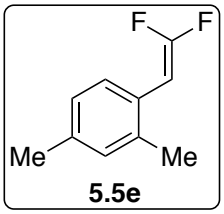
5.5c

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.



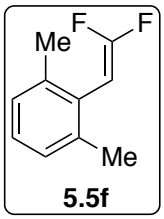
5.5d

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.

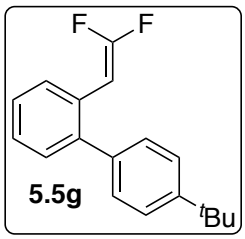


5.5e

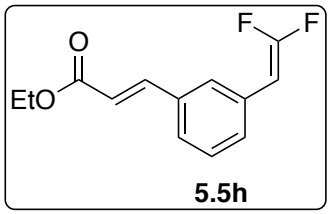
1-(2,2-difluorovinyl)-2,4-dimethylbenzene (5.5e): Compound **5.5e** corresponds to compound **3.8h** in Chapter 3, and was synthesized according to the procedure in the Chapter 3 Appendix.



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.

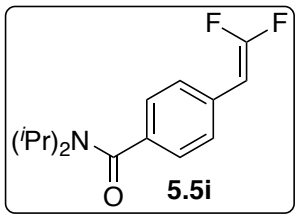


4'-(*tert*-butyl)-2-(2,2-difluorovinyl)-1,1'-biphenyl (5.5g): Compound **5.5g** corresponds to compound **2.5g** in Chapter 2, and was synthesized according to the procedure in the Chapter 2 Appendix.



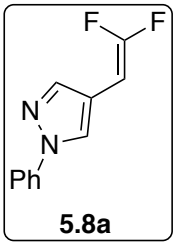
5.5h

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.



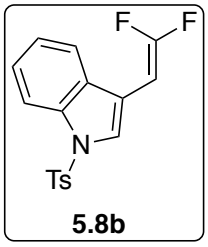
5.5i

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.



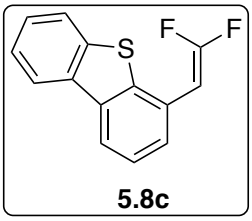
5.8a

4-(2,2-difluorovinyl)-1-phenyl-1*H*-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.



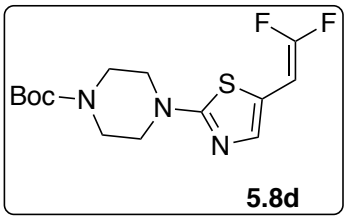
5.8b

3-(2,2-difluorovinyl)-1-tosyl-1*H*-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.



5.8c

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.



5.8d

***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

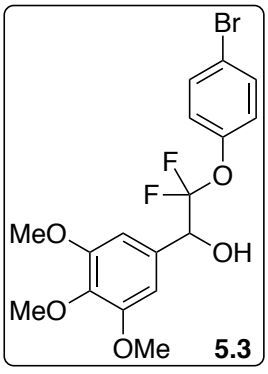
at R.T. for 10 min to allow adequate mixing. After mixing, an aliquot was removed from the vial and passed through a pad of silica gel into an NMR tube using acetone as eluent to remove $Pt(acac)_2$, after which the reaction was analyzed by ^{19}F NMR for completion and selectivity. After ^{19}F NMR 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_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-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 ^{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.

Preparation and Characterization of Compounds in Table 5-1:



5.3

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 PPh_3, 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).

^{1}H NMR (400 MHz, $CDCl_3$): 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)

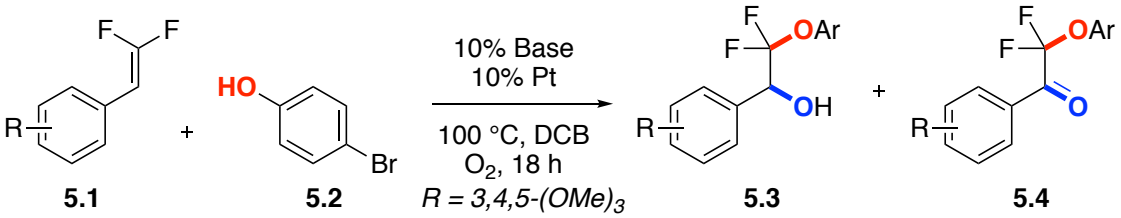
^{13}C NMR (126 MHz, $CDCl_3$): δ 153.1, 149.1 (t, *J* = 2.05 Hz), 138.4 (d, *J* = 2.06 Hz), 132.6, 131.0, 123.6, 122.4 (t, *J* = 273.70 Hz), 119.0, 105.0, 74.2 (t, *J* = 31.70 Hz), 61.0, 56.3

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{17}BrF_2O_5$ (M+) 418.0227, found 418.0212, 3.6 ppm.

Experimental Procedures for Table 5-1:



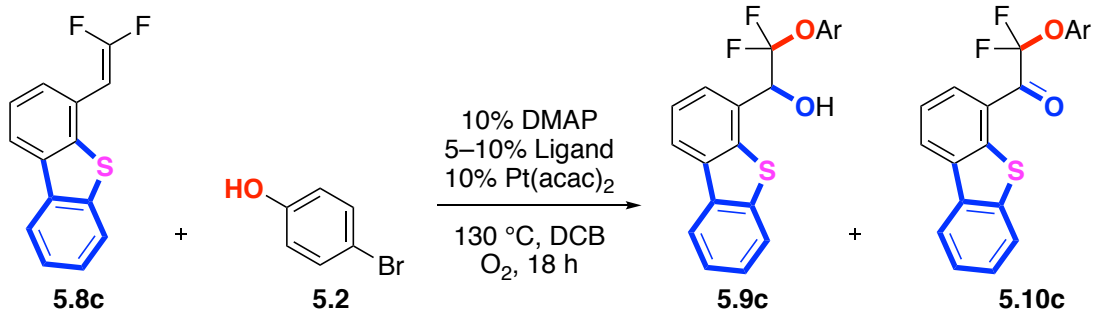
5.1 **5.2** **5.3** **5.4**

Entry	Metal	Base	Solvent	Conv.[b]	5.3[b]	5.4[b]
1	PtO_2	TBD	DCB	98	68	15
2	$Pt(PPh_3)_4$	TBD	DCB	95	66	7
3	PtO_2	–	DCB	84	10	5
4	$Pt(PPh_3)_4$	–	DCB	85	1	8
5[c]	PtO_2	–	DCB	34	1	0
6[c]	$Pt(PPh_3)_4$	Et_3N	DCB	87	1	8
7	$Pt(PPh_3)_4$	2,6-Lutidine	DCB	92	1	8
8	$Pt(PPh_3)_4$	Imidazole	DCB	94	72	12
9	$Pt(PPh_3)_4$	DABCO	DCB	90	67	7
10	$Pt(PPh_3)_4$	DBU	DCB	87	1	10
11	$Pt(PPh_3)_4$	DMAP	DCB	94	85	3
12	$Pt(PPh_3)_4$	DMAP	H_2O	87	28	1
13	$Pt(PPh_3)_4$	DMAP	IPA	34	0	0
14	$Pt(PPh_3)_4$	DMAP	1,4-Dioxane	38	1	0
15	$Pt(PPh_3)_4$	DMAP	MeCN	47	0	0
16	$Pt(PPh_3)_4$	DMAP	DMF	56	1	1
17	$Pt(PPh_3)_4$	DMAP	DMSO	77	0	2
18	$Pt(PPh_3)_4$	DMAP	PhMe	78	40	1
19	$Pt_2(dba)_3$	DMAP	DCB	83	32	10
20	$Pt(acac)_2$	DMAP	DCB	95	74	3
21[d]	$Pt(acac)_2$	DMAP	DCB	95	76	5
22[e]	$Pt(acac)_2$	DMAP	DCB	90	65	4
23[f]	$Pt(acac)_2$	DMAP	DCB	79	48	5

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.

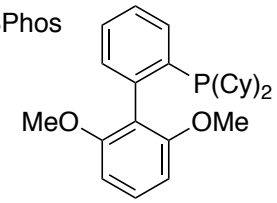
Experimental Procedures for Table 5-2:



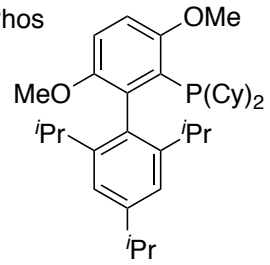
5.8c + **5.2** → **5.9c** + **5.10c**

Entry	Ligand (%)	Conv.[b]	5.9a[b]	5.10a[b]
1	PPh_3 (10%)	90	71	4
2	$OPPh_3$ (10%)	81	78	9
3	PCy_3 (10%)	67	58	3
4	$P(4\text{-}CF_3Ph)_3$ (10%)	88	73	6
5	SPhos (10%)	84	65	8
6	BrettPhos (10%)	82	69	8
7	^{t}Bu-XPhos (10%)	82	62	14
8	Xantphos (5%)	81	68	3
9	DPPE (5%)	91	84	4
10	DPPF (5%)	85	64	17
11	Bipyridine (5%)	89	33	35
12	Phenanthroline (5%)	86	52	35
13	BINAP (5%)	85	74	8

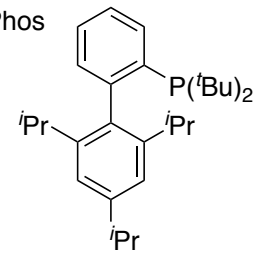
SPhos



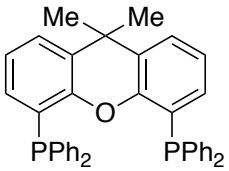
BrettPhos



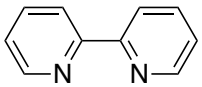
^{t}Bu-XPhos



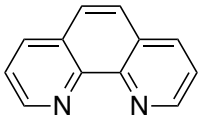
Xantphos



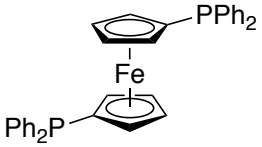
Bipyridine



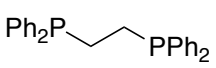
Phenanthroline



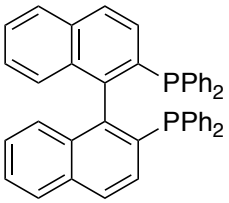
DPPF



DPPE

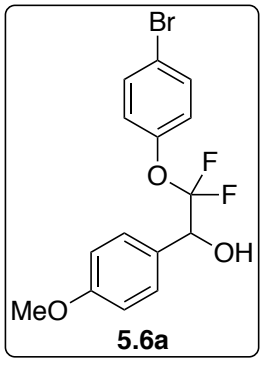


BINAP



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:



5.6a

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).

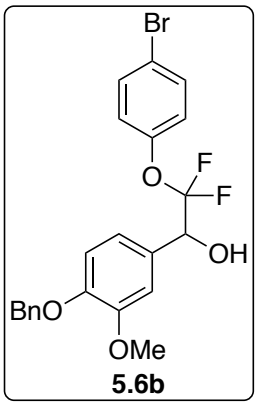
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.64 Hz, 2 H), 7.44–7.41 (m, 2 H), 7.01 (d, *J* = 8.91 Hz, 2 H), 6.96–6.92 (m, 2H), 5.04 (td, *J* = 7.18, 4.29 Hz, 1 H), 3.83 (s, 3 H), 2.57 (d, *J* = 4.27 Hz, 1 H)

^{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, 1305, 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 $C_{15}H_{13}BrF_2O_3Cl$ (M+Cl) 392.9705, found 392.9709, 1.0 ppm.



5.6b

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 PPh_3, 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)

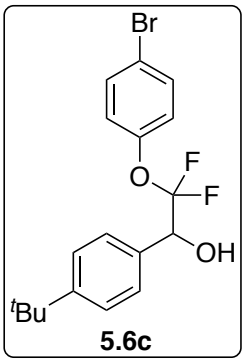
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (td, *J* = 7.21, 6.81, 1.94 Hz, 4 H), 7.41–7.34 (m, 2 H), 7.34–7.28 (m, 1 H), 7.11 (d, *J* = 1.93 Hz, 1 H), 7.06–6.96 (m, 3 H), 6.89 (d, *J* = 8.29 Hz, 1 H), 5.17 (s, 2 H), 5.00 (t, *J* = 7.12 Hz, 1 H), 3.90 (s, 3H), 2.83 (bs, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{22}H_{19}BrF_2O_4K$ (M+K) 503.0072, found 503.0078, 1.2 ppm.



5.6c

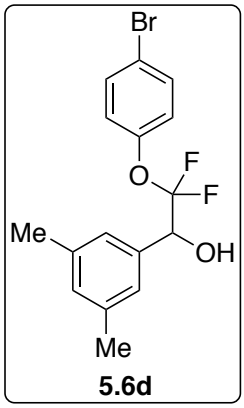
2-(4-bromophenoxy)-1-(4-(*tert*-butyl)phenyl)-2,2-difluoroethan-1-ol (5.6c): Following General Procedure A-1, 0.098 g (0.50 mmol) of compound **5.5c** was reacted with 0.0259 g (1.50 mmol) of 4-bromophenol in the presence of 0.006 g (0.050 mmol) of DMAP, 0.013 g (0.050 mmol) of PPh_3, and 0.020 g (0.050 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.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.62 Hz, 2 H), 7.44–7.43 (m, 4 H), 7.02 (d, *J* = 8.83 Hz, 2 H), 5.06 (td, *J* = 7.18, 4.50 Hz, 1 H), 2.56 (d, *J* = 4.50 Hz, 1 H), 1.34 (s, 9 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.3, 149.2, 132.6, 132.3, 127.5, 125.5, 123.6, 122.6 (t, *J* = 272.79 Hz), 119.0, 74.4 (t, *J* = 31.60 Hz), 34.8, 31.4

^{19}F NMR (376 MHz, $CDCl_3$): δ –82.82 (dd, *J* = 140.87, 7.24 Hz, 1 F), –83.22 (dd, *J* = 140.93, 7.21 Hz, 1 F)

HRMS (ESI–): calc. for $C_{18}H_{19}BrF_2O_2Cl$ (M+Cl) 419.0225, found 419.0240, 3.6 ppm.



5.6d

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_3, 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 0–15% EtOAc in hexanes, furnishing 0.103 g (58% yield) of desired product **5.6d** as a tan solid (MP = 79–81 °C)

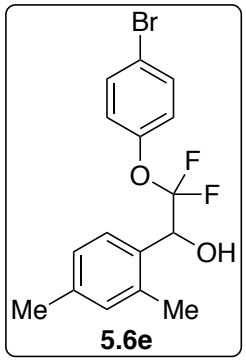
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.88 Hz, 2 H), 7.16 (bs, 2 H), 7.04 (bs, 2 H), 7.02 (bs, 1 H), 5.00 (t, *J* = 7.25 Hz, 1 H), 2.74 (bs, 1 H), 2.36 (s, 6 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{16}H_{15}BrF_2O_2Cl$ (M+Cl) 390.9912, found 390.9921, 2.3 ppm.



5.6e

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) 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 0–20% EtOAc in hexanes, furnishing 0.114 g (64% yield) of desired product **5.6e** as a pale oil

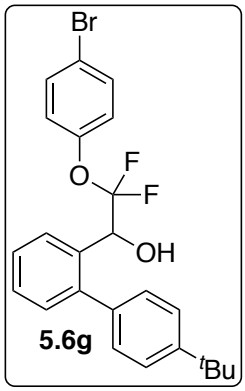
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.96 Hz, 1 H), 7.43 (d, *J* = 8.90 Hz, 2 H), 7.11 (d, *J* = 8.24 Hz, 1 H), 7.04 (d, *J* = 2.23 Hz, 2 H), 7.02 (s, 1 H), 5.35 (td, *J* = 7.18, 3.79 Hz, 1 H), 2.85 (d, *J* = 4.35 Hz, 1 H), 2.40 (s, 3 H), 2.35 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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}F NMR (376 MHz, $CDCl_3$): 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 $C_{16}H_{15}BrF_2O_2Cl$ (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.

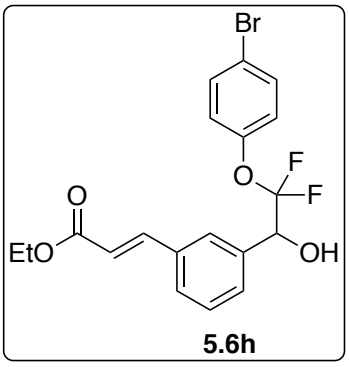
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (t, *J* = 1.66 Hz, 1 H), 7.66 (dt, *J* = 7.39, 1.71 Hz, 1 H), 7.60 (d, *J* = 8.45 Hz, 2 H), 7.52 (d, *J* = 2.18 Hz, 2 H), 7.52–7.49 (m, 2 H), 7.45 (d, *J* = 8.86 Hz, 2 H), 7.04 (d, *J* = 8.77 Hz, 2 H), 5.16 (t, *J* = 7.11 Hz, 1 H), 3.00 (bs, 1 H), 1.40 (s, 9 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): 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 $C_{24}H_{24}BrF_2O_2$ (M+H) 461.0928, found 461.1971, 2.0 ppm.



5.6h

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_2CO_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

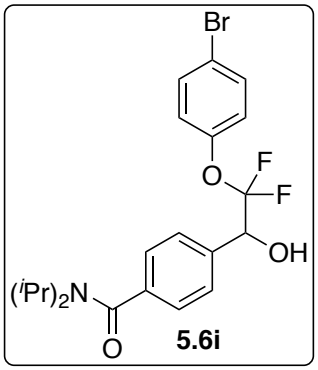
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 16.16 Hz, 2 H), 7.56 (d, *J* = 7.42 Hz, 1 H), 7.52 (dt, *J* = 7.88, 1.47 Hz, 1 H), 7.42–7.38 (m, 3 H), 6.98 (m, 2 H), 6.45 (d, *J* = 16.02 Hz, 1 H), 5.10 (t *J* = 7.05 Hz, 1 H), 4.25 (q, *J* = 7.11 Hz, 2 H), 3.53 (bs, 1 H), 1.32 (t, *J* = 7.13 Hz, 3 H)

^{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, $CDCl_3$): δ –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 $C_{19}H_{17}BrF_2O_4Cl$ (M+Cl) 460.9967, found 460.9999, 6.9 ppm.



5.6i

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)

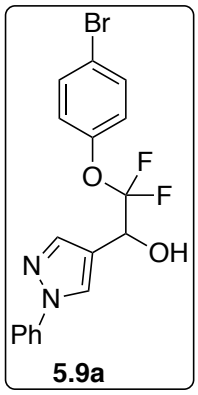
^{13}C NMR (126 MHz, DMSO-D$_6$, 60 °C): δ 169.3, 148.8 (d, *J* = 2.31 Hz), 138.7, 137.2, 132.3, 127.7, 124.7, 123.2, 122.6 (t, *J* = 272.21 Hz), 117.7, 72.0 (t, *J* = 31.34 Hz), 54.5, 20.2

^{19}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 $C_{21}H_{24}BrF_2NO_3Na$ (M+Na) 478.0805, found 478.0813, 1.7 ppm.

Experimental Procedures and Characterization of Compounds in Scheme 5-5:



5.9a

2-(4-bromophenoxy)-2,2-difluoro-1-(1-phenyl-1*H*-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 PPh_3, 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 15–40% EtOAc in hexanes, furnishing 0.083 g (42% yield) of desired product **5.9a** as a yellow solid (MP = 70–72 ˚C)

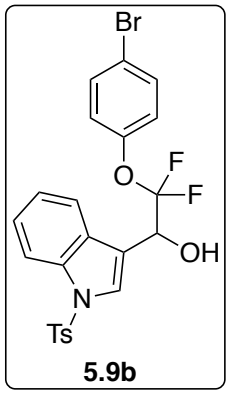
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1 H), 7.82 (s, 1 H), 7.65 (d, *J* = 7.51 Hz, 2 H), 7.43 (dd, *J* = 8.90, 7.22 Hz, 4 H), 7.29 (t, *J* = 7.45 Hz, 1 H), 7.04 (d, *J* = 8.57 Hz, 2 H), 5.16 (td, *J* = 6.91, 3.91 Hz, 1 H), 3.59 (d, *J* = 5.46 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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)

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{14}BrF_2N_2O_2$ (M+H) 395.0207, found 395.0220, 3.3 ppm.



5.9b

2-(4-bromophenoxy)-2,2-difluoro-1-(1-tosyl-1*H*-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).

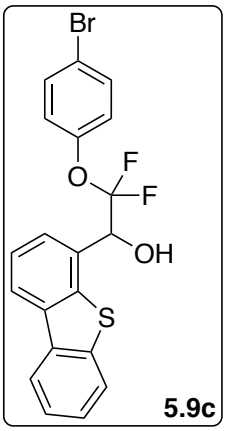
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dt, *J* = 8.49, 0.88 Hz), 1 H), 7.77 (d, *J* = 8.53 Hz, 3 H), 7.73 (d, *J* = 7.75 Hz, 1 H), 7.45–7.41 (m, 2 H), 7.34 (ddd, *J* = 8.38, 7.16, 1.28 Hz, 1 H), 7.28–7.24 (m, 1 H), 7.21 (d, *J* = 7.65 Hz, 2 H), 6.98 (dd, *J* = 8.76, 1.07 Hz, 2 H), 5.35 (td, *J* = 6.73, 4.53 Hz, 1 H), 2.68 (d, *J* = 4.95 Hz, 1 H), 2.34 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{23}H_{18}F_2NO_4S$ (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, $CDCl_3$): 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)

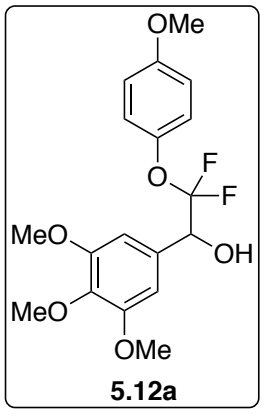
^{13}C NMR (126 MHz, $CDCl_3$): δ 149.0 (d, *J* = 3.01 Hz), 139.5, 139.2, 136.4, 135.3, 132.5, 129.9, 127.1, 126.2, 124.7, 124.6, 123.4, 122.7, 122.3, 121.7, 118.9, 73.7 (t, *J* = 32.23 Hz)

^{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 $C_{20}H_{13}BrF_2O_2SCl$ (M+Cl) 468.9476, found 468.9471, 1.1 ppm.

Experimental Procedures and Characterization of Compounds in Scheme 5-6:



5.12a

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

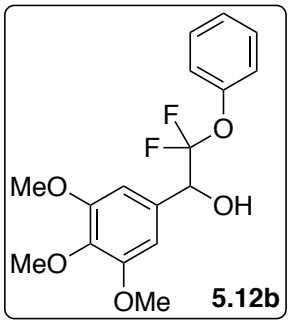
DMAP, 0.013 g (0.050 mmol) of PPh_3, and 0.020 g (0.050 mmol) of $Pt(acac)_2$ at 120 ˚C for 24 h. After workup with 1 N NaOH (aq.), the product was purified by flash chromatography using a gradient of 0–35% EtOAc in hexanes, furnishing 0.126 g (68% yield) of desired product **5.12a** as an orange oil.

^{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 $C_{18}H_{20}F_2O_6Cl$ (M+Cl) 405.0916, found 405.0911, 1.2 ppm



5.12b

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).

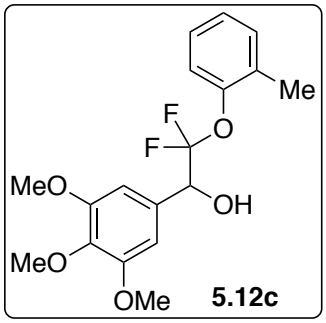
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (dd, *J* = 8.53, 7.23 Hz, 2 H), 7.20 (t, *J* = 7.42 Hz, 1 H), 7.14 (d, *J* = 7.18 Hz, 2 H), 6.78 (s, 2 H), 5.03 (ddd, *J* = 9.10, 6.73, 2.85 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 3.07 (d, *J* = 3.91 Hz, 1 H)

^{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 $C_{17}H_{19}F_2O_5$ (M+H) 341.1201, found 341.1195, 1.8 ppm.



5.12c

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.

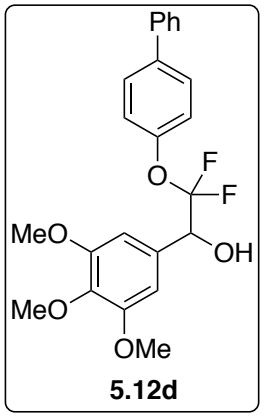
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.07 (m, 4 H), 6.80 (s, 2 H), 5.07 (dd, *J* = 7.79, 5.83 Hz, 1 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.93 (bs, 1 H), 2.05 (s, 3 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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, 1507, 1492, 1461, 1421, 1325, 1251, 1234, 1178, 1125, 1062, 1003, 922, 844, 819, 787, 745, 712, 694, 660, 559, 527 cm^{-1}

HRMS (ESI+): calc. for $C_{18}H_{20}F_2O_5Na$ (M+Na) 377.1177, found 377.1179, 0.5 ppm.



5.12d

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.

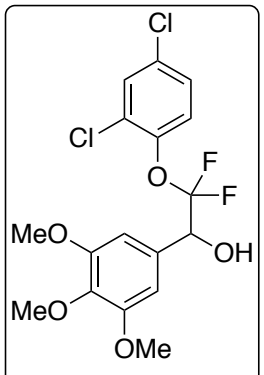
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.54 Hz, 4 H), 7.43 (t, *J* = 7.50 Hz, 2 H), 7.37–7.33 (m, 1 H), 7.22 (dd, *J* = 8.65, 0.91 Hz, 2 H), 6.81 (s, 2 H), 5.06 (td, *J* = 7.09, 3.94 Hz, 1 H), 3.90 (s, 6 H), 3.88 (s, 3 H), 2.90 (d, *J* = 4.01 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{23}H_{22}F_2O_5Na$ (M+Na) 439.1333, found 439.1344, 2.5 ppm.



5.12e

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 PPh_3, 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.

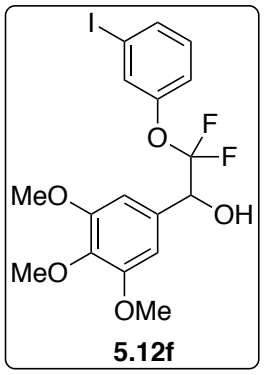
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 2.43 Hz, 1 H), 7.28–7.25 (m ,1 H), 7.21 (dd, *J* = 8.81, 2.42 Hz, 1 H), 6.79 (s, 2 H), 5.09 (t, *J* = 7.27 Hz, 1 H), 3.88 (s, 6 H), 3.86 (s, 3 H), 2.89 (bs, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{17}H_{16}Cl_2F_2O_5K$ (M+K) 446.9980, found 446.9998, 4.0 ppm.



5.12f

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 PPh_3, 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).

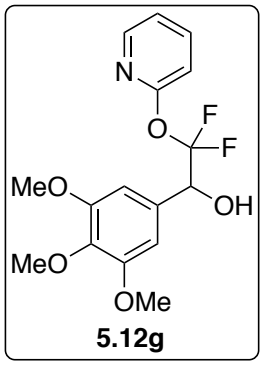
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (dt, *J* = 7.82, 1.28 Hz, 1 H), 7.51 (t, *J* = 1.90 Hz, 1 H), 7.13 (ddd, *J* = 8.34, 2.23, 1.03 Hz, 1 H), 7.06 (t, *J* = 8.00 Hz, 1 H), 6.77 (s, 2 H), 5.02 (td, *J* = 7.14, 3.90 Hz, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 2.67 (d, *J* = 3.26 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): 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}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{17}H_{17}F_2IO_5Cl$ (M+Cl) 500.9777, found 500.9782, 1.0 ppm.



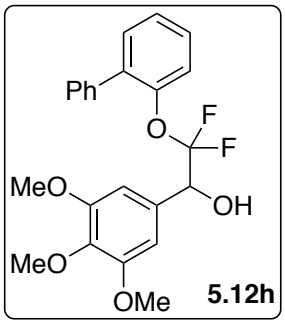
5.12g

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_3, and 0.007 g (0.020 mmol) of $Pt(acac)_2$ 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.

^{1}H NMR (500 MHz, $CDCl_3$): 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)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): δ –82.74 (dd, *J* = 141.16, 7.10 Hz, 1 F), –83.17 (dd, *J* = 141.09, 7.47 Hz, 1 F)



5.12h

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 **5.12h** as a pale yellow solid (MP = 42 °C).

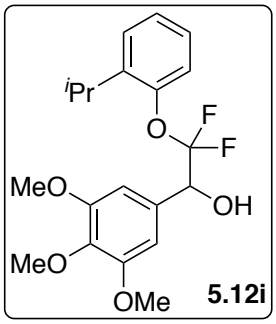
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.31 (m, 8 H), 7.29 (dd, *J* = 7.31, 1.53 Hz, 1 H), 6.56 (s, 2 H), 4.82 (td, *J* = 7.11, 4.18 Hz, 1 H), 3.85 (s, 3 H), 3.78 (s, 6 H), 2.32 (d, *J* = 4.17 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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 $C_{23}H_{22}F_2O_5K$ (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-*iso*-propylphenol 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.

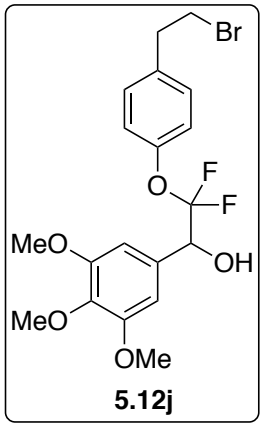
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dt, *J* = 7.74, 2.51 Hz, 2 H), 7.15 (ddd, *J* = 8.03, 5.34, 2.08 Hz, 2 H), 6.81 (s, 2 H), 5.09 (dt, *J* = 8.66, 4.45 Hz, 1 H), 3.87 (s, 6 H), 3.86 (s, 3 H), 2.82 (p, *J* = 6.92 Hz, 1 H), 2.74 (d, *J* = 3.95 Hz, 1 H), 1.03 (dd, *J* = 6.92, 1.01 Hz, 6 H)

^{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}F NMR (376 MHz, $CDCl_3$): δ –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 $C_{20}H_{24}F_2O_5Cl$ (M+Cl) 417.1280, found 417.1280, 0.0 ppm.



5.12j

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.

^{1}H NMR (400 MHz, $CDCl_3$): 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)

^{13}C NMR (126 MHz, $CDCl_3$): 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

^{19}F NMR (376 MHz, $CDCl_3$): 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}

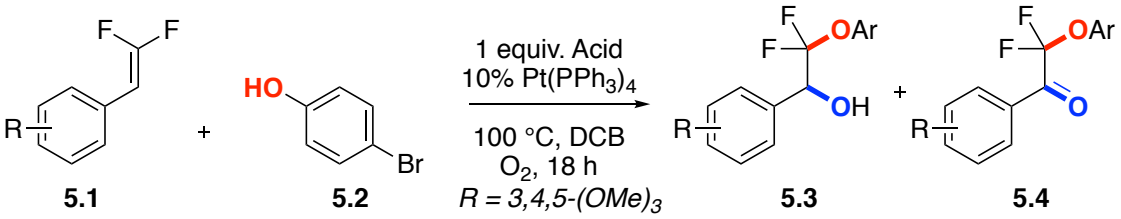
HRMS (ESI–): calc. for $C_{19}H_{21}BrF_2O_5Cl$ (M+Cl) 481.0229, found 481.0247, 3.7 ppm.

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), $CuCl_2$ (0.02

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 balloon 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 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 ^{19}F NMR for completion and selectivity.

Experimental Procedures for Table 5-3:

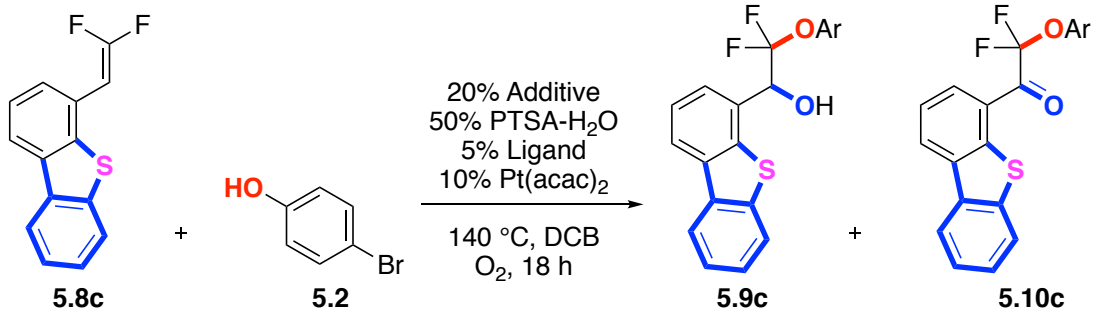


5.1 **5.2** **5.3** **5.4**

Entry	Acid	Conv.[b]	5.3[b]	5.4[b]
1	H_2SO_4	79	0	0
2	AcOH	72	40	8
3	TFA	92	0	8
4	Proline	25	1	0
5	PTSA-H_2O	>99	0	14
6	MsOH	>99	0	10
7	SDS	60	0	2
8	Isoquinoline-5-SO_4	40	16	5
9[c]	PTSA-H_2O	76	0	18
10[d]	PTSA-H_2O	57	0	8
11[e]	PTSA-H_2O	52	5	12
12[c,f]	PTSA-H_2O	76	0	31
13[c,f]	4-NH_2-C_6H_4-SO_4	60	0	4
14[c,f]	4-Cl-C_6H_4-SO_4	12	trace	18
15[c,f]	C_6H_5-SO_4	80	11	23
16[c,f]	2,4-Me_2-C_6H_3-SO_4	84	9	23

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 $Pt(PPh_3)_4$ 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 ^{19}F NMR for completion, yield, and selectivity.

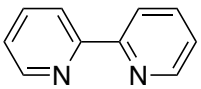
Experimental Procedures for Table 5-4:



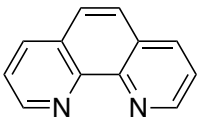
5.8c + **5.2** → **5.9c** + **5.10c**

Entry	Additive	Ligand	Conv.[b]	5.9c[b]	5.10c[b]
1	–	Bipyridine	89	0	48
2	–	Phenanthroline	82	0	44
3	–	Terpyridine	89	0	45
4	$CuCl_2$	PPh_3	>99	0	30
5	$CuCl_2$	Bipyridine	84	0	51
6	$CuCl_2$	Phenanthroline	80	0	66
7	$CuCl_2$	Terpyridine	89	0	66
8	$CuCl_2$	Bipyridine	81	0	48
9	$CuCl_2$	Phenanthroline	81	0	49
10	$CuCl_2$	Terpyridine	81	0	64
11[c,d]	$CuCl_2$	Terpyridine	84	14	64

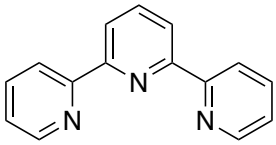
Bipyridine



Phenanthroline



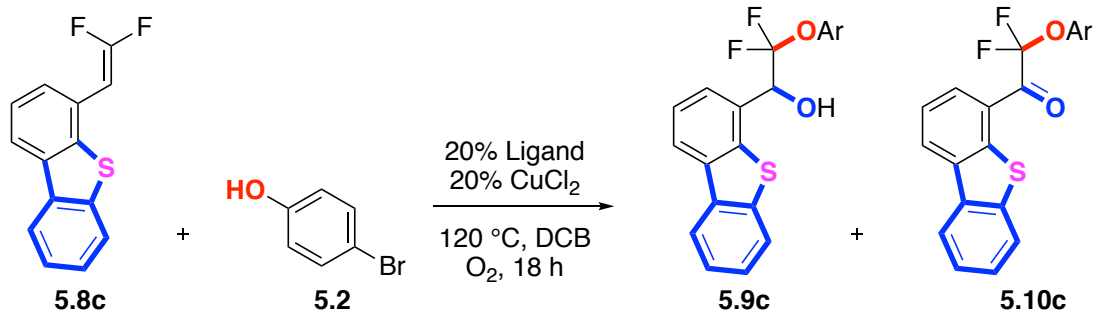
Terpyridine



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:

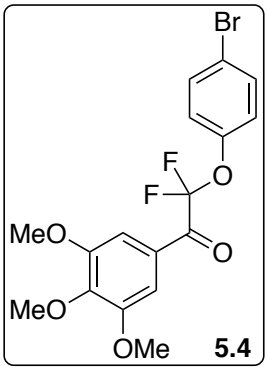


5.8c + **5.2** → **5.9c** + **5.10c**

Entry	Metal	Ligand	Solvent	Conv.[b]	5.9c[b]	5.10c[b]
1	$CuCl_2$	Bipyridine	DCB	75	16	68
2	$CuCl_2$	Phenanthroline	DCB	81	18	76
3	$CuCl_2$	Terpyridine	DCB	76	16	69
4	$CuSO_4$	Terpyridine	DCB	89	10	74
5	$Cu(OAc)_2$	Terpyridine	DCB	80	11	79
6	$Cu(OAc)_2$	Phenanthroline	DCB	82	8	60
7	$Cu(OAc)_2$	Bathophenanthroline	DCB	75	9	56
8	$Cu(OAc)_2$	Me_4-Phenanthroline	DCB	91	10	48
9	$Cu(OAc)_2$	$(OMe)_2$-Phenanthroline	DCB	82	13	68
10	$CuCl_2$	Phenanthroline	PhMe	80	10	45
11	$CuCl_2$	Phenanthroline	DMF	44	0	14
12	$CuCl_2$	Phenanthroline	DMSO	40	0	13
13	$CuCl_2$	Phenanthroline	Diglyme	67	0	28
14[c]	$Cu(OAc)_2$	Terpyridine	3:1 DCB:Diglyme	94	18	81
15[c]	$Cu(OAc)_2$	Terpyridine	3:1 DCB:DMSO	61	0	45
16[c,d]	$Cu(OAc)_2$	Terpyridine	95:5 DCB:DMSO	>99	7	83
17[c,d]	$Cu(OAc)_2$	Terpyridine	3:1 DCB:DMSO	87	2	65

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:

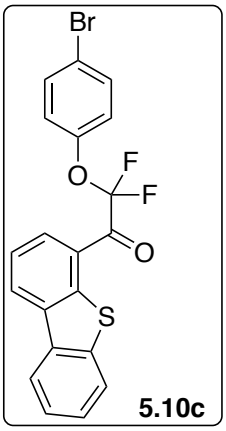


5.4

2-(4-bromophenoxy)-2,2-difluoro-1-(3,4,5-trimethoxyphenyl)ethan-1-one (5.4):

^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ –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, $CDCl_3$): δ 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, $CDCl_3$): δ –73.26 (s, 2 F)